

Precision Medicine Study Group

PRAEGNANT

Data and Biomaterial Proposal Form

No	Question	Answer
1	Proposal Identifier (to be completed by PRAEGNANT group)	
2	Title	Incidence and impact of Cytomegalovirus (CMV) infections in patients with metastatic breast cancer (MBC) and brain metastases (BM) within the PRAEGNANT network.
3	Contact Information (Name, Institution, Address, E-Mail, Phone Number)	<p>Prof. Dr. med. Volkmar Müller Department of Gynecology University Medical Center Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg Germany Phone: +49 15222815855 Fax: +49 40 7410 - 40070 vmueller@uke.de</p> <p>Prof. Dr. Klaus Überla Universitätsklinikum Erlangen Institute of Clinical and Molecular Virology University of Erlangen-Nuremberg Schlossgarten 4 D91054 Erlangen Tel.: 09131-8523563 klaus.ueberla@fau.de</p> <p>Prof. Dr. Peter A. Fasching University Hospital Erlangen Department of Gynecology and Obstetrics Comprehensive Cancer Center Erlangen-EMN Friedrich-Alexander University Erlangen-Nuremberg peter.fasching@uk-erlangen.de</p>
4	Background	Due to improvements in the treatment of patients with metastatic breast cancer, the development of brain metastases (BM) has become a major limitation of life expectancy and quality of life for many breast cancer patients. The improvement of management strategies for BM is thus

		<p>an important clinical challenge, especially among high risk patients such as HER2 positive and triple-negative patients. However, the formation of brain metastases as a multistep process is so far poorly understood [1]. In order to grow in the brain, single tumor cells need to pass the tight blood-brain-barrier (BBB). Furthermore, animal studies have shown that the tumor cells after passing the BBB do not only need a close contact with endothelial cells but also interact closely with many different brain residential cells. Thus, besides genetic predisposition of the tumor cells also cellular adaptation processes within the new microenvironment might determine the ability for a tumor cell to grow out as a metastasis. In this context, first reports have indicated that infection with Cytomegalovirus (CMV) might play a role in the development and growth of BM, also in breast cancer patients [2]. In glioblastoma patients, a preliminary report suggested even a survival advantage with a therapeutic anti-CMV intervention using Valgancilovir [3]. However, current studies are limited by low patient numbers and discordant results concerning the impact of CMV infection and therapeutic interventions. Also, most studies did not involve a relevant number of breast cancer patients. The PRAEGNANT Network is a registry with an integrated bio-material bank, which was designed to serve as a scientific study. As of May 2016, more than 130 patients with BM were enrolled. Therefore the PRAEGNANT cohort offers a unique opportunity to examine CMV status in patients with MBC and BM.</p>
5	Aim	<p>Primary aim: Examine the incidence and prognostic impact of CMV infections in all patients with BM with plasma available (app. 120 patients).</p> <p>Secondary aims: Compare the incidence and prognostic impact of CMV infections in patients with BM to a cohort of patients without BM.</p>
6a	Methods	An ELISA for IgG levels and PCR for CMV copy number in those patients with 300µl plasma.
6b	Which data and bio-materials are to be used?	See below (item 10).
7	Patient cohort	See above, point 5.
8	Preliminary test	See above, 6a.
9	Statistical Considerations	The existing number of patients should allow to sufficiently generate the proposed hypothesis.

10	What do you need from the PRAEGNANT study group (data, biomaterials, other support?)	300 Microliters of plasma at the first point after diagnosis of BM. Original Data from the PRAEGNANT Database
11	Please make a statement, why the proposed re- search is innovative	The proposed project should add new knowledge about mechanisms triggering BM development and growth in patients with BM. This might open a new perspective for the treatment of BM. Therefore, the project is of clinical relevance.
12	How is the project funded?	Institutional funding.
13	Please explain, how experienced you are in conducting the proposed kind of research	The investigators have a long experience in translational research projects. VM is PI of a network for BM in breast cancer. KÜ support for the CMV diagnostic and interpretation of study design.
14	Please list a maximum of 5 own publication, that support your proposal	<p>Witzel I, Oliveira-Ferrer L, Pantel K, Müller V, Wikman H. Breast cancer brain metastases: biology and new clinical perspectives. <i>Breast Cancer Research</i>. 2016;18(1). doi: 10.1186/s13058-015-0665-1.</p> <p>Taher C, Frisk G, Fuentes S, Religa P, Costa H, Assinger A, et al. High prevalence of human cytomegalovirus in brain metastases of patients with primary breast and colorectal cancers. <i>Translational oncology</i>. 2014;7(6):732-40. Epub 2014/12/17. doi: 10.1016/j.tranon.2014.09.008. PubMed PMID: 25500083; PubMed Central PMCID: PMC4311044.</p> <p>Söderberg-Nauclér C, Rahbar A, Stragliotto G. Survival in Patients with Glioblastoma Receiving Valganciclovir. <i>N Engl J Med</i>. 2013;369(10):985-6. doi: 10.1056/NEJMc1307587. PubMed PMID: 24004137.</p>
15	Decision (to be completed by PRAEGNANT Study Group)	