



**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: EARLY/ADVANCED/METASTATIC**

SEN-01/14

EudraCT 2014-000854-12

- Study protocol Synopsis-

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<b>Study Title</b>	<p>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</p> <p><b>PRAEGNANT BREAST CANCER</b></p>
<b>Study Code</b>	SEN-01/14, EudraCT 2014-000854-12, NCT02338167
<b>Sponsor</b>	<ul style="list-style-type: none"> <li>• Universitätsklinikum Tübingen Forschungsinstitut für Frauengesundheit Baden-Württemberg Calwerstraße 7; 72076 Tübingen</li> </ul>
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<b>Study &amp; Network Management</b>	<ul style="list-style-type: none"> <li>• ClinSol GmbH &amp; Co. KG; Kantstr. 26; 97074 Würzburg</li> </ul>
<b>Study Design</b>	The study will be conducted as a prospective interventional registry and diagnostic translational study. For comparative sensitivity analyses anonymized retrospective comparator cohorts may be documented as well. Enrollment of patients may only be initiated following approval of the ethics committee of the Universitätsklinikum Tuebingen.
<b>Study Duration</b>	A prospectively included patient remains in the study for a maximum of 60 months in early breast cancer setting and in the advanced/metastatic setting until death or withdrawal of consent.
<b>Inclusion Criteria</b>	
<b>EBC</b>	<ul style="list-style-type: none"> <li>• Adult breast cancer patients (age <math>\geq 18</math> years)</li> <li>• Patients with breast cancer and no evidence of distant metastases with a diagnosis not longer than 91 days before study entry.</li> <li>• Patients, who are able and willing to sign the informed consent form</li> </ul>
<b>MBC</b>	<ul style="list-style-type: none"> <li>• Adult breast cancer patients (age <math>\geq 18</math> years)</li> <li>• Patients with the diagnosis of invasive breast cancer (irrespective of status of BC, e.g. TNM, receptor status etc.)</li> <li>• Patients, who are able and willing to sign the informed consent form</li> <li>• Patients with metastatic or locally advanced disease proven by clinical measures (i.e. standard imaging).</li> </ul>
<b>Exclusion Criteria</b>	<ul style="list-style-type: none"> <li>• Patients who did not sign the informed consent form</li> <li>• Patients who are not eligible for observation due to severe comorbidities or unavailability according to the treating physician</li> </ul>
<b>Study treatment</b>	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.
<b>Study Background</b>	<p>Among patients with breast cancer the subgroup of patients with metastases are considered the group of patients with the worst prognosis. Not only regarding therapy decisions but also with regard to quality assured healthcare and health economics this entity of patients remains a challenge.</p> <p>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.</p> <p>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</p>

	<p>rare.</p> <p>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 aberrations 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.</p> <p>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.</p>	
<b>Study Objectives</b>		
<b>EBC (Early Breast Cancer)</b>	<b>Primary Objective</b>	<b>Outcome measure</b>
	Assessment of disease free survival (DFS)	DFS defined as the time to the first disease recurrence after study inclusion from time of primary diagnosis before or at study entry
	<b>Secondary Objectives</b>	<b>Outcome measure(s)</b>
	Assessment of distant disease-free survival (DDFS)	DDFS defined as the time to the first distant disease recurrence after study inclusion from time of primary diagnosis before or at study entry.
	Quality of life	Assessed with EORTC QLQ C-30 (Version 3.0), EORTC QLQ-BR23 and the EQ-Visual Analog Scale (VAS)
	Assessment of overall survival (OS)	OS is defined as the time to death from the date of the primary diagnosis before or at study entry.
	Assessment of breast cancer specific survival (BCSS)	BCSS is defined as the time to death due to breast cancer from the date of the primary diagnosis before or at study entry.
	Description of therapies used in the early breast cancer setting	Therapies will be categorized, and descriptive statistics will be presented.
	Percentage of women, who will receive results of molecular tests undertaken in the context of the scientific objectives of this trial.	Number of patients who will receive molecular testing results compared to the total number of included patients.
	Feasibility and satisfaction regarding receipt of molecular testing results (including hereditary genetic alterations)	Assessed with a physician and patient questionnaire and documentation of possible confirmatory testing for changes in therapy or eligibility for interventional clinical trial screening.
Therapy adherence	Defined as the percentage of patients in which treatments which are terminated as per patients' wish or because of treatment related side effect	
Health economics for women	EORTC QLQ C-30 (Version 3.0) (among oth-	

	with breast cancer	ers) and actual documented costs of diagnostic procedures, therapies, treatment of side effects and care for tumour-associated symptoms 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 breast cancer	Depression will be assessed by patient reported questionnaires e.g. CESD-R,
	Patient reported influencing factors on therapy adherence in patients with early breast cancer.	Patient reported adherence for orally administered therapies will be assessed with suitable questionnaires.
	Incidence of adverse events, serious adverse events will be reported.	NCI Common Toxicity Criteria Version 4.03.
<b>MBC (Metastatic Breast Cancer)</b>	<b>Primary Objective</b>	<b>Outcome measure</b>
	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 metastasis, somatic mutations, germline genetic variation, epigenetic changes and miRNA variation up to a total of 500,000 biomarkers.
	<b>Secondary Objectives</b>	<b>Outcome measure(s)</b>
	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 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.
	Percentage of women, who will receive results of molecular tests undertaken in the context of the scientific objectives of this trial.	Number of patients who will receive molecular testing results compared to the total number of included patients.
	Feasibility and satisfaction regarding receipt of molecular testing results (including hereditary	Assessed with a physician and patient questionnaire and documentation of possible confirmatory testing for changes in therapy

	genetic alterations)	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 which 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) (among others) and actual documented costs of diagnostic procedures, therapies, treatment of side effects and care for tumor-associated symptoms 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 suitable questionnaires.
	Incidence of adverse events, serious adverse events will be reported.	NCI Common Toxicity Criteria Version 4.03.
<b>Exploratory (EBC/MBC)</b>	<b>Exploratory Objectives</b>	<b>Outcome Measures</b>
	Correlation of the incidence of depression with germline genetic variation and therapies and gene expression from leukocytes. (see Sub-protocol section 5.2.5.)	Depression inventory values will be associated with blood biomarkers, single nucleotide polymorphisms and therapies.
	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 (mutations and or amplifications) and gene expression between primary tumor, metastatic tumor and circulating tumor cells (CTCs) (See sub-protocol section 5.2.1.)	Circulating tumor cells (CTC) from selected 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 Sub-protocol 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 Nucleotide Polymorphisms (see Sub-protocol section 5.2.2.).	Germline DNA will be used as reference for the genetic analysis of the tumor, CTCs and ctDNA. Additionally, genome-wide SNPs will be assessed and used for a genome-wide association study.
	Correlation of blood protein biomarkers with side effects, and progression (see sub-protocol 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 sub-protocol 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 Activity, Mental factors and Nutrition in patients with metastatic breast cancer (see sub-protocol section 5.2.7.)	Physical activity and nutrition will be assessed with patient reported questionnaires, e.g IPAQ and ER <sup>2</sup> .
	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.
<b>Sample Size</b>	<p>The PRAEGNANT Study is a study that aims at identifying biomarkers. 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 genome-wide level, often leading to hundreds of thousands of biomarker values. We assume that a total of 500,000 biomarkers will be considered for analyses. .</p> <p>Power calculation will be carried for three settings</p> <ul style="list-style-type: none"> <li>• <b>Setting 1:</b> metastatic breast cancer patients</li> <li>• <b>Setting 2:</b> early breast cancer patients in the adjuvant situation</li> <li>• <b>Setting 3:</b> early breast cancer patients in the neoadjuvant situation</li> </ul> <p>Primary study aim in Setting 1 and 2 is the identification of predictors of progression-free survival. 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 <math>\alpha = 0.05</math> will be calculated. P-values will be corrected according to the</p>	

Bonferroni method to address multiple testing. In Setting 1, the follow-up period will last until death or withdrawal of ICF and it is assumed that the median progression-free survival time for all patients is 10 months [1-3]. In Setting 2, the follow-up period will be 60 months and it is assumed that the 5-year disease-free survival time is 90% [4-7].

The following table provides power values for various assumed true HRs per SD when 3,500 patients and 10,000 patients, respectively, participate in the study [8].

Hazard ratio	Power (%)	
	Setting 1 (N = 3,500)	Setting 2 (N = 10,000)
1.06	3	46
1.07	8	77
1.08	20	94
1.09	38	99
1.10	59	100
1.11	77	100
1.12	90	100
1.13	96	100
1.14	99	100
1.15	100	100

For example, a biomarker whose true HR is 1.09 will be identified as significant predictor with 38% probability in Setting 1 and with 99% probability in Setting 2.

Patients who are treated neoadjuvantly (Setting 3) are investigated with regard to the pCR (pathological complete response rate). It is assumed that the overall pCR rate is 30%. For each biomarker, a simple logistic regression model with the biomarker as continuous predictor will be fitted. Odds ratios (HRs) per standard deviation (SD) and corresponding p-values likelihood ratio 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 ORs per SD when 2000 patients participate in the study [9].



		<b>Odds ratio</b>	<b>Power (%)</b>
		1.30	49
		1.32	61
		1.34	72
		1.36	81
		1.38	88
		1.40	93
		1.42	96
		1.44	98
		1.46	99
		1.48	99
		1.50	100

For adverse events incidences are reported based on the enrolled patient population as well as incidence densities (number of events/sum of person times in years) according to MedDRA system organ class and preferred term for adverse events (AEs), severe adverse events (SAEs), adverse drug effects and severe adverse drug effects.

<b>Study Sites</b>	Approx. 60 pilot sites under gynecological administration and sites with systemic therapy under hematological/oncological leadership.
<b>Study Duration</b>	
<b>MBC</b>	<ul style="list-style-type: none"> <li>• Start of documentation: Q III/ 2014</li> <li>• End of documentation: Q III / 2022 (planned)</li> <li>• Final analysis: Q III / 2023 (planned)</li> </ul>
<b>EBC</b>	<ul style="list-style-type: none"> <li>• Start of documentation: Q I/2019 (planned)</li> <li>• End of documentation: Q I/2026 (planned)</li> <li>• Final analysis: Q I / 2027 (planned)</li> </ul>