PROSPECTIVE **A**CAD**E**MIC TRANSLATIONAL RESEARCH NETWORK FOR THE OPTIMIZATION OF THE ONCO-LO**G**ICAL HEALTH CARE QUALITY I**N** THE ADJUVANT AND **A**DVA**N**CED/METASTATIC SE**T**TING: HEALTH CARE RESEARCH, PHARMACOGENOMICS, BIOMARKERS, HEALTH ECONOMICS

PRAEGNANT BREAST CANCER: ADVANCED/METASTATIC

SEN-01/14

EudraCT 2014-000854-12

- Study protocol Synopsis-

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Study Title	PROSPECTIVE ACADEMIC TRANSLATIONAL RESEARCH NETWORK FOR THE OPTIMIZATION OF THE ONCOLOGICAL HEALTH CARE QUALITY IN THE ADJUVANT AND ADVANCED/METASTATIC SETTING: HEALTH CARE RESEARCH, PHARMACOGENOMICS, BIOMARKERS, HEALTH ECONOMICS **PRAEGNANT BREAST CANCER**
Study Code	SEN-01/14, EudraCT 2014-000854-12, NCT02338167
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Project & Study Management	• ClinSol GmbH & Co. KG; Sanderstr. 27; 97070 Würzburg
Study Design	The study will be conducted as a prospective interventional registry and diagnostic translational study. Enrollment of patients may only be initiated following approval of the ethics committee of the Universitätsklinikum Tuebingen.
Study Duration	A patient remains in the study for a maximum of 36 months until death or withdrawal of consent. Median study duration per patient is estimated for approx. 2.5 years.
Inclusion Criteria	• Adult breast cancer patients (age ≥18 years) • Patients with the diagnosis of invasive breast cancer (irrespective of status of BC, e.g. TNM, receptor status etc.) • Patients, who are able and willing to sign the informed consent form • Patients with metastatic or locally advanced, inoperable disease proven by clinical measures (i.e. standard imaging).
Exclusion Criteria	• Patients who do not have the diagnosis of metastatic or locally advanced, inoperabe breast cancer • 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 treatment	No specific study treatment is defined. All treatments are prescribed and performed according to each center's medical practice. Any treatment choice or change in regimen is performed at the discretion of each treating physician.
Study Background	Among patients with breast cancer the subgroup of patients with metastases are considered the group of patients with the worst prognosis. Not only with regard to therapy decisions but also with regard to quality assured healthcare and health economics this entitiy of patients remains a challenge.

	Recently, novel advances 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. However molecular assessment of the patient and 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 make therapy decisions for the metastatic patients. Although molecular reassessment of tumor characteristics from tumor material of the metastasis is recommended in national guidelines, only a minority of patients is biopsied, because of the invasiveness of the procedure, even though biopsy related complications are reported to be rare. With modern analytic methods from blood based biomaterial there seems to be an opportunity to correlate blood based tumor assessments with actual characteristics of the tumor. These include expression analysis, tumor mutation analysis, tumor gene copy number abberations and others. One of the main aims of the PRAEGNANT study is therefore to establish an infrastructure for the comprehensive analysis of tumor and metastatic molecular characteristics of the patient and the tumor. Furthermore health care related outcomes as well as health economics provide novel approaches for integration of patients in study conduct and health care awareness and are study aims of the PRAEGNANT study.	
Study Objectives	**Primary Objective**	**Outcome measure**
	Discovery of biomarkers, which predict progression free survival (PFS). Biomarkers comprise comprehensive molecular analysis of gene expression, gene mutations, serum and tissue biomarkers.	PFS defined as the time to the first progression after study inclusion from the last time of progression before or at study entry. Analyses will be done separately for each therapy line. Biomarkers include gene expression profiling of the primary tumor and the corresponding metastatis, somatic mutations, germline genetic variation, epigenetic changes and miRNA variation up to a total of 500,000 biomarkers.
	Secondary Objectives	**Outcome measure(s)**
	Assessment of overall survival (OS)	OS is defined as the time to death from the date of the last progression before or at study entry.
	Assessment of breast cancer specific survival (BCSS)	BCSS is defined as the time to to death due to breast cancer from the date of the last progression before or at study entry.
	Objective response	Objective response is defined as the best-documented response to the therapy started at study entry or the last therapy started before study entry.
	Description of therapies used in the metastatic setting	Therapies will be categorized and descriptive statistics will be presented.
Study Objectives (continued)	Percentage of women, who will receive results of molecular tests	Number of patients who will receive molecular testing results compared to the total

	undertaken in the context of the scientific objectives of this trial.	number of included patients.
	Feasibility and satisfaction regarding receipt of molecular testing results (including hereditary genetic alterations)	Assessed with a phsysician and patient questionnaire and documentation of possible confirmatory testing for changes in therapy or eligibility for interventional clinical trial screening.
	Quality of life	Assessed with e.g., EORTC QLQ C-30 (Version 3.0), EORTC QLQ-BR23 and the EQ-Visual Analog Scale (VAS)
	Therapy adherence	Defined as the percentage of patients in which treatments are terminated as per patients' wish or because of treatment related side effect.
	Health economics for women with metastatic and/or locally advanced, inoperable breast cancer	EORTC QLQ C-30 (Version 3.0), and actual documented costs of diagnostic procedures, therapies, treatment of side effects and care for tumour-associated symtoms will be used to calculate health care costs, quality adjusted life years (QALY) and incremental cost effectiveness ratios (ICER) between patient groups.
	Influencing Factors of Depression in patients with metastatic breast cancer	Depression will be assessed by patient reported questionnaires e.g. CESD-R.
	Patient reported influencing factors on therapy adherence in patients metastatic and/or locally advanced, inoperable breast cancer.	Patient reported adherence for orally administered therapies will be assessed with questionnaires such as the Morisky Medical Adherence Scale 8 items (MMAS-8)
	Incidence of adverse events, serious adverse events will be reported.	NCI Common Toxicity Criteria Version 4.03.
	Exploratory Objectives	**Outcome Measures**
	Correlation of the incidence of depression with germline genetic variation and therapies and gene expression from leukocytes. (see Subprotocol section 5.2.5.)	Depression inventory values will be associated with blood biomarkers, single nucleotid polymorphisms and therapies.
Study Objectives (continued)	Correlation of gene alterations (mutations and or amplifications) and gene expression between primary tumor and metastatic tumor for the prediction of side effects and prognosis. (See core projects section 5.1.)	DNA and RNA of the primary tumor will be extracted of archival formalin fixed, paraffin embedded tumor samples and analyzed mutations, mutation changes, and differentially expressed genes. Additionally FFPE will be used for the construction of a TMA for antibody staining.
	Correlation of gene alterations	Circulating tumor cells (CTC) from selected

	(mutations and or amplifications) and gene expression between primary tumor, metastatic tumor and circulating tumor cells (CTCs) (See subprotocol section 5.2.1.)	patients will be analyzed for mutations and gene amplifications. Findings will be compared to mutations assessed from FFPE tumor material.
	Correlation of gene alterations (mutations and or amplifications) between primary tumor, metastatic tumor and circulating tumor DNA (see Subprotocol section 5.2.3.).	Circulating DNA (ctDNA) will be analyzed for genetic variation and compared to mutations assessed from FFPE tumor material.
	Prediction of therapy response, prognosis and side effects with germline Single Nucleotid Polymorphisms (see Subprotocol section 5.2.2.).	Germline DNA will be used as reference for the genetic analysis of the tumor, CTCs and ctDNA. Additionally genomewide SNPs will be assessed and used for a genomewide association study.
	Correlation of blood protein biomarkers with side effects, and progression (see subprotocol section 5.2.4.).	EGFR (1068), HSP27 (pS78), IL-1a, IL-1b, IL-2, IL-6, Il-8, PAI-1, sEGFR, ERK1/2, mTOR, TNF-a, TNF-b. PINP, CTX, Vitamin D, PTH, OPG, RANKL, Sclerostin, DKK-1.
	Identification of risk factors for the development of metastatic disease in healthy women (see subprotocol section 5.2.2.)	Patients will be matched to a pool of controls, which are not part of the PRAEGNANT study, but which have been recruited during the same time.
	Influencing Factors of Physical Acticity, Mental factors and Nutrition in patients with metastatic breast cancer (see subprotocol section 5.2.7.)	Physical activity and nutrition will be assessed with patient reported questionnaires, e.g IPAQ and ER^2.
	Time to progression from the beginning of subsequent therapy lines until the next progression.	All molecular and other measures that might predict prognosis will be associated with these times to progression as well.
	Time to death from the beginning of subsequent therapy lines	All molecular and other measures that might predict prognosis will be associated with these times to death as well.
Sample Size	PRAEGNANT is a study that aims at identifying biomarkers in metastatic and/or locally advanced, inoperable breast cancer patients. Within the study, comprehensive biomaterials are obtained, which will be used to possibly assess gene expression profiling, methylation patterns, and other blood biomarkers. Current assessment techniques measure these biomarkers on a genomewide level, often leading to hundreds of thousands of biomarker values. We assume that a total of 500,000 biomarkers will enter analysis. Primary aim of the study is the identification of predictors of progression-free survival within these biomarkers. As there are very few validated other predictors for progression-free survival in the metastastic setting [1-3], no other possible confounders will be taken into consideration. The study will have an accrual period of approximately 36 months, during which	

<table>
<tr><td></td><td>patients enter the study and a follow-up period of maximum 36 months. It is assumed that the median progression-free survival time for all patients is 10 months [4-6]. For each biomarker, a simple Cox regression model with the biomarker as continuous predictor will be fitted. Hazard ratios (HRs) per standard deviation (SD) and corresponding p-values of two-sided Wald tests with significance level $\alpha = 0.05$ will be calculated. P-values will be corrected according to the Bonferroni method to address multiple testing.
The following table provides power values for various assumed true HRs per SD when 3500 patients participate in the study.

<table>
<tr><th>HR</th><th>POWER (%)</th></tr>
<tr><td>1,1</td><td>33</td></tr>
<tr><td>1,11</td><td>51</td></tr>
<tr><td>1,12</td><td>69</td></tr>
<tr><td>1,13</td><td>83</td></tr>
<tr><td>1,14</td><td>92</td></tr>
<tr><td>1,15</td><td>97</td></tr>
<tr><td>1,16</td><td>99</td></tr>
<tr><td>1,17</td><td>100</td></tr>
</table>

For example, a biomarker whose true HR is 1.15 will be identified as significant predictor with 97% probability.</td></tr>
<tr><td>Study Sites</td><td>Approx. 30 pilot sites: 15 breast centers under gynecological administration and 15 sites with systemic therapy under haemotological/oncological leadership.</td></tr>
<tr><td>Study Duration</td><td>• Start of documentation: Q III/ 2014
• End of documentation: Q III/ 2020
• Final analysis: Q IV / 2021</td></tr>
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