Precision Medicine Study Group

PRAEGNANT Studie

Data and Biomaterial Proposal Form

No	Question	Answer
1	Proposal Identifier (to be completed by PRAEGNANT group)	
2	Title	Discovery Study of Mutations in Tumor and circulating DNA by sequencing methods.
3	Contact Information (Name, Institution, Address, E-Mail, Phone Number)	Jens Huober and Amelie Schramm, University of Ulm, Dept of Gynecology, Breast Center, Prittwitzstrasse 43, 89075 Ulm. Phone: 0049 731 50058509, jens.huober@uniklinik-ulm.de; amelie.schramm@uniklinik-ulm.de
4	Background	Metastatic breast cancer is a hetergenous disease and metastases can be biologically different compared to the primary tumor. There are some data describing differences in hormone receptor status and HER2 status between primary tumor and metastases. However, it is currently not fully understood how often and to what extent mutations may vary between the primary tumor and metastatic disease. To understand this phenomenon will be of clinically relevance since driver mutations in the metastases could be targeted with newer compounds. To gain tumor biopsies from metastases is sometimes not easy to achieve and additional not very comfortable for the patient. The detection of circulating DNA (cDNA) in the blood could be a preferable alternative with the advantage that it is easy to gain and can be frequently investigated in the course of the metastatic disease.
5	Aim	To compare the mutational status of a tumor biopsy from a newly diagnosed metastasis to the mutational status of the primary tumor, the primary involved lymph node (if there were initially positive nodes) and to the mutational status of the cDNA taken at first metastasis and at progression after first and second line therapy.
6a	Methods	Next generation sequencing of tumor and circulating DNA.
6b	Which data and biomaterials are to be used?	Tissue from: 1. Primary tumor 2. Primary involved lymph node 3. first metastasis cDNA: 1. Before start of first-line treatment 2. after first cycle of first-line treatment 3. at relapse before switch to second-line treatment 3. at relapse before switch to third-line treatment
7	Patient cohort	Prospective longitudinal evaluation of 15 patients with first and

		second line treatment of each intrinsic subtype (ER+, HER2+, Triple negative), in total 45 patients to be enrolled.
8	Preliminary test	Not applicable
9	Statistical Considerations	Descriptive analysis.
10	What do you need from the PRAEGNANT study group (data, biomaterials, other support?)	Participating centers with high volume of metastatic breast cancer patients to quickly conduct this prospective study under the umbrella of the PRAEGNANT study group. Laboratory support to evaluate the tumor and liquid biopsies by DNA sequencing.
11	Please make a statement, why the proposed research is innovative	Precision medicine leading to individually tailored treatment approaches are one of the major goals in the treatment of metastatic breast cancer. The identification of potential druggable mutations are important for this new approach. However, mutations may change from primary tumor to the first appearance of metastases and even in the course of metastatic disease mutations can change leading to resistance to the actual targeted treatment. Tumor biopsies in the course of disease over several lines of therapy are frequently not feasible and due to several sites of metastatic disease mutations may vary from organ to organ. Circulating DNA is much easier to harvest and may better identify the leading mutation which needs to be therapeutically addressed. So far very few prospectively collected longitudinal data are available comparing tumor and liquid biopsies. For this reason, this study proposal can significantly contribute to further development of individual tailored treatment approaches.
12	How is the project funded?	Not yet funded
13	Please explain, how experienced you are in conducting the proposed kind of research	Several years of conducting clinical trials and translational studies in patients with breast cancer in the metastatic and adjuvant setting.
14	Please list a maximum of 5 own publication, that support your proposal	**Huober J*,** Denkert C, Loibl S, Prinzler J, Kronenwett R, Darb-Esfahani S, Brase JC, Solbach C, Mehta K, Fasching PA, Sinn BV, Engels K, Reinisch M, Hansmann ML, Tesch H, von Minckwitz G, Untch M. (2013) HER2 and ESR1 mRNA expression levels and response to neoadjuvant trastuzumab plus chemotherapy in patients with primary breast cancer.(* both contributed equally) Breast Cancer Res.;15(1):R11 Loibl S, Darb-Esfahani S, **Huober J**, Klimowicz A, Furlanetto J, Lederer B, Hartmann A, Eidtmann H, Pfitzner B Fasching PA, Tiemann K, Jackisch C, Mehta K, von Minckwitz G, Untch M, Denkert C (2016) Integrated Analysis of PTEN and p4EBP1 Protein Expression as Predictors

		for pCR in HER2-Positive Breast Cancer. Clin Cancer Res; 22:2675-83. Loibl S, von Minckwitz G, Schneeweiss A, Paepke S, Lehmann A, Rezai M, Zahm DM, Sinn P, Khandan F, Eidtmann H, Dohnal K, Heinrichs C, **Huober J**, Pfitzner B, Fasching PA, Andre F, Lindner JL, Sotiriou C, Dykgers A, Guo S, Gade S, Nekljudova V, Loi S, Untch M, Denkert C (2014) PIK3CA mutations are associated with lower rates of pathologic complete response to anti-human epidermal growth factor receptor 2 (her2) therapy in primary HER2-overexpressing breast cancer. J Clin Oncol;32:3212-20. **Schramm A**, Friedl TW, Schochter F, Scholz C, de Gregorio N, **Huober** J, Rack B, Trapp E, Alunni-Fabbroni M, Müller V, Schneeweiss A, Pantel K, Meier-Stiegen F, Hartkopf A, Taran FA, Wallwiener D, Janni W, Fehm T (2016) Therapeutic intervention based on circulating tumor cell phenotype in metastatic breast cancer: concept of the DETECT study program. Arch Gynecol Obstet; 293:271-81.
15	Decision (to be completed by PRAEGNANT Study Group)	