



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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1 Summary

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
Sponsor	<ul style="list-style-type: none"> Universitätsklinikum Tübingen Forschungsinstitut für Frauengesundheit Baden-Württemberg Calwerstraße 7; 72076 Tübingen
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Study & Network Management	ClinSol GmbH & Co. KG, Kantstraße 26, 97074 Würzburg Dr. Erik Belleville, Dr. Christina Hartmann, Dr. Susanne Moritz
Study Design	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 Tübingen.
Study Duration	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.
Inclusion Criteria	
EBC	<ul style="list-style-type: none"> • Adult breast cancer patients (age ≥ 18 years) • Patients with breast cancer and no evidence of distant metastases with a diagnosis not longer than 91 days before study entry. • Patients, who are able and willing to sign the informed consent form
MBC	<ul style="list-style-type: none"> • 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 disease proven by clinical measures (i.e. standard imaging).
Exclusion Criteria	<ul style="list-style-type: none"> • 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	<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 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>

	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		
EBC (Early Breast Cancer)	Primary Objective	Outcome measure
	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
	Secondary Objectives	Outcome measure(s)
	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 [1]
	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 with 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 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.
MBC (Metastatic Breast Cancer)	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 metastasis, 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 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 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.
	Quality of life	Assessed with e.g. EORTC QLQ C-30 (Version 3.0), EORTC QLQ-BR23 and the EQ-Visual Analog Scale [1]
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.
Exploratory (EBC/MBC)	Exploratory Objectives	Outcome Measures
	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.

	<p>Prediction of therapy response, prognosis and side effects with germline Single Nucleotide Polymorphisms (see Sub-protocol section 5.2.2.).</p>	<p>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.</p>															
	<p>Correlation of blood protein biomarkers with side effects, and progression (see sub-protocol section 5.2.4.).</p>	<p>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.</p>															
	<p>Identification of risk factors for the development of metastatic disease in healthy women (see sub-protocol section 5.2.2.)</p>	<p>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.</p>															
	<p>Influencing Factors of Physical Activity, Mental factors and Nutrition in patients with metastatic breast cancer (see sub-protocol section 5.2.7.)</p>	<p>Physical activity and nutrition will be assessed with patient reported questionnaires, e.g IPAQ and ER².</p>															
	<p>Time to progression from the beginning of subsequent therapy lines until the next progression.</p>	<p>All molecular and other measures that might predict prognosis will be associated with these times to progression as well.</p>															
	<p>Time to death from the beginning of subsequent therapy lines</p>	<p>All molecular and other measures that might predict prognosis will be associated with these times to death as well.</p>															
<p>Sample Size</p>	<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>Over the last 10 to 15 years most therapeutic developments and scientific analyses have been restricted to the therapeutic (molecular) subgroups listed in the following table together with the respective frequencies in that population.</p> <p>Molecular subtypes with the respective frequencies for early disease and advanced breast cancer</p> <table border="1" data-bbox="427 1608 1372 1863"> <thead> <tr> <th></th> <th colspan="2">Frequency in patients with</th> </tr> <tr> <th>Molecular Subtype</th> <th>Early breast cancer [2]</th> <th>Advanced breast cancer [3]</th> </tr> </thead> <tbody> <tr> <td>Triple negative</td> <td>12%</td> <td>11%</td> </tr> <tr> <td>HER2-neg HR-pos</td> <td>77%</td> <td>61%</td> </tr> <tr> <td>HER2-positive</td> <td>11%</td> <td>28%</td> </tr> </tbody> </table> <p>Median survival times, 5-year survival rates and pCR rates in molecular subtype-specific patient groups are shown in the following table.</p>			Frequency in patients with		Molecular Subtype	Early breast cancer [2]	Advanced breast cancer [3]	Triple negative	12%	11%	HER2-neg HR-pos	77%	61%	HER2-positive	11%	28%
	Frequency in patients with																
Molecular Subtype	Early breast cancer [2]	Advanced breast cancer [3]															
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Prognosis and Efficacy outcomes for advanced and early breast cancer patients

Molecular Subtype	Prognosis / Efficacy Data			
	Median PFS in advanced breast cancer [4-6]	Median OS in advanced breast cancer [7-9]	5 year disease-free survival rate in early breast cancer [2]	pCR rates in early breast cancer after neoadjuvant chemotherapy [10]
Triple negative	5 months	12 months	69%	34%
HER2-neg HR-pos	14 months	40 months	87%	10%
HER2-positive	6 months	22 months	78%	30%

Power calculation will be carried out for three settings

- **Setting 1:** metastatic breast cancer patients for PFS and OS
- **Setting 2:** all early breast cancer patients in the adjuvant situation for DFS
- **Setting 3:** early breast cancer patients in the neoadjuvant situation after neoadjuvant chemotherapy for pCR rates

Power calculations for patients with advanced breast cancer

As most therapies are developed within molecular subgroups sample size is increased to have reasonable numbers in all molecular subgroups. Power is provided for all subgroups and for progression-free survival and overall survival according to the median survival time.

For each biomarker (up to 500,000), a simple Cox regression model with the biomarker as continuous predictor will be fitted. Hazard ratios (HRs) per standard deviation [11] 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 accrual time is assumed to be 36 months and the follow up time is assumed to be 36 months.

The following table provides power values for various assumed true HRs per SD and progression-free survival when 10,000 patients across all subtypes participate in the study [12].

Hazard ratio	Power (%)		
	PFS	TNBC (N = 1,100)	HER2-neg /HR-pos (N = 6,100)
1.05	0	5	0
1.06	0	17	1
1.07	0	40	4
1.08	0	67	10
1.09	1	87	22
1.10	2	97	38

1.11	3	99	57
1.12	6	100	75
1.13	10	100	87
1.14	16	100	94
1.15	24	100	98
1.16	34	100	99
1.17	45	100	100
1.18	56	100	100
1.19	67	100	100
1.20	76	100	100
1.21	84	100	100

The following table provides power values for various assumed true HRs per SD and overall survival when 10,000 patients across all subtypes participate in the study [12].

Hazard ratio	Power (%)			
	OS	TNBC (N = 1,100)	HER2-neg /HR-pos (N = 6,100)	HER2-pos (N=2,800)
1.05	0	0	1	0
1.06	0	0	4	1
1.07	0	0	11	2
1.08	0	0	25	5
1.09	1	1	46	11
1.10	1	1	67	21
1.11	3	3	84	36
1.12	5	5	94	52
1.13	8	8	98	69
1.14	14	14	100	82
1.15	21	21	100	91
1.16	30	30	100	96
1.17	40	40	100	98
1.18	51	51	100	99
1.19	61	61	100	100
1.20	71	71	100	100
1.21	80	80	100	100
1.22	86	86	100	100

Power calculations for patients with early breast cancer

Prognosis for patients with early breast cancer is clearly more favorable than for patients in the metastatic setting. Similar to the metastatic setting therapies are developed in distinct molecular subgroups (**Fehler! Verweisquelle konnte nicht gefunden werden.**). Disease-free 5-year survival rates are shown in the table “Prognosis and Efficacy outcomes for advanced and early breast cancer patients”.

Again for each biomarker (up to 500,000), a simple Cox regression model with the biomarker as continuous predictor will be fitted. Hazard ratios (HRs) per standard

deviation [11] 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 accrual time is assumed to be 36 months and the follow up time is assumed to be 60 months.

The following table provides power values for various assumed true HRs per SD and progression-free survival when 10,000 patients across all subtypes participate in the study [12].

Hazard ratio DFS	Power (%)		
	TNBC (N = 1,200)	HER2-neg /HR-pos (N = 7,700)	HER2-pos (N=1,100)
1.10	0	3	0
1.12	0	10	0
1.14	1	26	0
1.16	2	49	0
1.18	4	72	1
1.20	8	88	2
1.22	14	96	3
1.24	23	99	6
1.26	35	100	10
1.28	48	100	15
1.30	61	100	22
1.32	73	100	31
1.34	83	100	41
1.36	89	100	51
1.38	94	100	61
1.40	97	100	70
1.42	99	100	78
1.44	99	100	85

Study Sites	Approx. 60 pilot sites under gynecological administration and sites with systemic therapy under hematological/oncological leadership.
Study Duration	
MBC	<ul style="list-style-type: none"> Start of documentation: Q III/ 2014 End of documentation: Q III / 2030 (planned) Final analysis: Q IV / 2030 (planned)
EBC	<ul style="list-style-type: none"> Start of documentation: Q IV / 2022 (planned) End of documentation: Q III / 2030 (planned) Final analysis: QIV / 2030 (planned)

2 Responsibilities

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Biomaterial Archive

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Protocol

3 References

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