## Precision Medicine Study Group

## PRAEGNANT Studie

## Data and Biomaterial Proposal Form

| No | Question | Answer |
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| 1 | Proposal Identifier (to be completed by PRAEGNANT group) | |
| 2 | Title | **Thyroid Dysfunction in Metastasized Breast Cancer - Prevalence and Clinical Impact** |
| 3 | Contact Information (Name, Institution, Address, E-Mail, Phone Number) | Nationales Centrum für Tumorerkrankungen (NCT) Heidelberg und Universitätsfrauenklinik Heidelberg<br>Dr. rer. nat. Sabine Heublein<br>PD Dr. med. Frederik Marmé<br>Prof. Dr. med. Andreas Schneeweiss<br><br>Klinikum der Universität München, Klinik und Poliklinik für Frauenheilkunde und Geburtshilfe<br>Prof. Dr. rer. nat. Udo Jeschke<br>PD Dr. Nina Ditsch |
| 4 | Background | There is increasing evidence of breast cancer (BC) being associated to thyroid dysfunction. In line with this an elevated incidence of thyroid dysfunction was observed in BC patients [1-3]. While several studies found relative hyperthyreosis [1,4-6], others reported aggravating hypothyroidism during BC therapy or demonstrated an increased prevalence of autoimmune thyroid disorders [2,7]. A former prospective clinical trial of our group revealed higher levels of auto-immune antibodies targeting thyroid hormone receptors (TRAKs) and of thyroidal effector hormones (triiodothyronine (fT3), Thyroxine (fT4)) in BC patients as compared to controls [1]. A Swedish population-based cohort study reported similar results and in addition found T3 to be associated with BC aggressiveness and disease specific mortality. However properly powered prospective trials are scarce and to the best of our knowledge no data have been published in a large cohort of metastasized BC (mBC) cases.<br>Additional information supporting a link of thyroid hormones and BC derives from translational approaches. First, thyroid hormones have been demonstrated to mediate estrogen-like effects on BC cells. Second, BC tissues as well as BC cell lines commonly express thyroid hormone receptors and TRs have been demonstrated to strongly influence oncogenic characteristics of BC cells [8-10]. A recent study of our group highlighted TRs and other non-steroidal nuclear hormone receptors to be expressed in the major fraction of triple negative BC and to predict overall survival of *BRCA1* mutated BC [10,11]. |

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| 5 | Aim | • To define the **prevalence of thyroid dysfunction** (as determined by serum markers and patients' medical history) in patients diagnosed for mBC<br>• To identify whether **thyroid serum markers (fT3, fT4, TSH) are correlated to clinico-pathological parameters** (listed below) of mBC.<br>○ age at diagnosis, menopausal status, ethnicity, body mass index, concomitant diagnoses<br>○ tumor histology, biological marker status, staging, grade, *BRCA* genotype<br>○ anatomical site of first distant metastasis, sensitivity towards anti-hormonal treatment / chemotherapy<br>○ overall survival, progression free survival, quality of life, patient-reported outcome<br>• To determine **which percentage of mBC patients identified with aberrant thyroid hormone levels within the planned sub-study is actually treated** for thyroid dysfunction.<br>• To examine **expression of TRs in mBC tissue** in those cases identified with thyroid dysfunction |
| 6a | Methods | Standard statistical methods will be performed thus to test for the associations listed in No. 5.<br>In the case serum thyroid markers (**fT3, fT4, TSH, carrier proteins**) are unknown they will be **determined from stored patient blood samples** (see [1] for methodical details) by standardized, automated laboratory methods.<br>In those cases identified with thyroid dysfunction further analysis (i.e. determination of **TRAK, TPO, TG** (see [1] for methodical details)), **expression of TRs in mBC tissue** (see [10] for methodical details)) will be performed thus to determine the kind of dysfunction and its potential biological impact in more detail. |
| 6b | Which data and biomaterials are to be used? | Data regarding serum levels of fT3, fT4, TSH at initial diagnosis of distant metastasis and during progression will be collected from patient files where available. In the case serum thyroid markers cannot be identified from patient files (e.g. had not been determined, are not available) they will be determined from stored study blood samples. The same applies for determination of TRAK, TPO, TG (only in cases where applicable, see No. 6a). Expression of TRs will be performed on FFPE tissue samples of those cases identified with thyroid dysfunction.<br>Clinico-pathological data will be derived from patient files and from the PRAEGNANT database. |
| 7 | Patient cohort | PREAGNANT study participants diagnosed with mBC and with clinical data and at least one serum sample (initial diagnosis, progression 1, progression 2 etc.) available. |
| 8 | Preliminary test | Testing of thyroid hormones and TRs has been performed successfully in prospective and retrospective settings by our group |

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| | | [1,8-10]. Data deriving from these trials are fundamental for the project applied for within this proposal. |
| 9 | Statistical Considerations | From averaging previous data we estimate that about 25 % of mBC patients will be diagnosed a thyroid dysfunction (literature reports a prevalence of 12 % [1] up to 50 % [12]). Thus to analyze about 100 mBC cases diagnosed with thyroid dysfunction, we aim to include at least 400 patients. According to G-Power 3.1.7 analysis we will need to perform statistics on at least 387 patients thus to study a sufficient number of mBC patients. |
| 10 | What do you need from the PRAEGNANT study group (data, biomaterials, other support?) | • Data regarding thyroid serum markers and clinico-pathological data will be derived from **patient files** and from the **PRAEGNANT database**.<br>• In the case serum thyroid markers cannot be identified from patient files they will be determined from **stored study blood samples**.<br>• Expression of TRs will be performed on **FFPE** tissue samples of those cases identified with thyroid dysfunction. |
| 11 | Please make a statement, why the proposed research is innovative | Though several studies on thyroid function in breast cancer have been performed so far, properly powered prospective trials are scarce and to the best of our knowledge no data have been published in a large cohort of metastasized mBC cases.<br>Thyroid function may especially influence efficacy of antihormonal treatments, which are commonly applied to mBC patients and thus thyroid function may evolve to be a relevant parameter during routine clinical assessment of these patients. However no data upon this topic exist so far.<br>In case thyroid function turns out to be of clinical impact in mBC, treatment of and screening for this 'secondary diagnosis' may be ascribed a higher level of significance. |
| 12 | How is the project funded? | Data collection will be performed by two MD students. In case of a positive statement by the PRAEGNANT study group we will apply for further funding. |
| 13 | Please explain, how experienced you are in conducting the proposed kind of research | All applicants are very experienced in performing this kind of research. AS, FM, ND and SH will focus on collection and interpretation of clinical patient data, while AS, SH and UJ will coordinate and validate determination of thyroid serum markers and TRs. |
| 14 | Please list a maximum of 5 own publication, that support your proposal | Heublein S, Mayr D, Meindl A, Angele M, Gallwas J, Jeschke U, Ditsch N (2015) Thyroid Hormone Receptors Predict Prognosis in BRCA1 Associated Breast Cancer in Opposing Ways. PLoS One 10: e0127072. **[awarded with the "Posterpreis in der Kategorie Senologie der Bayerischen Gesellschaft für Gynäkologie und Geburtshilfe 2015"]**<br><br>Heublein S, Mayr D, Friese K, Jeschke U, Ditsch N (2014) Vitamin-D-Rezeptor, Retinoid-X-Rezeptor und Peroxisom-Proliferator-aktivierter-Rezeptor-γ als Prognoseparameter für BRCA1 mutierte |

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| | | Brustkrebspatientinnen. Geburtshilfe Frauenheilkd 74: PO_Onko05_14. **[awarded with the "Posterpreis 2015 der German Breast Group (GBG)"]**<br><br>Ditsch N, Toth B, Himsl I, Lenhard M, Ochsenkuhn R, Friese K, Mayr D, Jeschke U (2013) Thyroid hormone receptor (TR)alpha and TRbeta expression in breast cancer. Histol Histopathol 28: 227-237.<br><br>Ditsch N, Liebhardt S, Von Koch F, Lenhard M, Vogeser M, Spitzweg C, Gallwas J, Toth B (2010) Thyroid function in breast cancer patients. Anticancer Res 30: 1713-1717. |
| 15 | Decision (to be completed by PRAEGNANT Study Group) | |

## References


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2. Rasmusson B, Feldt-Rasmussen U, Hegedus L, Perrild H, Bech K, Hoier-Madsen M (1987) Thyroid function in patients with breast cancer. Eur J Cancer Clin Oncol 23: 553-556.
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5. Ferreira E, da Silva AE, Serakides R, Gomes MG, Cassali GD (2007) Ehrlich tumor as model to study artificial hyperthyroidism influence on breast cancer. Pathol Res Pract 203: 39-44.
6. Tsuchiya A, Kimijima I, Suzuki S, Higuchi I, Watanabe I, Endo S (1981) Breast cancer concurrent with hyperthyroidism: a case report. Jpn J Surg 11: 108-110.
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11. Heublein S, Mayr D, Friese K, Jeschke U, Ditsch N (2014) Vitamin-D-Rezeptor, Retinoid-X-Rezeptor und Peroxisom-Proliferator-aktivierter-Rezeptor-γ als Prognoseparameter für BRCA1 mutierte Brustkrebspatientinnen. Geburtshilfe Frauenheilkd 74: PO_Onko05_14.
12. Giustarini E, Pinchera A, Fierabracci P, Roncella M, Fustaino L, Mammoli C, Giani C (2006) Thyroid autoimmunity in patients with malignant and benign breast diseases before surgery. Eur J Endocrinol 154: 645-649.