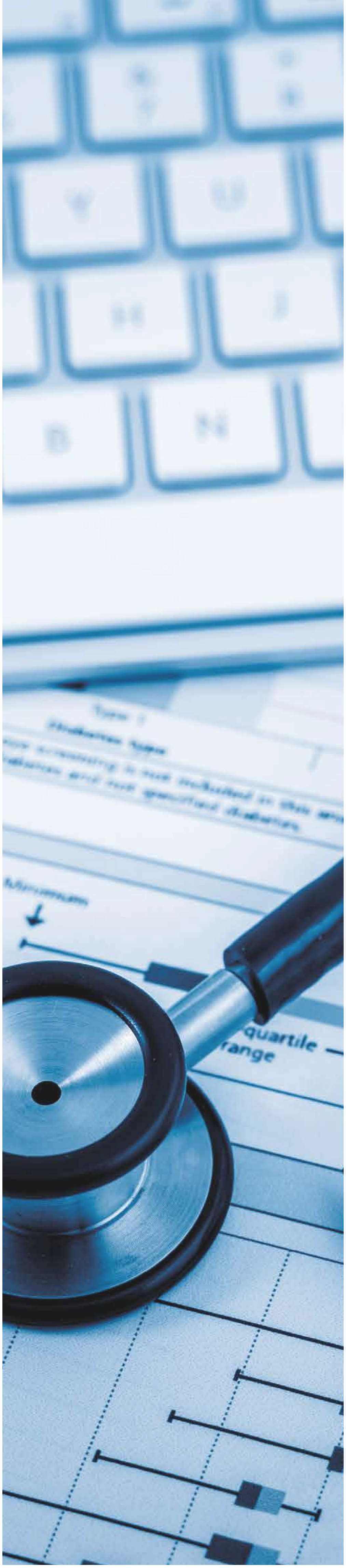

GBG

GERMAN
BREAST
GROUP

Heilung durch Innovation, Kompetenz und Partnerschaft

Annual Scientific Report

2019

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Annual Scientific Report

2019

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Introduction

Introduction

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1. About the German Breast Group

The German Breast Group (GBG), a leading cooperative study group in the field of breast cancer in Germany, provides the comprehensive management of clinical trials in all major therapeutic categories: prevention, neoadjuvant, adjuvant, and palliative. The vision of the GBG is best described as healing by innovation, competence and partnership, from the protocol design and feasibility assessments to the final study report. Through project management in combination with the expert data management and statistical analyses, the GBG delivers consistent high-quality results in order to improve treatment therapies of cancer patients and their quality of life.

The main focus of the GBG is on the investigator initiated trials (IIT). These are clinical studies based on the work of doctors conducting research and are focused on the optimization of therapy and the overall improvement of its quality, unlike industrial studies which are typically affected by approval and marketing aspects.

The GBG currently manages over 40 clinical trials. All services provided by GBG are to the highest standard of the International Conference on Harmonisation of Good Clinical Practice (ICH-GCP1998) and if necessary regulatory requirements. We offer a comprehensive range of services, including:

- Idea and Conception of Study Design
- Clinical Project Management
- Clinical Monitoring
- Data Management
- Biometric and Statistics
- External Documentation
- Translational Research
- Biobanking
- Pathological Central Laboratory
- Continuous Medical Education
- Medical Writing
- Sponsorship
- Quality Control

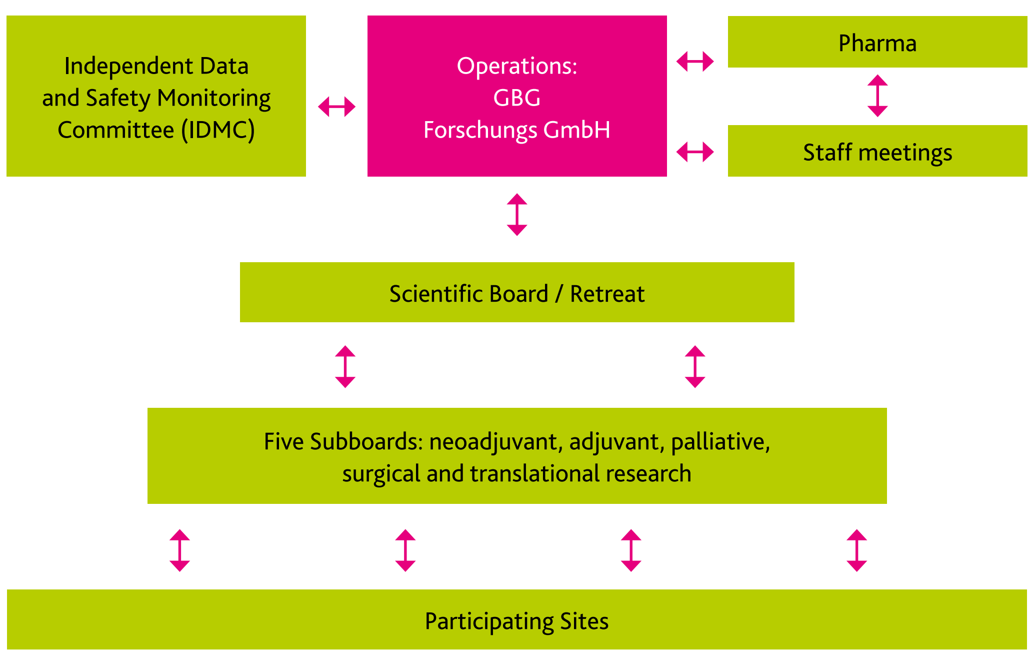


Figure 1: Structure of the German Breast Group

2. Infrastructure of the German Breast Group

Participating sites

Participating sites are actively recruiting sites. An official membership is not required, however any physician who takes part in our trials automatically becomes a member of the study group. Usually, most of our investigators work in gynecological institutions such as university clinics, general hospitals, specialist practices and general practices. For several years an increasing number of gynecologic and medical oncologists have been taking part in our trials, thus enriching the trial conception with their knowledge.

Recruitment of patients

Patients are recruited through the participating sites which provide detailed information on the GBG studies to the patient. This way, all existing uncertainties are clarified and an absolute transparency on the conduct of clinical trials can be ensured. Patients are treated according to the latest scientific findings and are carefully controlled and monitored. Thanks to the clinical trials, breast cancer therapies are nowadays carried out on the highest possible standard. The annual patient recruitment is shown in figure 2.

Subboards

Five subboards were active during the last year in the fields of neoadjuvant, adjuvant, palliative, and surgical therapy as well as in the field of translational research. Members of the subboards are all well-known professionals, experienced in treating breast cancer patients and active in the field of breast cancer research and clinical studies. When a subboard decides to launch a new study, the GBG Forschungs GmbH plans, organizes and manages the study, in line with the GBG's belief that a clinical study must be directly related to the potential improvement of the therapy and its benefits for the patient. Thus, a strict quality monitoring is essential and is ensured by following the GBG in-house standard operating procedures (SOP). The members of the subboards meet once a year face-to-face and 3 times via telephone conferences. Our subboards have been active discussing current studies, research results and further innovative study designs.

The members of our subboards in 2019 are shown below:

Neoadjuvant
Prof. Dr. J. U. Blohmer, Berlin
Prof. Dr. C. Denkert, Marburg
Prof. Dr. P. Fasching, Erlangen
Dr. C. Hanusch, München
Prof. Dr. J. Huober, Ulm
Prof. Dr. Ch. Jackisch, Offenbach
Dr. T. Link, Dresden
Prof. Dr. S. Loibl, Neu-Isenburg
PD Dr. K. Rhiem, Köln
Prof. Dr. A. Schneeweiss, Heidelberg
Prof. Christine Solbach, Frankfurt am Main
Prof. Dr. M. Untch, Berlin

Adjuvant
Prof. Dr. W. Janni, Ulm
Prof. Dr. S. Loibl, Neu-Isenburg
Prof. Dr. F. Marme, Mannheim
Prof. Dr. V. Möbus, Frankfurt am Main
Prof. Dr. T. Reimer, Rostock
Dr. M. Reinisch, Essen
Dr. S. Schmatloch, Kassel
Prof. Dr. M. Schmidt, Mainz
PD Dr. B. Sinn, Berlin
Prof. Dr. E. Stickeler, Aachen
Prof. Dr. M. Untch, Berlin

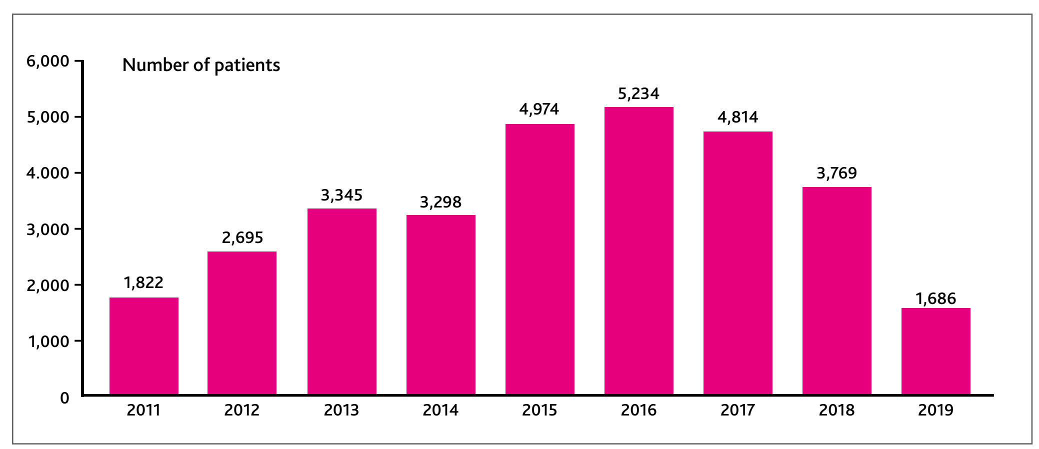


Figure 2: Annual recruitment of patients

Palliative
Prof. Dr. T. Decker, Ravensburg
Prof. Dr. C. Denkert, Marburg
Prof. Dr. S. Loibl, Neu-Isenburg
Dr. K. Lübbe, Hannover
Prof. Dr. C. Mundhenke, Bayreuth
Prof. Dr. V. Müller, Hamburg
Prof. Dr. M. Schmidt, Mainz
Dr. J. Seitz, Heidelberg (until 08/16/2019)
Prof. Dr. M. Thill, Frankfurt am Main

Surgical
PD Dr. B. Ataseven, Essen
Prof. Dr. C. Denkert, Marburg
Prof. Dr. B. Gerber, Rostock
Prof. Dr. M. Golatta, Heidelberg
Prof. Dr. M. Hahn, Tübingen
Prof. Dr. J. Heil, Heidelberg
Dr. D. Krug, Kiel
Prof. Dr. T. Kühn, Esslingen
Prof. Dr. S. Loibl, Neu-Isenburg

Translational Research
Prof. Dr. C. Denkert, Marburg
Prof. Dr. P. Fasching, Erlangen
PD Dr. T. Karn, Frankfurt am Main
Prof. Dr. S. Loibl, Neu-Isenburg
PD Dr. M. van Mackelenbergh, Kiel
Prof. Dr. F. Marme, Mannheim
Prof. Dr. V. Müller, Hamburg
Prof. Dr. C. Schem, Hamburg
PD Dr. B. Sinn, Berlin
Prof. Dr. E. Stickeler, Aachen

The Independent Data and Safety Monitoring Committee (IDMC)
As early as in 2006, the GBG established the Independent Data and Safety Monitoring Committee (IDMC) to ensure continual improvement of working processes in clinical trials, in-house observation, monitoring and consultation.

The IDMC reviews all GBG sponsored trials regarding:

1. Objectives, the scientific impact of the findings and adverse events (AE, SAE, non-breast cancer deaths) of ongoing trials,
2. All major modifications to the trial protocol (including accrual goals),
3. The interim and final efficacy analysis of trials, when the protocol-specified number of recruited patients or events has been reached.

Staff Meetings
Staff meetings are conducted on a regular basis, either at the GBG headquarters or via telephone conferences, to ensure sufficient information transfer between the responsible study project managers, study chairs and representatives of the supporting pharmaceutical companies.

3. Cooperations with other study groups

The GBG maintains outstanding cooperative relations with peer national and international study groups, including:

ABCSG:
Austrian Breast & Colorectal Cancer Study Group

AFT:
Alliance Foundation Trials

AGO:
Arbeitsgemeinschaft Gynäkologische Onkologie

AGO-B:
Breast Study Group

ANZBCTG:
Australia and New Zealand Breast Cancer Trials Group

BIG:
Breast International Group

BOOG:
Borstkanker Onderzoeksgroep Nederland

CCTG:
Canadian Cancer Trials Group

CECOG:
Central European Cooperative Oncology Grou

CIRG:
Cancer International Research Group

CRUK:
Cancer Research UK

CTI:
Cancer Trials Ireland

CTRU:
Clinical Trials Research Unit

DKG:
Deutsche Krebsgesellschaft

EORTC
European Organisation for Research and Treatment of Cancer

Fondazione Michelangelo:
Scientific organization based in Italy

GEICAM:
Grupo Español de Investigación del Cáncer de Mama

IBCSG:
International Breast Cancer Study Group

ICCG:
International Collaborative Cancer Group

ICR CTSU:
The Institute of Cancer Research

IDDI
International Drug Development Institute, Inc.

IKP Stuttgart:
Dr. Margarete Fischer-Bosch-Institut für Klinische Pharmakologie

JBCRG:
Japan Breast Cancer Research Group

NOGGO:
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie

NSABP:
National Surgical Adjuvant Breast and Bowel Project

PrECOG, LLC:
Cancer Clinical Trials Research Company, US

SAKK:
Swiss Group for Clinical Cancer Research

SBG:
Scandinavian Breast Cancer Group

SOLTI:
Grupo Español de Estudio Tratamiento y otras Estrategias Experimentales en Tumores Solidos

UCBG:
French breast cancer intergroup UNICACER

UNICANCER:
UNICANCER Group, France

Universitätsklinikum Hamburg-Eppendorf

Universität Rostock

UZL:
University Hospital of Leuven

WSG:
Westdeutsche Studiengruppe

4. Publications in 2019

Timely publication of study results is a prerequisite for all clinical trials. GBG is responsible for an unbiased and independent release of all study results and the subsequent, related translational research projects.

Our research reports were published in leading scientific journals like the New England Journal of Medicine, The Lancet, Journal of Clinical Oncology, The Lancet Oncology, Journal of the National Cancer Institute, Annals of Oncology, European Journal of Cancer, Breast Cancer Research and Treatment and others.

Our studies are constantly presented as oral presentations, poster discussions or posters at international congresses such as ASCO, SABCS, ESMO and DGS.

Peer-review articles, reviews and congress contributions in 2019 are listed in 4.1., 4.2. and 4.3.

4.1. Peer-reviewed articles in 2019

1. Golshan M, Loibl S, Wong SM, Houber JB, O'Shaugnessy J, et al. Breast Conservation After Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer: Surgical Results From the BrighTNess Randomized Clinical Trial JAMA Surg. 2020;doi:10.1001/jamasurg. 2019.5410 (2019 online ahead of print).
2. Papakonstantinou A, Matikas A, Bengtsson NO, Malmström P, Hedayati E, et al. Efficacy and Safety of Tailored and Dose-Dense Adjuvant Chemotherapy and Trastuzumab for Resected HER2-Positive Breast Cancer: Results From the Phase 3 PANTHER Trial. Cancer. 2019;doi:10.1002/cncr.32653.
3. Cuzick J, Sestak I, Forbes JF, Dowsett M, Cawthorn S, et al. Use of anastrozole for breast cancer prevention (IBIS-II): long-term results of a randomised controlled trial. Lancet. 2019;doi:10.1016/S0140-6736(19) 32955-1.
4. Sinn BV, Weber KE, Schmitt WD, Fasching PA, Symmans WF, et al. Human leucocyte antigen class I in hormone receptor-positive, HER2-negative breast cancer: association with response and survival after neoadjuvant chemotherapy. Breast Cancer Res. 2019;21:142.
5. Witzel I, Loibl S, Wirtz R, Fasching PA, Denkert C, et al. Androgen receptor expression and response to chemotherapy in breast cancer patients treated in the neoadjuvant TECHNO and PREPARE trial. Br J Cancer. 2019 2019; 121:1009–1015.
6. Heitz F, Kümmel S, Lederer B, Solbach C, Engels K, Ataseven B, Sinn B, Blohmer JU, Denkert C, Barinoff J, Fisseler-Eckhoff A, Loibl S. Impact of Nuclear Oestrogen Receptor Beta Expression in Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy. Geburtshilfe Frauenheilkd. 2019; 79: 1110-1117.
7. Hui R, Pearson A, Cortés J, Campbell C, Poirot C, et al. Lucitanib for the treatment of HR(+)/ HER2(-) metastatic breast cancer: results from the multicohort phase II FINESSE study. Clin Cancer Res. 2019;doi:10.1158/ 1078-0432.CCR-19-1164.
8. Golshan M, Wong SM, Loibl S, Huober JB, O'Shaughnessy J, et al. Early assessment with magnetic resonance imaging for prediction of pathologic response to neoadjuvant chemotherapy in triple-negative breast cancer: Results from the phase III BrighTNess trial. Eur J Surg Oncol. 2019;doi:10.1016/j.ejso.2019.10.002
9. Papakonstantinou A, Hedayati E, Hellström M, Johansson H, Gnant M, et al. Neutropenic complications in the PANTHER phase III study of adjuvant tailored dose-dense chemotherapy in early breast cancer. Acta Oncol. 2020;59:75–81 (2019 online ahead of print).
10. Banys-Paluchowski M, Loibl S, Witzel I, Mundhenke C, Lederer B, et al. Clinical Relevance of Collagen Protein Degradation Markers C3M and C4M in the Serum of Breast Cancer Patients Treated with Neoadjuvant Therapy in the GeparQuinto Trial. Cancers (Basel). 2019;11:1186.
11. Krug D, Lederer B, Seither F, Nekljudova V, Ataseven B, et al. Post-Mastectomy Radiotherapy After Neoadjuvant Chemotherapy in Breast Cancer: A Pooled Retrospective Analysis of Three Prospective Randomized Trials. Ann Surg Oncol. 2019;26:3892-3901.
12. Kümmel A, Kümmel S, Blohmer JU, Faridi A, Nitz U, et al. Autologous Lipotransfer - Daily Therapeutic Practice in Breast Cancer: An Intergroup Analysis Encompassing NOGGO, WSG, GBG, AWO Gyn and DGPRÄC. Breast Care (Basel). 2019;14:165-169.
13. Martín M, Loibl S, Hyslop T, De la Haba-Rodríguez J, Aktas B, et al. Evaluating the addition of bevacizumab to endocrine therapy as first-line treatment for hormone receptor-positive metastatic breast cancer: a pooled analysis from the LEA (GEICAM/ 2006-11_GBG51) and CALGB 40503 (Alliance) trials. Eur J Cancer. 2019;117:91-98.
14. Furlanetto J, von Minckwitz G, Lederer B, Möbus V, Schneeweiss A, et al. Fatal events during clinical trials: an evaluation of deaths during breast cancer studies. Breast Cancer. 2019;26:826-834.
15. Loibl S, Untch M, Burchardi N, Huober J, Sinn BV, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple negative breast cancer - clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019;doi: 10.1093/annonc/mdz158.
16. Untch M, Jackisch C, Schneeweiss A, Schmatloch S, Aktas B, et al. NAB-Paclitaxel Improves Disease-Free Survival in Early Breast Cancer: GBG 69-GeparSepto. J Clin Oncol. 2019;37:2226-2234.
17. Laakmann E, Witzel I, Fasching PA, Rezai M, Schem C, et al. Development of central nervous system metastases as a first site of metastatic disease in breast cancer patients treated in the neoadjuvant trials GeparQuinto and GeparSixto. Breast Cancer Res. 2019;21:60.
18. Noske A, Möbus V, Weber K, Schmatloch S, Weichert W, et al. Relevance of tumour-infiltrating lymphocytes, PD-1 and PD-L1 in patients with high-risk, nodal-metastasised breast cancer of the German Adjuvant Intergroup Node-positive study. Eur J Cancer. 2019;114:76-88.
19. Denkert C, Budczies J, Regan MM, Loibl S, Dell'Orto P, et al. Clinical and analytical validation of Ki-67 in 9069 patients from IBCSG VIII+IX, BIG1-98 and GeparTrio trial: systematic modulation of inter-observer variance in a comprehensive in silico ring trial. Breast Cancer Res Treat. 2019;176:557-568.
20. Kuemmel S, Holtschmidt J, Gerber B, Von der Assen A, Heil J, et al. Prospective, Multicenter, Randomized Phase III Trial Evaluating the Impact of Lymphoscintigraphy as Part of Sentinel Node Biopsy in Early Breast Cancer: SenSzi (GBG80) Trial. J Clin Oncol. 2019;37:1490-1498.
21. Loibl S, Treue D, Budczies J, Weber K, Stenzinger A, et al. Mutational Diversity and Therapy Response in Breast Cancer: A Sequencing Analysis in the Neoadjuvant GeparSepto Trial. Clin Cancer Res. 2019; 25:3986-3995.
22. Lambertini M, Di Maio M, Poggio F, Pagani O, Curigliano G, et al. Knowledge, attitudes and practice of physicians towards fertility and pregnancy-related issues in young BRCA-mutated breast cancer patients. Reprod Biomed Online. 2019; 38:835-844.
23. Escala-Garcia M, Guo Q, Dörk T, Canisius S, Keeman R, et al. Genome-wide association study of germline variants and breast cancer-specific mortality. Br J Cancer. 2019;120:647-657.
24. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials. Lancet. 2019;393: 1440-1452.
25. Janning M, Müller V, Vettorazzi E, Cubas-Cordova M, Gensch V, et al. Evaluation of

soluble carbonic anhydrase IX as predictive marker for efficacy of bevacizumab: A biomarker analysis from the geparquinto phase III neoadjuvant breast cancer trial. Int J Cancer. 2019;145:857-868.

26. Eggemann H, Bernreiter AL, Reinisch M, Loibl S, Taran FA, et al. Tamoxifen treatment for male breast cancer and risk of thrombo-embolism: prospective cohort analysis. Br J Cancer. 2019;120:301-305.

27. Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. Am J Hum Genet. 2019;104:21-34.

28. Shu X, Wu L, Khankari NK, Shu X-O, Wang TJ, et al. (Breast Cancer Association Consortium). Associations of obesity and circulating insulin and glucose with breast cancer risk: a Mendelian randomization analysis. Int J Epidemiol. 2019;48:795–806.

4.2. Peer-reviewed reviews in 2019

1. Froehlich K, Schmidt A, Heger JI, Al-Kawlani B, Aberl CA, Jeschke U, Loibl S, Markert UR. Breast cancer, placenta and pregnancy. Eur J Cancer. 2019;115:68-78. Review.

4.3. Congress contributions in 2019

SABCS:
San Antonio Breast Cancer Symposium, December 10-14, 2019, San Antonio, Texas, USA

van Mackelenberg M, Seither F, Möbus V et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy. A meta-analysis of individual patient data from 12 randomized trials including 15,457 patients. SABCS 2019; GS1-07, oral presentation.

Williams T, Schneeweiss A, Jackisch C et al. Caveolin gene expression predicts for response and clinical outcomes of patients treated with preoperative paclitaxel-based chemotherapy regimens in early stage breast cancer. SABCS 2019; P1-10-01, poster.

Blohmer J, Link T, Kümmel S et al. Investigating denosumab as an add-on treatment to neo-adjuvant chemotherapy and two different nab-paclitaxel schedules in a 2x2 design in primary breast cancer - First results of the GeparX study. SABCS 2019; GS3-01, oral presentation.

Fasching PA, Denkert C, Benz S et al. Tumor immune-cell activity assessed by RNAseq is an independent predictor of therapy response and prognosis after neoadjuvant chemotherapy in HER2 negative breast cancer patients - an analysis of the GeparSepto trial. SABCS 2019; PD5-08, poster discussion.

Fröhlich K, Plösch T, Seither F et al. Histological and epigenetic analyses of placenta tissue from breast cancer patients and healthy participants. SABCS 2019; P4-04-08, poster.

Loibl S, Untch M, Buyse M et al. Pathologic complete response (pCR) and prognosis following neoadjuvant chemotherapy plus anti-HER2 therapy of HER2-positive early breast cancer (EBC). SABCS 2019; P5-06-02, poster.

Szeto C, Denkert C, Fasching PA et al. Landscape of immune-cell signatures in early high-risk breast cancer (BC) reveals clinically-relevant enrichment of immune subpopulations. SABCS 2019;P6-10-04, poster.

Furlanetto J, Möbus V, Schneeweiss A et al. Germline (g)BRCA1/2 mutations (m) and hematological toxicities in patients (pts) with triple negative breast cancer (TNBC) treated with neoadjuvant chemotherapy (NACT). SABCS 2019;P6-10-03, poster.

Piccart M, Procter M, Fumagalli D et al. Interim overall survival analysis of APHINITY (BIG 4-11): A randomized multicenter, double-blind, placebo-controlled trial comparing chemotherapy plus trastuzumab plus pertuzumab versus chemotherapy plus trastuzumab plus placebo as adjuvant therapy in patients with operable HER2-positive early breast cancer. SABCS 2019;GS1-04, oral presentation.

Cuzick J, Sestak I, Forbes J et al. (IBIS-II investigators). Ten year results of the international breast cancer intervention study II. SABCS 2019;GS4-04, oral presentation.

Mano MS, Loibl S, Mamounas EP et al. Adjuvant trastuzumab emtansine (T-DM1) vs trastuzumab (H) in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer: KATHERINE subgroup analysis. SABCS 2019;P3-14-01, poster.

Geyer CE Jr, Loibl S, Rastogi P et al. A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo: NSABP B-59/GBG 96-GeparDouze. SABCS 2019;OT2-04-08, poster.

Jerusalem G, Farah S, Chirgwin J et al. Sole (study of letrozole extension), a phase 3 randomized clinical trial of continuous vs intermittent letrozole in postmenopausal women who have received 4-6 years of adjuvant endocrine therapy for lymph node-positive, early breast cancer (bc): final analysis and sole estrogen substudy (sole-est). SABCS 2019; P5-12-01, poster.

DGP:
103. Jahrestagung der Deutschen Gesellschaft für Pathologie, June 13-15, 2019, Frankfurt am Main, Germany

Sinn BV, Loibl S, Karn T et al. Expression von PD-L1 und dynamische Veränderungen tumor-infiltrierender Lymphozyten bei neoadjuvanter Chemotherapie mit Immun-Checkpunkt-Blockade beim frühen triple-negativen Mammakarzinom. DGP 2019, AG05.02, oral presentation.

ESMO:
European Society for Medical Oncology, September 27-October 1, 2019 Barcelona, Spain

Furlanetto J, Nekljudova V, Schneeweiss A et al. Impact of chemotherapy-induced ovarian failure (CIOF) on disease-free survival (DFS) and overall survival (OS) in young women with early breast cancer (EBC). Ann Oncol 2019;Volume 30, Issue Suppl_5, 180PD, poster discussion.

Marmé F, Solbach C, Michel L et al. Utility of the CPS+EG scoring system in triple-negative breast cancer treated with neoadjuvant chemotherapy. Ann Oncol 2019;Volume 30, Issue Suppl_5, 182PD, poster discussion.

Werutsky G, Untch M, Hanusch C et al. Risk factors for locoregional recurrence (LRR) after neoadjuvant chemotherapy: pooled analysis of prospective neoadjuvant breast cancer (BC) trials. Ann Oncol 2019;Volume 30, Issue Suppl_5, 188P, poster.

Tesch H, Loibl S, Kast K et al. Chemotherapy (CT)-induced anaemia in patients (pts) treated with dose-dense regimen: Results of the prospectively randomised anaemia substudy from the neoadjuvant GeparOcto study. Ann Oncol 2019;Volume 30, Issue Suppl_5, 195P, poster.

Untch M, Geyer C, Huang C et al. Peripheral neuropathy (PN), thrombocytopenia (TCP) and central nervous system (CNS) recurrence: an update of the phase III KATHERINE trial of post-neoadjuvant trastuzumab emtansine (T-DM1) or trastuzumab (H) in patients (pts) with residual invasive HER2-positive breast cancer (BC). Ann Oncol 2019;Volume 30, Issue Suppl_5, LBA19, oral presentation.

DGS:
Deutsche Gesellschaft für Senologie 39. Jahrestagung, June 27-29, 2019, Berlin, Germany

Banys-Paluchowski M, Loibl S, Witzel I et al. Clinical relevance of collagen protein degradation markers C3M and C4M in the serum of breast cancer patients treated with neoadjuvant therapy in the GeparQuinto trial. DGS 2019, #094, poster.

Reimer T. Update NSEMA-Studie. DGS 2019; oral presentation.

ASCO:
American Society of Clinical Oncology, Annual Meeting May 31-4 June, 2019, Chicago, IL, USA

Denkert C, Link T, Jank P et al. Comparison of an automated cartridge-based system for mRNA assessment with central immunohistochemistry in the neoadjuvant GeparX trial. J Clin Oncol 2019;37.15_suppl.3075, poster.

Loibl S, Sinn BV, Karn T et al. Exome analysis of oncogenic pathways and tumor mutational burden (TMB) in triple-negative breast cancer (TNBC): Results of the translational biomarker program of the neoadjuvant double-blind placebo controlled GeparNuevo trial. J Clin Oncol 2019;37.15_suppl.509, poster discussion.

Seliger B, Karn T, Denkert C et al. Correlation of the tumor mutational burden with the composition of the immune cell subpopulations in peripheral blood of triple-negative breast cancer patients undergoing neoadjuvant therapy with durvalumab: Results from the prospectively randomized GeparNuevo trial. J Clin Oncol 2019;37.15_suppl.588, poster.

Pohl-Rescigno E, Hauke J, Rhiem K et al. Germline mutation status and therapy response in high-risk early breast cancer: Results of the GeparOcto study (NCT02125344). J Clin Oncol 2019;37.15_suppl.573, poster.

Fasching PA, Jackisch C, Rhiem K et al. GeparOLA: A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients (pts) with HER2-negative early breast cancer (BC) and homologous recombination deficiency (HRD). J Clin Oncol 2019;37.15_suppl.506, oral presentation.

Geyer CE, Loibl S, Rastogi P et al. NSABP B-59/GBG 96-GeparDouze: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with triple-negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. J Clin Oncol 2019; 37.15_suppl.TPS605, poster.

Krop IE, Paulson J, Campbell C et al. Genomic correlates of response to adjuvant trastuzumab (H) and pertuzumab (P) in HER2+ breast cancer (BC): Biomarker analysis of the APHINITY trial. J Clin Oncol 2019;37.15_suppl.1012, oral presentation.

Schneeweiss A, Loib S, Mamounas EP et al. Patient-reported outcomes (PROs) from KATHERINE: A phase III study of adjuvant trastuzumab emtansine (T-DM1) versus trastuzumab (H) in patients (pts) with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer. J Clin Oncol 2019; 37.15_suppl.513, poster discussion.

Metzger O, Stover DG, Asad S et al. Immunophenotype and proliferation to predict for response to neoadjuvant chemotherapy in TNBC: Results from BrighTNess phase III study. J Clin Oncol 2019; 37.15_suppl.510, poster discussion.

ESMO-Breast Cancer 2019, May 2-4, 2019, Berlin, Germany

Huober J, Schneeweiss A, Blohmer JU et al. Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy: pooled analysis based on the GBG database. Ann Oncol 2019; 30 (suppl_3): iii34-iii38; #1080, oral presentation.

Jank P, Loibl S, Fasching PA et al. Influence of PIK3CA mutations on breast cancer proliferation, lymphocyte infiltration and clinical outcome: pooled analysis of 484 patients from three prospective multicentre GBG trials. Ann Oncol 2019; 30 (suppl_3): iii1-iii26, #15P, poster.

Loibl S, Jackisch C, Rastogi P et al. GeparDouze/NSABP B-59: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy with atezolizumab or placebo in patients with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. Ann Oncol 2019; 30 (suppl_3): iii34-iii38, #122TiP, poster.

Denkert C, Link T, Jank P et al. (on behalf of the GBG neoadjuvant and translational subboard). Expression of ER, PR, HER2 and Ki-67 in the neoadjuvant GeparX trial - comparison of central immunohistochemistry (IHC) with an automated cartridge-based system for mRNA assessment. Ann Oncol 2019; 30 (suppl_3): iii1-iii26, #25P, poster.

Karn T, Denkert C, Weber KE et al. Para-necrotic expression of VEGFA metagene signature identified by single-cell profiling. Ann Oncol 2019; 30 (suppl_3): iii1-iii26, #9O, poster discussion.

4.4. GBG-Publications Grading System

To set internal publication goals and to measure our own success, we established our GBG in-house grading system as follows:

- 7 GBG points for preparation or final publication in a high quality peer-reviewed journal with an impact factor greater than 5,
- 5 GBG points for publication preparation or final publication in a journal with an impact factor of less than 5,
- 3 GBG points for an oral presentation or poster discussion,
- and 2 GBG points for a poster presentation at an international congress.

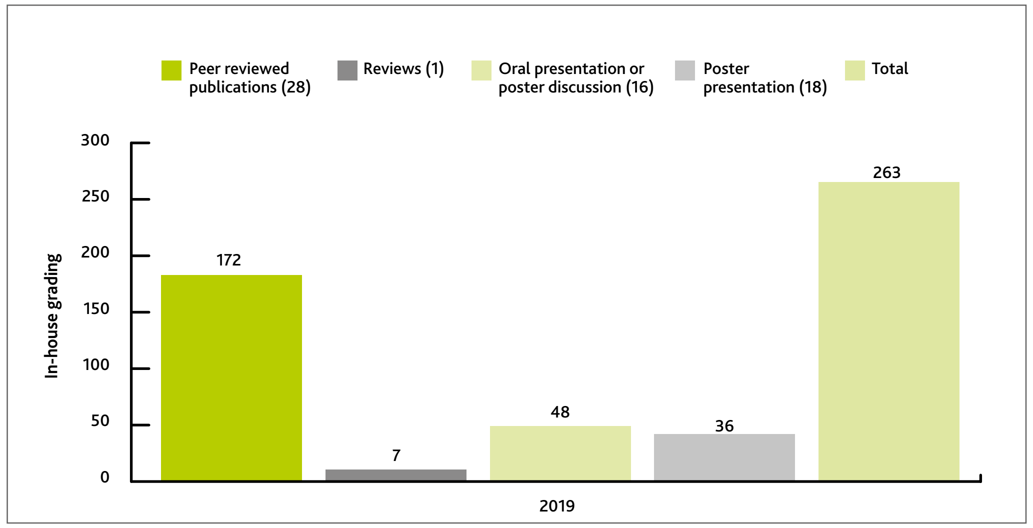


Figure 3: Overview of GBG's in-house grading for publications in 2019

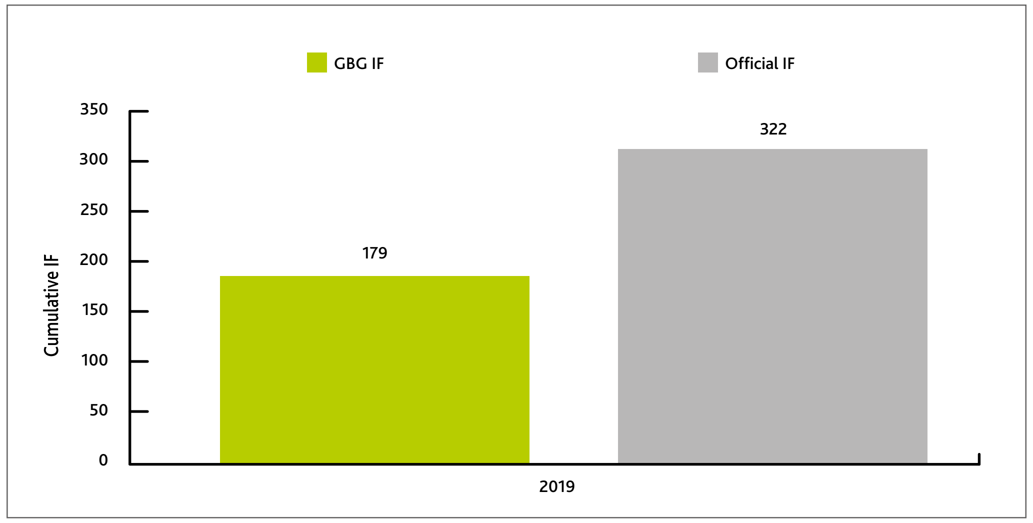


Figure 4: GBG and official Impact Factor (IF) in 2019

4.5. Guideline for Authorship

In order to guarantee a maximum of transparency when assigning the co-authorship we have established internal GBG guideline for authorship. The details are listed below:

General Rules

- Important positions: 1st author, senior author, corresponding author
- Shared authorship for 1st and 2nd author, if applicable
- Separate rules for:
- Main publication on primary endpoint
- Publications on secondary endpoints
- Translational research publications
- No honorary authorships
- Author positions can be transferred to a junior person, if also involved in the study

Score for Authors (will be used to select and rank co-authors)

1 point for every fulfilled criteria:

- Regular participating in TCs and meetings of Subboard and/or Protocol board
- Protocol writing
- Recruitment among best 3rd of participating sites
- Statistical Analysis Plan development
- Manuscript preparation
- In time response to emails concerning the trial and the manuscript (within 4 weeks)
- In time response for COI (within 2 weeks) (negative point for subsequent publications)

What to do before submission

- Select journal
- Ask potential authors for their interest to become co-author
- Present proposed list of authors to subboard / protocol board
- Circulate manuscript amongst authors
- Collect COI

Publication on primary endpoint

- 1st author: PI (or Co-PI group 1)
- Subboard / protocol board members according to Score*
- Best recruiters
- Biometrician,
- Senior author (Co-PI group 2, or group chairman)
- Addendum with study team, subboard / protocol board member, and all other recruiters with 3+ patients as „on behalf of the study groups"

* Subboard and protocol board members will share in general authorships with best recruiters on a 2:1 basis

Publication on secondary endpoints / retrospective analyses

- 1st author: „project" leader
- Subboard / protocol board members according to score for this sub-project*
- Best recruiters for this sub-project
- Biometrician
- PI or group chairman (if involved in sub-project)

* Subboard and protocol board members will share in general authorships with best recruiters on a 2:1 basis

Publications on translational research project

- Project leader (should prepare manuscript)
- Involved team member of this TRAFO project
- TRAFO board / protocol board members*
- Biomaterial provider
- 1-2 local pathologists providing most tumor tissue
- Biometrician
- PI (if involved in TRAFO project)

* Subboard and protocol board members will share in general authorships with best biomaterial providers on a 2:1 basis

4.6. Oral and poster presentations

pCR and relapse
(ESMO Breast Cancer 2019)

Heilung durch Innovation, Kompetenz und Partnerschaft

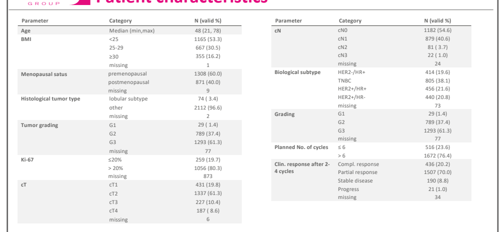
Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy: pooled analysis based on the GBG Meta Database

Huober J, Schneeweiss A, Blohmer JU, Denkert C, Tesch H, Hanusch C, Salat C, Rhiem K, Rezai M, Solbach C, Fasching PA, Jackisch C, Mehta K, Nekljudova V, Seither F, von Minckwitz G, Loibl S, Untch M

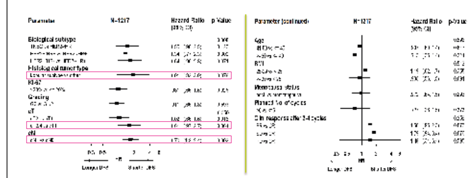
Patients and methods

- 2188 patients with pCR (ypT0/is ypN0) from GeparTrio, GeparQuattro, GeparQuinto, GeparSixto and GeparSepto trial were included
- Objectives were disease-free survival (DFS), distant DFS (DDFS), overall survival (OS)
- Multivariate Cox regression models included potential risk factors as well as study ID
- Survival rates were estimated using Kaplan-Meier method
- After a median follow up of 59 months 290 DFS, 197 DDFS and 130 OS events were observed

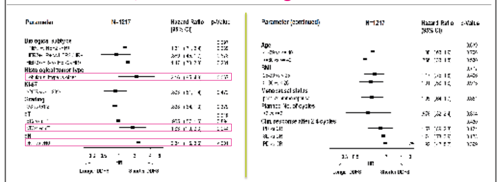
Patient characteristics



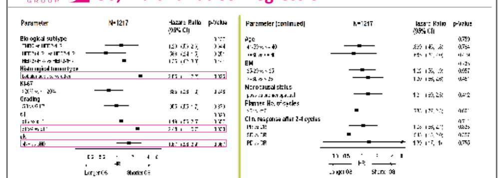
DFS, multivariat Cox regression



DDFS, multivariat Cox regression



OS, multivariat Cox regression



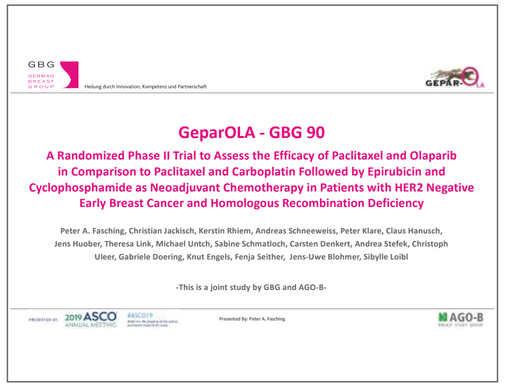
DFS in subgroups

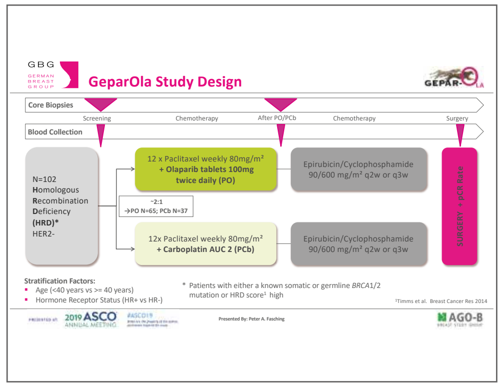
Subgroup	Parameter	Category	Hazard Ratio	95% CI	p value
HER2-/HR- (N= 805)	Histological tumor type	Other			
		Lobular subtype	**4.59**	(1.6, 13)	**0.004**
	Initial cT stadium	cT1			0.831
		cT2	0.821	(0.40, 1.7)	0.585
		cT3/4	0.936	(0.36, 2.4)	0.892
	Initial cN stadium	cN0			
		cN+	**1.96**	(1.1, 3.6)	**0.029**
HER2+/HR- (N= 440)	Histological tumor type	Other			
		Lobular subtype	1.70	(0.20, 15)	0.631
	Initial cT stadium	cT1			0.007
		cT2	1.86	(0.51, 6.8)	0.346
		cT3/4	**4.66**	(1.3, 17)	**0.019**
	Initial cN stadium	cN0			
		cN+	1.42	(0.73, 2.7)	0.302

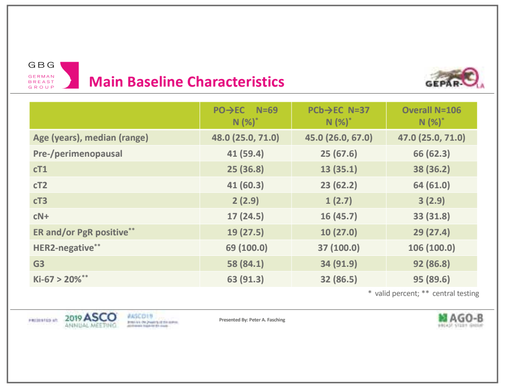
Conclusions

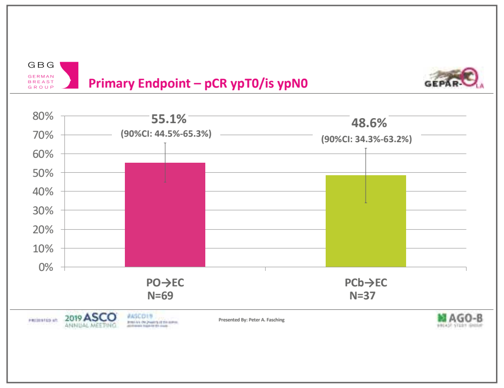
- Despite favourable prognosis following a pCR still ~15% of patients will have a DFS event and 10% a distant relapse after 5 years
- Lobular histology, greater tumor size and initially involved lymph nodes consistently indicated higher risk for DFS, DDFS and OS after a pCR
- Thus factors predicting a higher risk were not adverse biological tumor features or therapy schedule but initial tumor load and histological type
- The importance of these risk factors seems to vary by biological subtype
- Initial tumor stadium and histology can be helpful about further treatment decisions following surgery

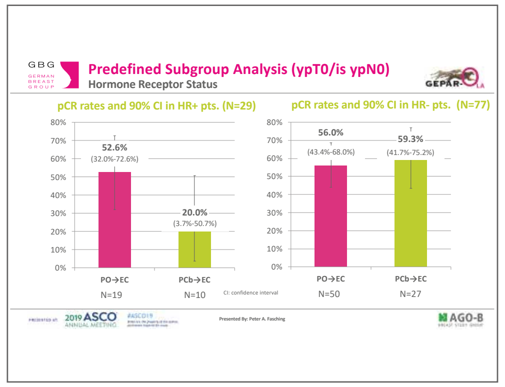
GeparOLA study
(ASCO 2019)

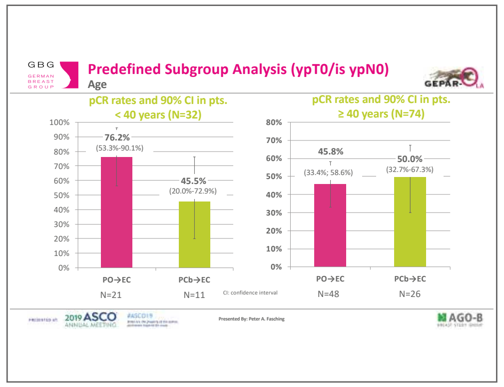


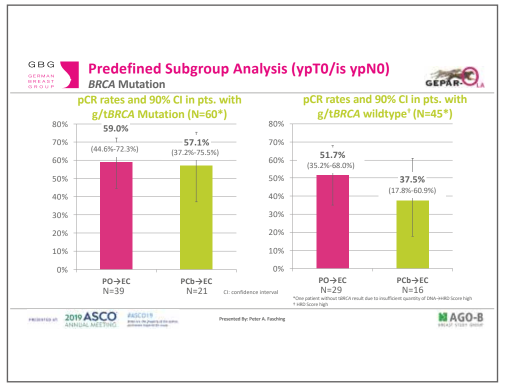


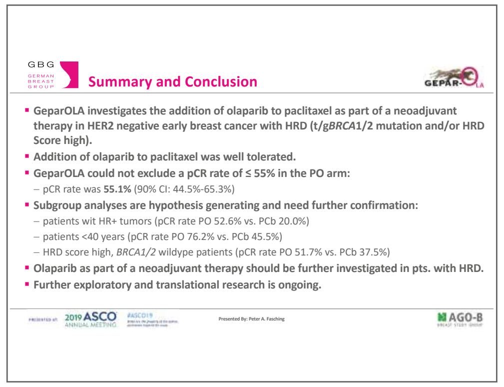




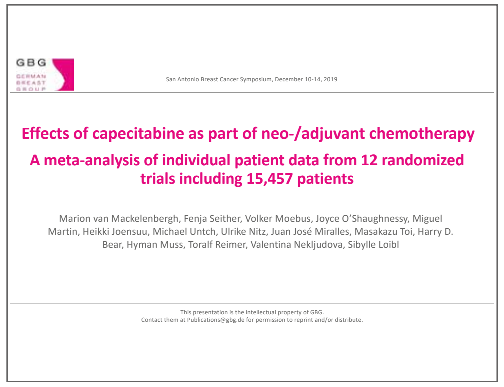


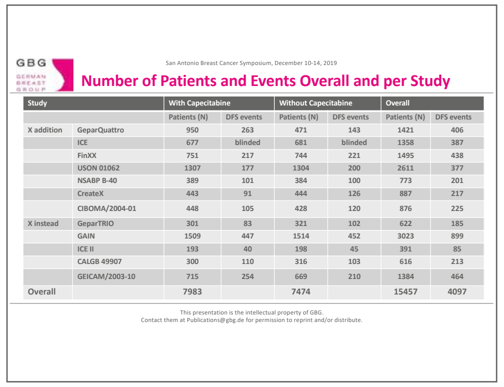


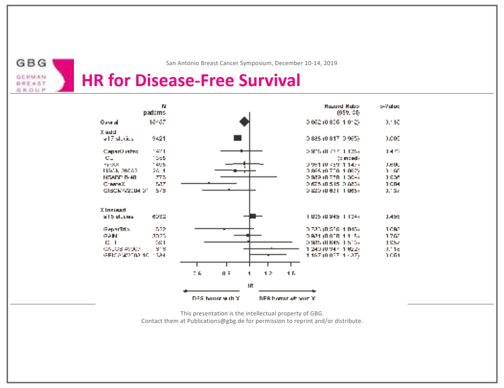


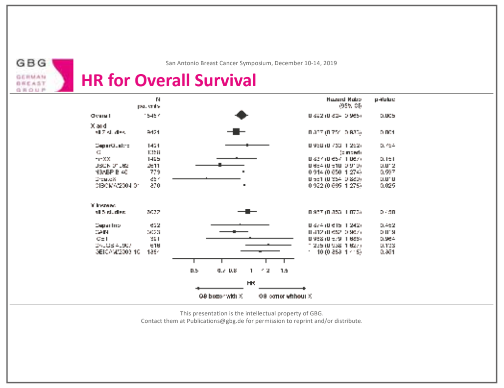


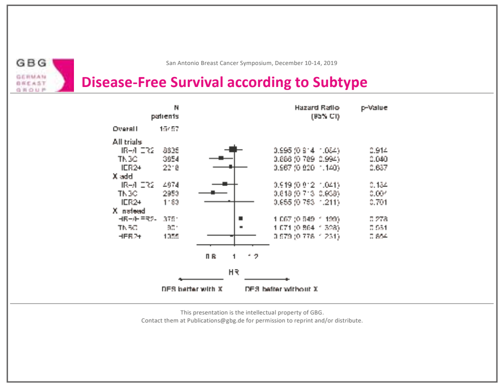
Capecitabine meta-analysis
(SABCS 2019)

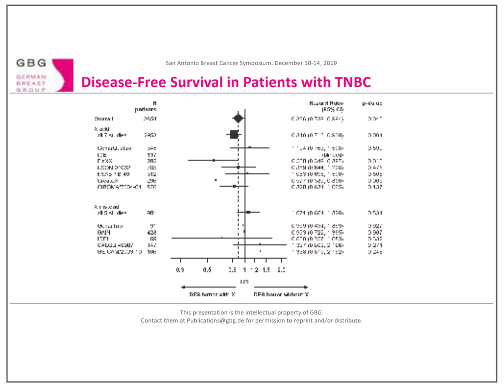


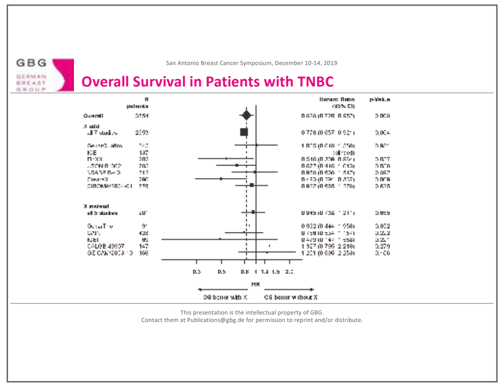


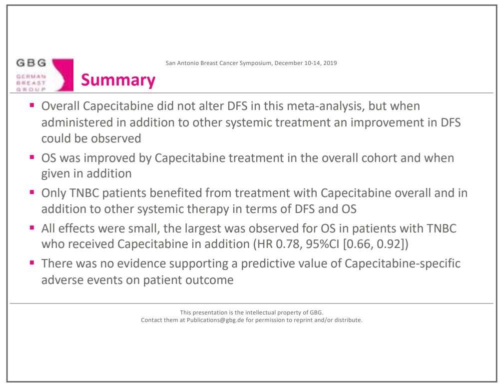




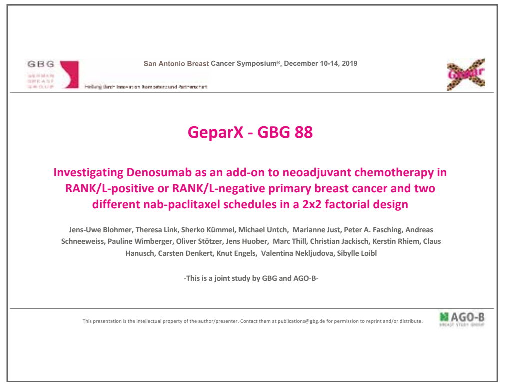


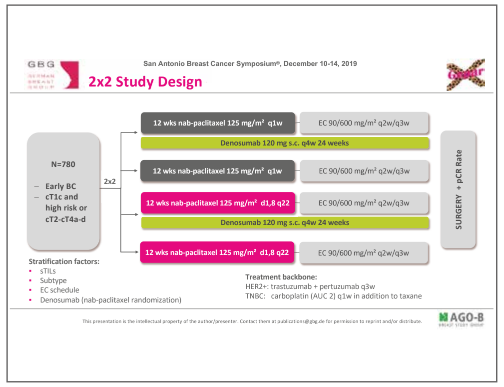


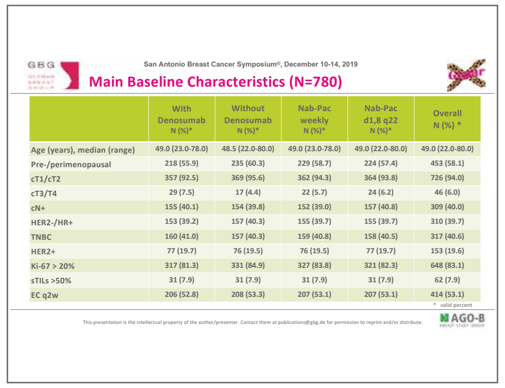




GeparX study
(SABCS 2019)






San Antonio Breast Cancer Symposium®, December 10-14, 2019

Main Baseline Characteristics (N=780)

	With Denosumab N (%)*	Without Denosumab N (%)*	Nab-Pac weekly N (%)*	Nab-Pac d1,8 q22 N (%)*	Overall N (%) *
Age (years), median (range)	49.0 (23.0-78.0)	48.5 (22.0-80.0)	49.0 (23.0-78.0)	49.0 (22.0-80.0)	49.0 (22.0-80.0)
Pre-/perimenopausal	218 (55.9)	235 (60.3)	229 (58.7)	224 (57.4)	453 (58.1)
cT1/cT2	357 (92.5)	369 (95.6)	362 (94.3)	364 (93.8)	726 (94.0)
cT3/T4	29 (7.5)	17 (4.4)	22 (5.7)	24 (6.2)	46 (6.0)
cN+	155 (40.1)	154 (39.8)	152 (39.0)	157 (40.8)	309 (40.0)
HER2-/HR+	153 (39.2)	157 (40.3)	155 (39.7)	155 (39.7)	310 (39.7)
TNBC	160 (41.0)	157 (40.3)	159 (40.8)	158 (40.5)	317 (40.6)
HER2+	77 (19.7)	76 (19.5)	76 (19.5)	77 (19.7)	153 (19.6)
Ki-67 > 20%	317 (81.3)	331 (84.9)	327 (83.8)	321 (82.3)	648 (83.1)
sTILs >50%	31 (7.9)	31 (7.9)	31 (7.9)	31 (7.9)	62 (7.9)
EC q2w	206 (52.8)	208 (53.3)	207 (53.1)	207 (53.1)	414 (53.1)

* valid percent

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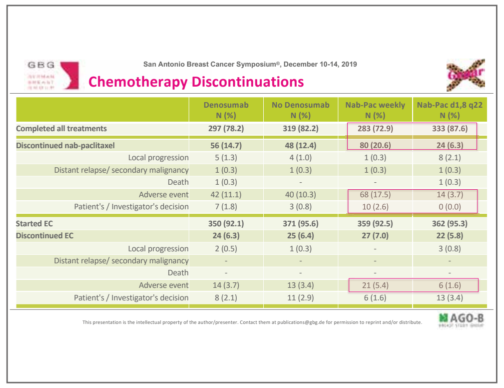
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Chemotherapy Discontinuations

	Denosumab N (%)	No Denosumab N (%)	Nab-Pac weekly N (%)	Nab-Pac d1,8 q22 N (%)
Completed all treatments	297 (78.2)	319 (82.2)	283 (72.9)	333 (87.6)
Discontinued nab-paclitaxel	56 (14.7)	48 (12.4)	80 (20.6)	24 (6.3)
Local progression	5 (1.3)	4 (1.0)	1 (0.3)	8 (2.1)
Distant relapse/ secondary malignancy	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Death	1 (0.3)	-	-	1 (0.3)
Adverse event	42 (11.1)	40 (10.3)	68 (17.5)	14 (3.7)
Patient's / Investigator's decision	7 (1.8)	3 (0.8)	10 (2.6)	0 (0.0)
Started EC	350 (92.1)	371 (95.6)	359 (92.5)	362 (95.3)
Discontinued EC	24 (6.3)	25 (6.4)	27 (7.0)	22 (5.8)
Local progression	2 (0.5)	1 (0.3)	-	3 (0.8)
Distant relapse/ secondary malignancy	-	-	-	-
Death	-	-	-	-
Adverse event	14 (3.7)	13 (3.4)	21 (5.4)	6 (1.6)
Patient's / Investigator's decision	8 (2.1)	11 (2.9)	6 (1.6)	13 (3.4)

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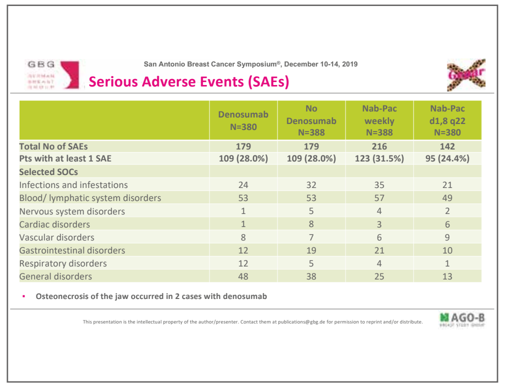
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Serious Adverse Events (SAEs)

	Denosumab N=380	No Denosumab N=388	Nab-Pac weekly N=388	Nab-Pac d1,8 q22 N=380
Total No of SAEs	179	179	216	142
Pts with at least 1 SAE	109 (28.0%)	109 (28.0%)	123 (31.5%)	95 (24.4%)
Selected SOCs				
Infections and infestations	24	32	35	21
Blood/ lymphatic system disorders	53	53	57	49
Nervous system disorders	1	5	4	2
Cardiac disorders	1	8	3	6
Vascular disorders	8	7	6	9
Gastrointestinal disorders	12	19	21	10
Respiratory disorders	12	5	4	1
General disorders	48	38	25	13

- Osteonecrosis of the jaw occurred in 2 cases with denosumab

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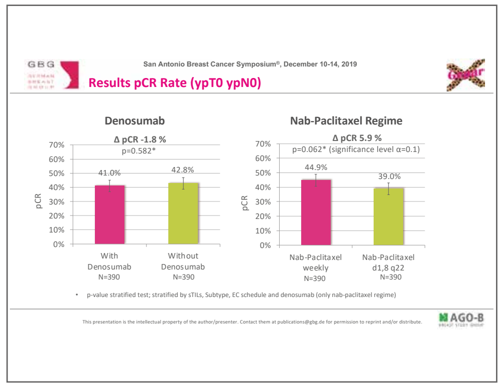

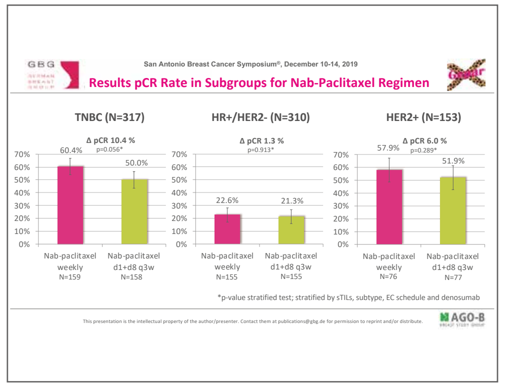

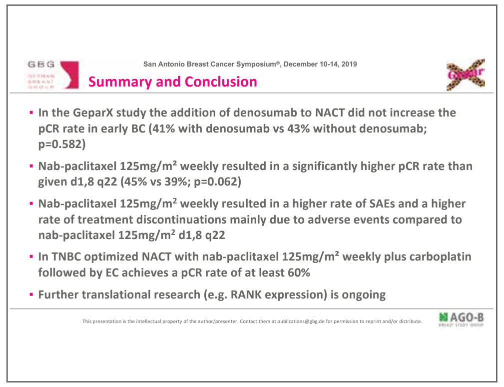

A Randomized, Double-Blind, Phase III Trial of Neoadjuvant Chemotherapy with Atezolizumab/Placebo in Patients with Triple-Negative Breast Cancer Followed by Adjuvant Continuation of Atezolizumab/Placebo (NSABP B-59/GeparDouze)

122 TIP

Sibylle Loibl[1], Christian Jackisch[2], Priya Rastogi[3], Sabine Seiler[1], Peter C Lucas[4], Carsten Denkert[5], Joseph Costantino[4], Valentina Nekljudova[1], Norman Wolmark[5], Charles Geyer[6]

[1]German Breast Group, Neu-Isenburg; [2]Sana Klinikum Offenbach; [3]National Surgical Adjuvant Breast and Bowel Project (NSABP), Magee-Womens Hospital of UPMC, Pittsburgh, USA; [4]NSABP, University of Pittsburgh, USA; [5]Institut für Pathologie, Philipps-Universität Marburg; [6]NSABP, Allegheny Health Network Cancer Institute, Pittsburgh, USA; [7]NSABP, Pittsburgh, Virginia Commonwealth University, Massey Cancer Center in Richmond, USA

Background

- Triple-negative breast cancer (TNBC) is a heterogeneous group of cancers characterized by:
  - <1% of cells positive for ER and PgR receptors
  - Negative for HER2 amplification or overexpression
- TNBC is associated with higher percentages of pathological complete response (pCR) to neoadjuvant chemotherapy (NACT), and women with a pCR have a favorable prognosis.
- Patients with TNBC and residual disease following NACT have higher risk for recurrence than patients with other subtypes of breast cancer with residual disease.[1,2]
- Poor survival once metastatic disease develops.
- Therapeutic blockade of PD-L1 binding by atezolizumab has resulted in relevant anti-tumor efficacy in TNBC.[3,4]
- Primary efficacy results of IMpassion130 have demonstrated clinically relevant activity in patients with untreated metastatic TNBC coupled with an acceptable safety profile.[5]

Study Overview

- GeparDouze (NSABP B-59/GBG96; NCT 03281954) is a phase III, randomized, double-blind, placebo-controlled study of neoadjuvant administration of atezolizumab/placebo in combination with anthracycline-/taxane-/carboplatin-based NACT in patients with early TNBC. After surgery patients will reinitiate atezolizumab/placebo as adjuvant therapy to complete 1 year of treatment (Figure 1).
- This study includes a cardiac safety lead-in for the first 60 patients who initiate AC/EC in order to identify any cardiac toxicity (recruitment completed).
- Biospecimen Collection: Tumor samples before study entry, prior to 2nd dose of atezolizumab/placebo and at time of definitive surgery.
- GeparDouze will randomize (1:1) 1520 patients. Stratification variables are:
  - Region (North America; Europe)
  - Tumor size (1.1-3.0cm; >3.0cm)
  - Schedule of epirubicin (E) or doxorubicin (A) in combination with cyclophosphamide (C) (q2w; q3w)
  - Clinical nodal status (positive; negative)

Objectives and Endpoints

- ***Co-primary objectives:*** To determine whether the addition of atezolizumab to chemotherapy improves:
  - the pCR in the breast and post-therapy lymph nodes (ypT0/Tis ypN0)
  - the event-free survival (EFS)
- ***Secondary objectives (selection):***
  - To assess other pCR definitions, survival endpoints, toxicity and cardiac safety.
- ***Correlative objectives (selection):***
  - Evaluate expression of PD-L1, and percentages of TILs as predictors for pCR and EFS.
  - Evaluate percentages of TILs in patients with residual breast cancer after surgery as predictor for EFS.
  - Use baseline and on-therapy specimens to explore potential new biomarkers of response and resistance.

In Preparation: Initial Amendment

Aim:

- To add PD-L1 status as stratification factor.
- To allow entry and randomization of patients with asymptomatic laboratory-identified endocrinopathies discovered on baseline TSH and AM cortisol:
  - hypothyroidism
  - hyperthyroidism
  - adrenal insufficiency
- To add immune nephritis and myositis as immune toxicities and provide management guidelines.

Figure 1. GeparDouze Study Design

Patients with HER2-negative, ER-negative and PgR-negative invasive breast cancer diagnosed by core needle biopsy
N=1520

1:1 RANDOMIZATION

ARM 1: Weekly Paclitaxel x 12 + Carboplatin q3wks x 4* + **Placebo***** followed by AC/EC x 4** **+ Placebo*****

ARM 2: Weekly Paclitaxel x 12 + Carboplatin q3wks x 4* + **Atezolizumab ***** followed by AC/EC x 4** **+ Atezolizumab*****

SURGERY
Lumpectomy or mastectomy and axillary staging

ARM 1: **Placebo***** to complete 1 year of therapy

ARM 2: **Atezolizumab***** to complete 1 year of therapy

* Carboplatin AUC 5 IV q3wks x 4 doses in combination with paclitaxel 80mg/m² IV weekly x 12 doses

** Doxorubicin 60mg/m² IV or epirubicin 90mg/m² IV in combination with cyclophosphamide 600mg/m² IV x 4 doses; q2wks vs q3wks per investigator's decision

*** Atezolizumab 1200mg or placebo IV q3wks initiated with chemotherapy and administered for 1 year with break for surgery

Key Inclusion Criteria

- Age ≥ 18 years
- Females or males
- Diagnosis of invasive adenocarcinoma of the breast by core needle biopsy
- Primary tumor must be:
  - T_2 or T_3 if node negative
  - T_{1c}, T_2, or T_3 if node positive
- Central testing must confirm
  - HER2 negativity by ASCO/CAP guidelines
  - ER and PgR negativity by ASCO/CAP guidelines
- Patients with synchronous bilateral or multicentric HER2-negative breast cancer are eligible as long as the highest risk tumor is ER-negative and PgR-negative and meets stage eligibility criteria
- LVEF ≥55%

Key Exclusion Criteria

- Excisional biopsy or lumpectomy performed prior to study entry
- Surgical axillary staging procedure prior to randomization. Exception: FNA or core biopsy of an axillary node is permitted for any patient
- Definitive clinical or radiologic evidence of metastatic disease
- Previous therapy with anthracyclines or taxanes for any malignancy
- Cardiac disease (history of and/or active disease) that would preclude the use of the drugs included in the treatment regimens
- Active or history of autoimmune disease or immune deficiency with the following exceptions:
  - Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone
  - Patients with controlled Type 1 diabetes mellitus on a stable dose of insulin regimen
  - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only […]

Conclusion

- GeparDouze is a phase III, double-blind, placebo-controlled study of atezolizumab/placebo in combination with NACT in patients with TNBC followed by atezolizumab/placebo as adjuvant therapy.
- Recruitment has started in 12/2017 and is expected to take place across ~ 150 sites in North America and Europe.
- GeparDouze will provide important data on efficacy and safety of atezolizumab in patients with early TNBC.

References and Conflict of Interest

References:

- 1. Liedtke C, et al. J Clin Oncol. 2008; 26: 1275-81; 2. Hahnen E, et al. JAMA Oncol. 2017; 3(10): 1378-85; 3. Adams S, et al. J Clin Oncol. 2016; 34.15_suppl, Abstract 1009, 4. Schmid P, et al. Cancer Res. 2017; 77(13 Suppl):Abstract 2986; 5. Schmid P, et al. N Engl J Med 2018:379(22):2108-21.

Conflict of interest (COIs):

- **During the conduct of the study:** S Loibl, P Rastogi, S Seiler, P Lucas, J Costantino and C Geyer report grants from Genentech/Roche; C Jackisch reports personal fees from Roche and Celgene; C Denkert reports personal fees from Roche; N Wolmark reports other COIs from Genentech/Roche.
- **Relevant financial activities outside the submitted work :** S Loibl : AstraZeneca, Pfizer, Celgene, Amgen, Abbvie, Daichi and from Eirgenix; P Rastogi: AstraZeneca, Genentech/Roche and from Lilly;P. Lucas: Amgen, and Bayer/Loxo; C Denkert: Sividon Diagnostics, Teva, Novartis, Pfizer, Amgen, MSD, Daiichi, Celgene, AstraZeneca and patent application EP18209672 (cancer immunotherapy); C Geyer: AstraZeneca, Abbvie, Celgene, Genentech/Roche.

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15P

Influence of *PIK3CA* mutations on breast cancer proliferation, lymphocyte infiltration and clinical outcome: pooled analysis of 868 patients from three prospective multicentre GBG trials

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Background

The *PI3K* signaling pathway is frequently dysregulated in breast cancer (BC), effected through mutations in *PIK3CA*, which encodes for the catalytically subunit p110-alpha. An influence of *PIK3CA* mutations in therapy response resistance associated with a worse clinical outcome has previously been shown for HER2+ BC [1]. Mutations in exon 9 or 20 may play a role in cell proliferation and therapy response [2].

OBJECTIVES

- Examine correlation between *PIK3CA* mutation status and clinical pathological markers (proliferation [Ki-67], tumor infiltrating lymphocytes [TILs], pathological complete response [pCR])
- Examine correlation between *PIK3CA* mutations status and (clinical) outcome (overall and disease-free survival [OS, DFS])

Patients and Methods

We investigated *PIK3CA* mutation status in 868 BC patients, randomized in three clinical multicenter trials: GeparQuattro (NCT00288002), GeparQuinto (NCT00567554), GeparSixto (NCT01426880). Classical Sanger sequencing in exon 9 and 20 was performed on formalin-fixed paraffin embedded pretherapeutical core biopsies with a tumor content >=20%.

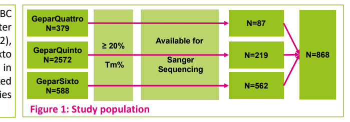

Figure 1: Study population

Results

Figure 2: Percentage of patients with overall high Ki-67 expression (>20% IHC) and in subgroups of hormone receptor (HR)+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC)

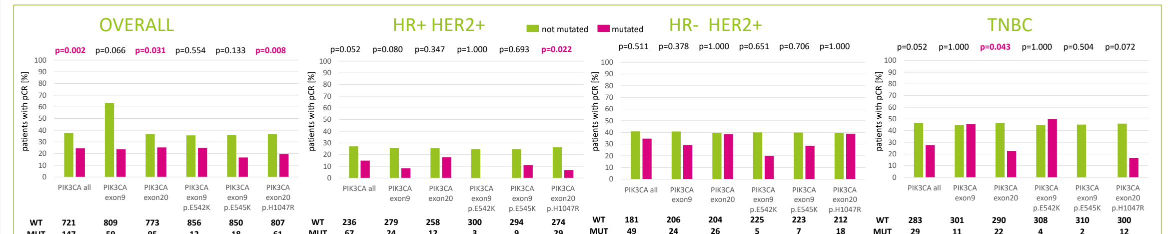

Figure 3: Percentage of patients with pathologic complete response (pCR, ypT0 ypN0) and in subgroups of hormone receptor (HR)+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC)

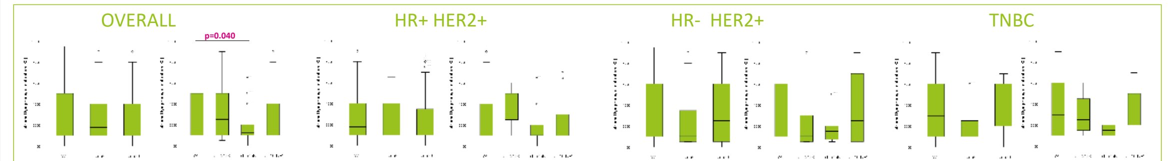

Figure 4: Boxplots of stromal TILs vs. *PIK3CA* mutation status in exons (exon 9 and 20) and typical hotspots (p.542, p.545 in exon 9 and p.1047 in exon 20) and in subgroups of hormone receptor (HR)+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC)

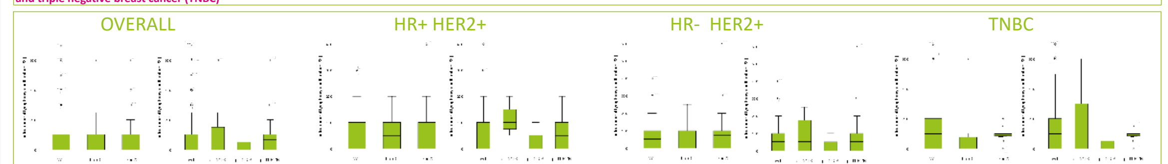

Figure 5: Boxplots of intratumoral TILs vs. *PIK3CA* mutation status in exons (exon 9 and 20) and typical hotspots (p.542, p.545 in exon 9 and p.1047 in exon 20) and in subgroups of hormone receptor (HR)+/HER2+, HR-/HER2+, and triple negative breast cancer (TNBC)

Table 1: Baseline characteristics

Parameter	Category	*PIK3CA* wildtype Overall N (%) = 721 (83.1)	*PIK3CA* mutated (any) Overall N (%) = 147 (16.9)	p-value by Chi²-test
Age, years	<60	617 (85.6)	125 (85.0)	0.898
	≥ 60	104 (14.4)	22 (15.09	
cT	cT1	160 (22.3)	37 (25.2)	0.898
	cT2	407 (56.7)	82 (55.8)	
	cT3	84 (11.7)	14 (9.5)	
	cT4a-c	22 (3.1)	4 (2.7)	
	cT4d	45 (6.3)	10 (6.8)	
cN	N0	392 (55.2)	65 (44.5)	0.063
	N1	275 (38.7)	74 (50.7)	
	N2	34 (4.8)	6 (4.1)	
	N3	96 (1.3)	1 (0.7)	
Tumor grading	G1	16 (2.2)	1 (0.7)	0.466
	G2	277 (38.5)	56 (38.4)	
	G3	426 (59.2)	89 (61.0)	
ER central	positive	471 (65.3)	81 (55.1)	0.024
	negative	250 (34.7)	66 (44.9)	
PR central	positive	543 (75.3)	99 (67.3)	0.050
	negative	178 (24.7)	48 (32.7)	
HER2 central	positive	304 (42.2)	31 (21.1)	< 0.001
	negative	417 (57.8)	116 (78.9)	
Ki67 central	≤ 20%	128 (21.4)	32 (26.2)	0.282
	> 20%	470 (78.6)	90 (73.8)	

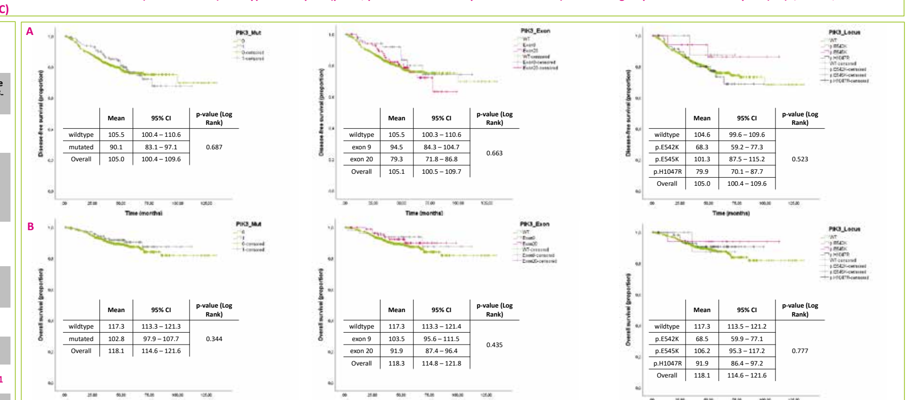

Figure 6: Survival curves. A) disease-free survival based on *PIK3CA* mutations status . B) overall survival based on *PIK3CA* mutation status

Summary of Results

Mutation analysis of exon 9 and 20 were sin 868 case successful: *PIK3CA* was mutated in 16.9% of the cases.
Hormone receptor positive (HER2 negative) tumors were too rare (N=23) for statistical analyses and were excluded and not shown.
Detection of a *PIK3CA* mutation was not associated_significantly with a higher proliferation rate (Ki67 >20%: 73.8% mut. vs. 78.6% WT, p=0.282). Triple negative tumors were rarely Ki67 high when exon 20 was mutated (p=0.004) (Figure 2). Detection of any *PIK3CA* mutation was associated significantly with lower pathologic complete response (pCR, ypT0 ypN0) (24.5% in *PIK3CA* mutated vs. 37.7% in wildtype; p=0.002). This effect was seen when exon 20 or p.1047 in exon 20 was mutated (Figure 3).
Lower stromal lymphocyte infiltration was seen when p.542 in exon 9 was mutated, compared to wildtype in overall group (p=0.012), but not detectable in molecular subtypes (Figure 4). *PIK3CA* mutations have no significant influence in stromal TILs (Figure 5). There were no significant differences in disease free or overall survival between the groups (Figure 6).

Conclusion

PIK3CA is with 16.9% a frequently mutated gene in breast cancer [2]. Only in the HR+/HER2+ group *PIK3CA* mutation p.H1047R results in higher proliferation, but is reversed in TNBC when exon 20 was mutated.
According to pathologic complete response, *PIK3CA* could used as a biomarker for a worse outcome and is reliable for all molecular subgroups.
In the overall group the mutation p.E452K of *PIK3CA* is associated with lower stromal lymphocyte infiltration. *PIK3CA* mutations are not associated with differences in intratumoral lymphocyte infiltration. In survival analyses (DFS and OS) no statistical relevance occurred.

References and Conflict of Interest

(**1**) Loibl S et al. J Clin Oncol 2014; 32:3212-20.; (**2**) Wu H et al. Cancer Manag Res 2019; 11:1473-1492.
VM received speaker honoraria from Amgen, Astra Zeneca, Celgene, Daiichi-Sankyo, Eisai, Pfizer, Novartis, Roche, Teva, Janssen-Cilag and consultancy honoraria from Genomic Health, Hexal, Roche, Pierre Fabre, Amgen, Novartis, MSD, Daiichi-Sankyo and Eisai, Lilly, Tesaro and Nektar. Research support from Novartis, Roche, Seattle Genetics; **CD** is shareholder and cofounder: Sividon Diagnostics, has collaboration: VmScope – standardized immunohistochemistry software, received Honoraria/Consultation: Teva, Novartis, Pfizer, Roche, Amgen, MSD, Daiichi and has a patent application: EP18209672 - cancer immunotherapy; **SL** received honoraria in form of research grants to her institution from AbbVie, Amgen, AstraZeneca, Celgene, Novartis, Pfizer, Roche, Seattle Genetics, Teva, Vifor and PRIME, has a leadership role at GBG, BIG EB and ESMO Breast conference; All other authors have no conflict of interest to declare.

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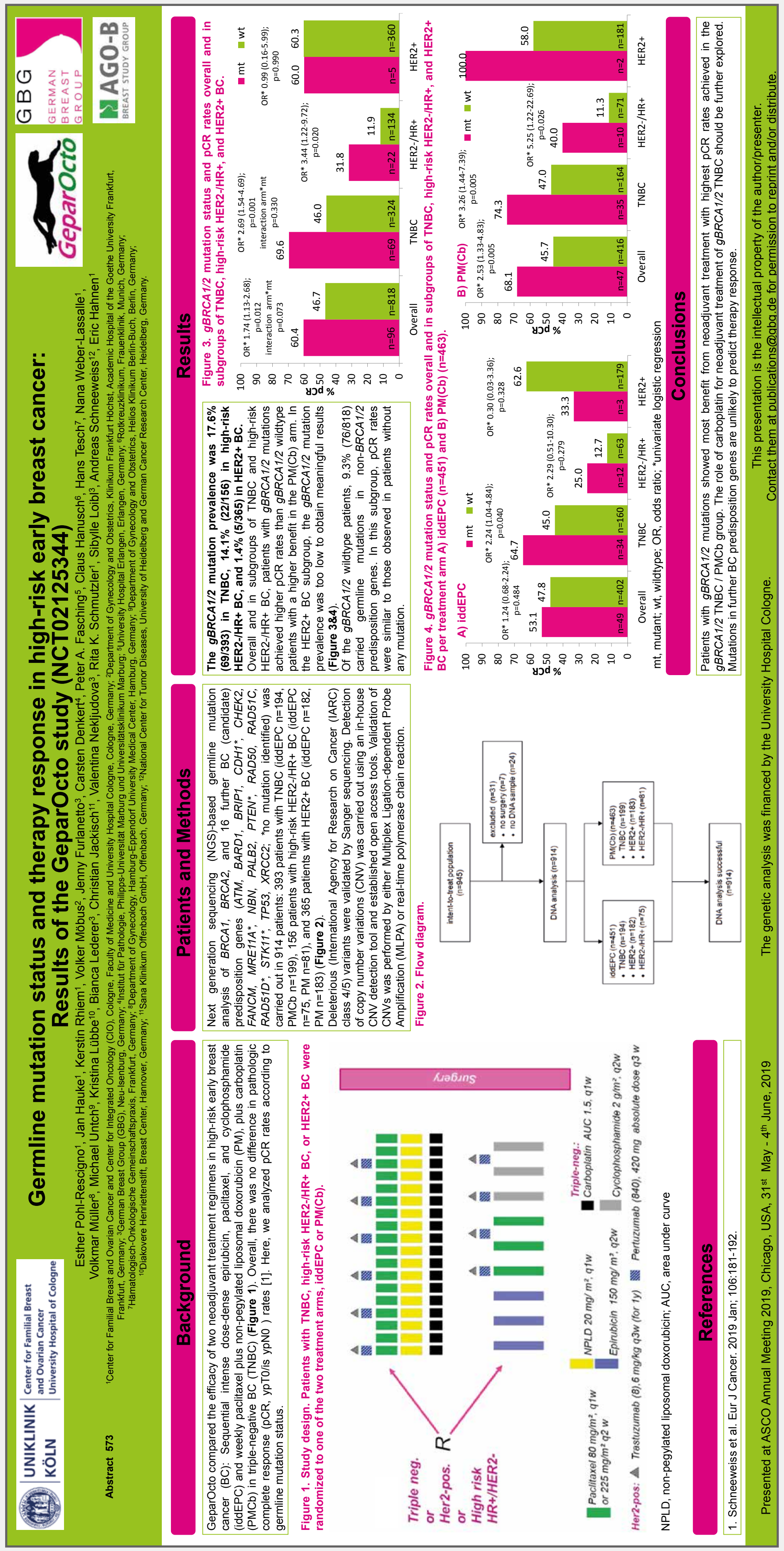
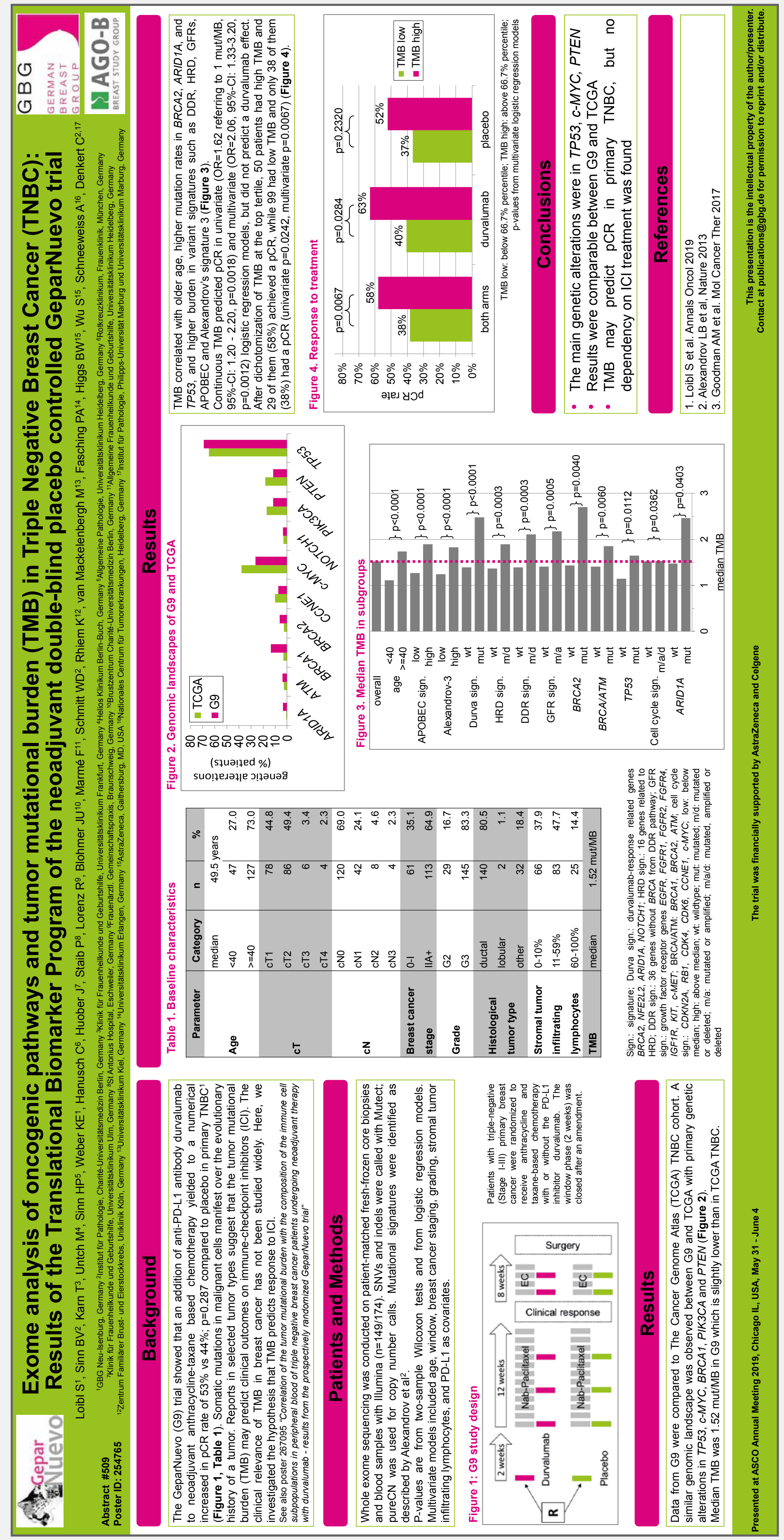
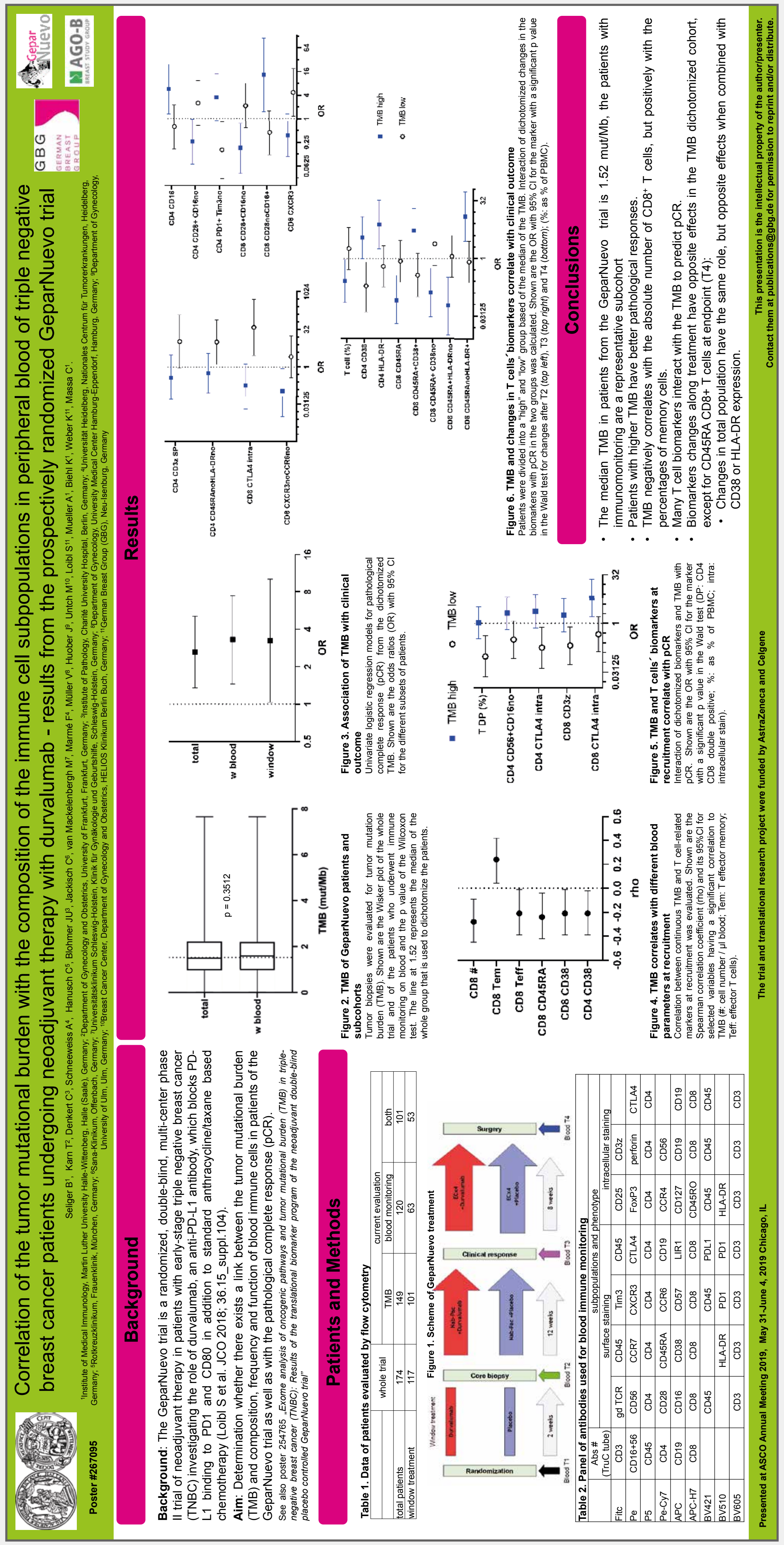
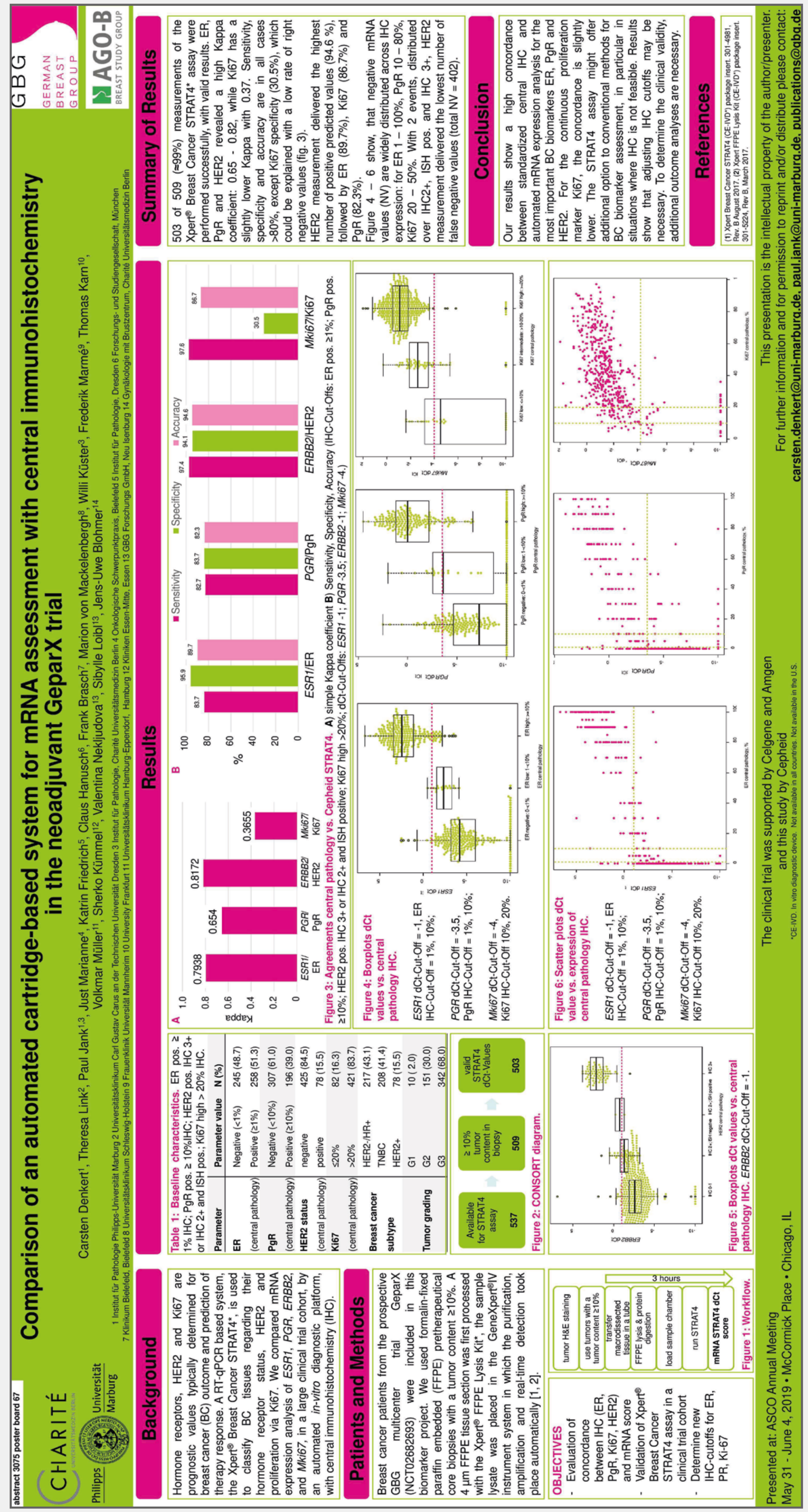

Germline mutation status and therapy response in high-risk early breast cancer: Results of the GeparOcto study (NCT02125344)
GeparOcto
Background
Patients and Methods
Results
Conclusions
References
Presented at ASCO Annual Meeting 2019, Chicago, USA, 31st May - 4th June, 2019


Exome analysis of oncogenic pathways and tumor mutational burden (TMB) in Triple Negative Breast Cancer (TNBC): Results of the Translational Biomarker Program of the neoadjuvant double-blind placebo controlled GeparNuevo trial
Background
Patients and Methods
Results
Conclusions
References


Correlation of the tumor mutational burden with the composition of the immune cell subpopulations in peripheral blood of triple negative breast cancer patients undergoing neoadjuvant therapy with durvalumab - results from the prospectively randomized GeparNuevo trial
Background
Patients and Methods
Results
Conclusions
Presented at ASCO Annual Meeting 2019, May 31-June 4, 2019 Chicago, IL


Comparison of an automated cartridge-based system for mRNA assessment with central immunohistochemistry in the neoadjuvant GeparX trial
Background
Patients and Methods
Results
Summary of Results
Conclusion
References

Impact of Chemotherapy-induced Ovarian Failure (CIOF) on Disease-free Survival (DFS) and Overall Survival (OS) in Young Women with Early Breast Cancer (EBC)

180PD

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GBG GERMAN BREAST GROUP

Background

Young patients with BC have a risk of developing premature ovarian failure. The incidence of chemotherapy-induced amenorrhea (CIA) ranges between 45-61% among different studies.[1,2]
We have previously reported that the majority of young women experienced chemotherapy-induced ovarian failure after chemotherapy (CT) for EBC. Age, CT regimen, duration and density influenced the rate of CIOF.[3] Moreover, nearly 70% of women regain premenopausal hormone levels of follicle-stimulating hormone (FSH) and estradiol (E2) within 2 years after end of CT. However, only less than one third maintain their fertility potential as predicted by anti-Müllerian hormone (AMH).[4]
Previous data showed, that CT-induced amenorrhea was associated with a better DFS and OS in premenopausal patients with EBC, regardless of the hormone-receptor status.[5]
Here we report results on the impact of CIOF on DFS and OS in young women with EBC.

Patients and Methods

Overall, 740 patients aged ≤45 years treated with anthracycline/taxane (A/T)-based CT for EBC from 4 German neo-/adjuvant trials were examined. Centrally assessed E2 and FSH in paired blood samples collected at baseline and 4 weeks after the last therapy infusion were considered. CIOF was defined as estradiol <52.2 ng/L and FSH >12.4IU/L after CT for those patients with premenopausal hormone levels at baseline. 696 patients with premenopausal hormone levels at baseline were included in the present analysis.

Objectives:

1. Distribution of E2 and FSH values at end of treatment (EOT)
2. 4-year DFS and OS (rate, hazard ratio (HR) and 95% confidence interval (CI)) overall and in subgroups by hormone-receptor status (positive, negative) and age (<30, 30-34, 35-39, ≥40 years)
3. DFS according to FSH values (10 unit increase in FSH values and quartiles) at EOT.

Results

- Among the 740 examined patients, median age was 40 (range 21-45) years; 57.2% had BMI 18.5-<25, 41.1% ≥25; 32% of the patients had luminal, 35.9% HER2+, 32.0% triple-negative BC; 94.1% (N=696) had premenopausal hormone levels at baseline. Overall, 8.1% of patients received taxane treatment only before EOT; 44.5% of patients received dose-dense CT; CT duration was 24 weeks for 47.4% of the patients, 12 weeks for 8.1% of the patients. Median follow-up was 49.6 months. 4-year DFS and OS rates as well as HR overall and in subgroups are presented in Table 1.
- At EOT E2 levels were under the detectable threshold for most patients (n=395), whereas FSH level were approximately normally distributed (Figure 1). Each 10 unit increase in FSH values was associated with a reduction in the risk of a DFS event by HR_{10unit} =0.91 95%CI [0.87-0.96], p<0.001. Patients with FSH levels at EOT within the first (lower) quartiles (Q), had the worst DFS compared to patients with FSH levels within Q2-4, whereas patients within Q4 (upper) had the better DFS.

Table 1. 4-year DFS and OS rates as well as HR overall and in subgroups

	DFS				OS			
	4-year rate (%)		log rank p-value	HR [95% CI]*	4-year rate (%)		log rank p-value	HR [95% CI]*
	no CIOF	CIOF			no CIOF	CIOF		
overall (n=696)	65.2	84.0	**<0.001**	2.06 [1.36-3.12]	89.5	92.7	0.272	1.46 [0.74-2.90]
hormone-receptor status								
negative (n=301)	71.6	79.6	0.266	1.47 [0.74-2.89]	91.8	88.7	0.729	0.81 [0.25-2.67]
positive (n=395)	61.8	87.5	**<0.001**	2.69 [1.57-4.60]	88.4	95.9	**0.035**	0.49 [1.04-5.99]
age (years)								
<30 (n=60)	68.3	92.6	**0.026**	4.87 [1.05-22.63]	90.3	95.5	0.254	3.48 [0.36-33.99]
30-34 (n=99)	59.9	80.1	0.108	1.99 [0.85-4.68]	96.3	92.1	0.934	0.94 [0.19-4.56]
35-39 (n=200)	63.5	81.9	0.116	1.85 [0.85-4.04]	84.9	93.2	0.380	1.75 [0.49-6.23]
≥40 (n=337)	69.3	85.2	0.565	1.41 [0.44-4.51]	86.7	92.4	0.361	1.93 [0.46-8.17]

*HR no CIOF vs CIOF. Abbreviations: CIOF, chemotherapy-induce ovarian failure; HR, Hazard Ratio

Figure 1. Distribution of estradiol (A) and FSH (B) values at the end of treatment

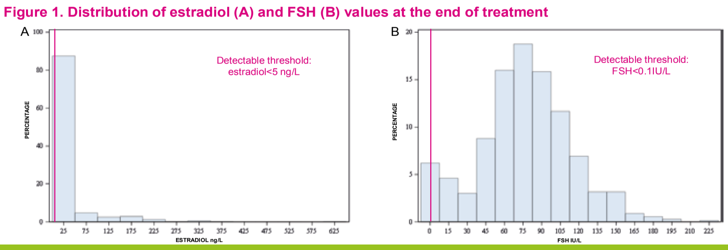
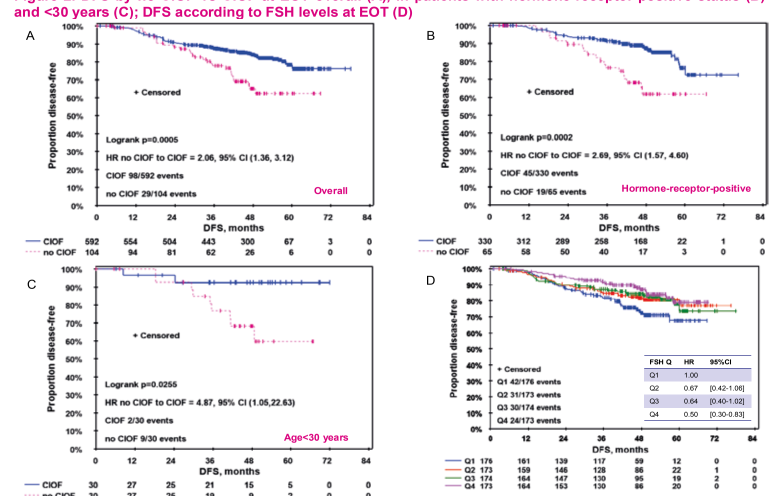


Figure 2. DFS by no CIOF vs CIOF at EOT overall (A), in patients with hormone-receptor-positive status (B) and <30 years (C); DFS according to FSH levels at EOT (D)



Abbreviation: Q, Quartile; Q1, lower quartile; Q4, upper quartile

Conclusions

Patients with CIOF after A/T-based CT for EBC show a better DFS, especially in women with hormone-receptor positive EBC or <30 years. The improvement in DFS seems to translate in an OS advantage in patients with hormone-receptor positive EBC. Patients with the highest levels of FSH at EOT derived a great benefit in DFS compared to patients with lower FSH levels.

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AGO-B BREAST STUDY GROUP

Utility of the CPS+EG scoring system in triple-negative breast cancer treated with neoadjuvant chemotherapy

#4042

GBG GERMAN BREAST GROUP

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Background

- Pathologic complete response (pCR) after neoadjuvant chemotherapy (NACT) is associated with superior disease free (DFS) and overall survival (OS).[1]
- This association is strongest in triple-negative breast cancer (TNBC).[1]
- Post-neoadjuvant therapy has become a standard option for patients not achieving a pCR after NACT, especially in HER2+ disease and TNBC.[2,3]
- The CPS+EG system, based on pre-treatment clinical (CS) and post-treatment pathologic stage (PS), grade and estrogen receptor status, leads to a refined estimate of prognosis after NACT in all comers and HR+/HER2-.[4,5,6]

Here, we investigate if CPS+EG scoring provides a superior estimate of prognosis in TNBC after NACT to select patients for post-neoadjuvant therapy.

Patients and Methods

Trial design

10526 patients have been treated within 9 prospective randomized neoadjuvant trials conducted by the German Breast Group (GBG) and the Arbeitsgemeinschaft Gynäkologische Onkologie-Breast (AGO-B) study group until 2013. All trials investigated anthracycline and taxane-based chemotherapy regimens. The CPS+EG score was calculated as depicted in **Figure 1**. ER, PgR, HER2 and grade were assessed on pretreatment core biopsies. For this analysis we only included patients with HER2-negative disease. Excluded patients and reasons are summarized **Figure 2**. The primary goal was to investigate if CPS+EG scoring provides a superior estimate of prognosis in TNBC after NACT to select patients for post-neoadjuvant therapy.

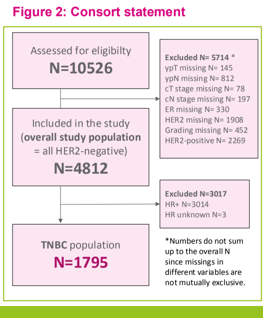
Statistical consideration

Disease-free survival (DFS) was plotted as Kaplan Meier curves. Local progression during NACT was not counted as an event. Log-rank p-values were calculated to compare different stages or risk scores. Five-year survival analysis (DFS), including percentage of survival and associated 95% confidence intervals, was conducted using IBM SPSS Statistics 25.

Figure 1: CPS+EG score point assignment

Clinical Stage		
I	0	T1N0; T0N1mi, T1N1mi
IIA	0	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2N2
IIIB	2	T4N0-2
IIIC	2	Any T N3
Pathologic Stage		
0	0	T0/isN0
I	0	T1N0; T0N1mi, T1N1mi
IIA	1	T0N1; T1N1; T2N0
IIB	1	T2N1; T3N0
IIIA	1	T0-2 N2
IIIB	1	T4 N0-N2
IIIC	2	Any T N3
Tumor Biologic Factors		
ER negative	1	
Nuclear grade 3	1	

Figure 2: Consort statement



Results

In HER2- patients, CPS+EG leads to a refined estimate of prognosis (**Figure 3a**). TNBC patients who achieved a pCR had a 5-year DFS of 86% (n=822, 45.8%), whereas patients with residual stage I had a 5-year DFS of 77.5% (n=383; 21.3%). CPS+EG score was unable to identify non-pCR patients with a sufficiently good prognosis, to avoid post-neoadjuvant therapy (**Figure 3b**). The best prognostic TNBC CPS+EG groups (score 1/2) in non-pCR patients had a 5-year DFS of 77.5% and 74.4%, respectively (n=362; 37.2%) (**Figure 3b**). CPS+EG identified a small group of patients (n=26; 3.2%) at high risk of recurrence despite pCR, mainly based on initial stage (CS+EG score > 3; 5-year DFS 61.4%) that might benefit from additional treatment (**Figure 3b**). However, prognosis of patients with a CPS+EG score of 3 (5-year DFS: 64%), could be further discriminated by pCR (5-year DFS: 83.9% vs 49.7%) (**Figure 4**).

Figure. 3a: HER2-
DFS stratified according to clinical stage, pathologic stage and CPS+EG

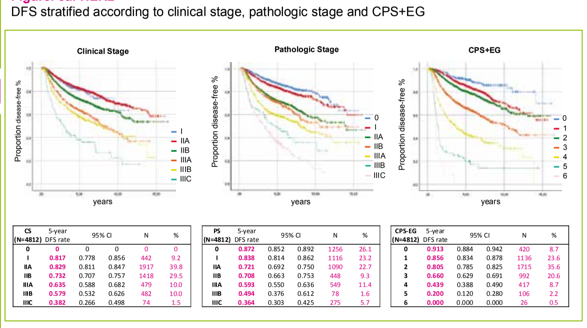


Figure 3b: TNBC
DFS stratified according to clinical stage, pathologic stage and CPS+EG

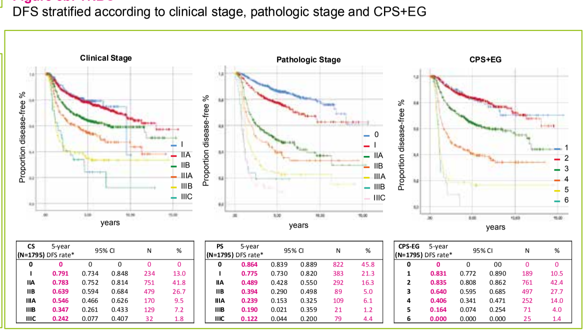
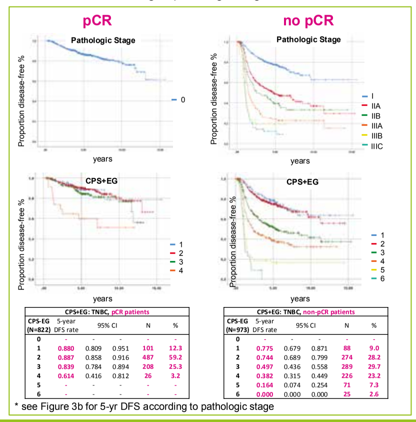


Table 1: Baseline characteristics

		complete database		HER2 negative CPS+EG cohort		TNBC CPS+EG cohort	
		N	valid %	N	valid %	N	valid %
All patients		10526		4812		1795	
pre-treatment clinical tumour stage	cT1	1184	11.3	666	13.8	322	17.9
	cT2	6481	62.0	2994	62.2	1120	62.4
	cT3	1585	15.2	645	13.4	215	12.0
	cT4a-c	586	5.6	263	5.5	45	2.5
	cT4d	612	5.9	243	5.1	92	5.1
pre-treatment clinical nodal status	cN0	5314	51.4	2550	53.1	1016	56.6
	cN1	4460	42.4	2001	41.6	678	37.8
	cN2	422	4.0	181	3.8	68	3.8
	cN3	133	1.3	74	1.5	32	1.8
Tumor grade	1	352	3.5	185	3.8	24	1.3
	2	5275	52.4	2437	50.6	491	27.4
	3	4447	44.1	2190	45.5	1280	71.3
ER status	Negative	4030	39.5	1982	41.2	1795	100.0
	Positive	6166	60.5	2830	58.8	NA	
HER-2 status	Negative	6349	73.7	4812	100.0	1795	100.0
	Positive	2269	26.3	NA		NA	
pCR (ypT0/Tis ypN0)		**2572**	**24.4**	**1256**	**26.1**	**822**	**45.8**

Figure 4: TNBC split by pCR status
DFS stratified according to pathologic stage and CPS+EG



* see Figure 3b for 5-yr DFS according to pathologic stage

Conclusions

- In TNBC the CPS+EG score does not lead to a clinically useful better categorization of patients into distinct prognostic groups beyond pCR and pathologic stage
- CPS+EG fails to identify a prognostic favourable subgroup not achieving a pCR, which might not be considered candidates for post-neoadjuvant stragies
- However, CPS+EG identifies a small subgroup of patients with TNBC and HER2- BC at high risk of recurrence despite a pCR. These are defined by G3 and clinical stage IIIB/C tumours.

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Chemotherapy-induced anaemia in patients treated with dose-dense regimen: Results of the prospectively randomised anaemia substudy from the neoadjuvant GeparOcto study

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Background

Iron deficiency anaemia is a frequent adverse event in cancer patients treated with chemotherapy. Clinical use of parenteral (IV) ferric carboxymaltose (FCM) has been shown to be an efficient treatment for anaemia and can prevent red blood cell transfusion[1]. This substudy compared the use of FCM with physician's choice (PhCh) anaemia therapy in breast cancer (BC) patients treated with CT.

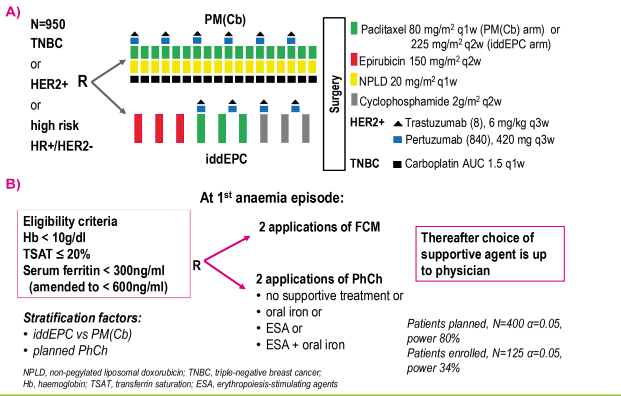
Patients and Methods

Study design of the GeparOcto main and supportive anaemia studies are shown in Fig. 1.

Primary objective: to compare the frequency of patients achieving Hb≥11g/dl at 6 weeks of anaemia treatment with FCM vs PhCh. If an additional treatment was performed during the anaemia study, this was counted as not reached the primary endpoint.

Main secondary objectives: median time to achieve Hb≥11g/dl; changes in iron parameters (serum ferritin and transferrin saturation [TSAT]) at baseline (BL) vs different time points (4, 8, 12, 16 weeks and end of chemotherapy [EOT]); blood transfusion in both arms. Patients without Hb assessment after BL were counted as not achieved Hb≥11g/dl.

Figure 1: Study design of the GeparOcto main (A) and supportive anaemia (B) studies



Results

Figure 2: Consort statement

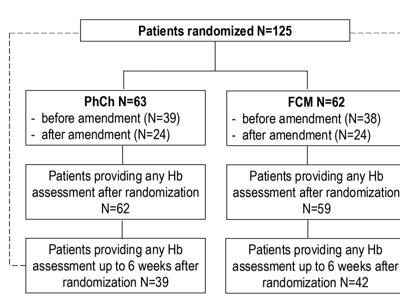
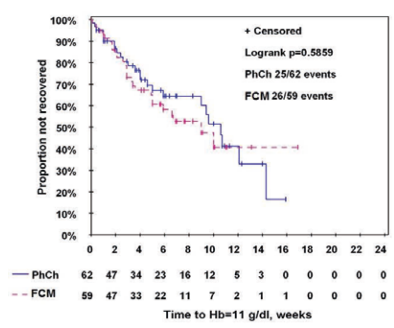


Table 1. Baseline characteristics

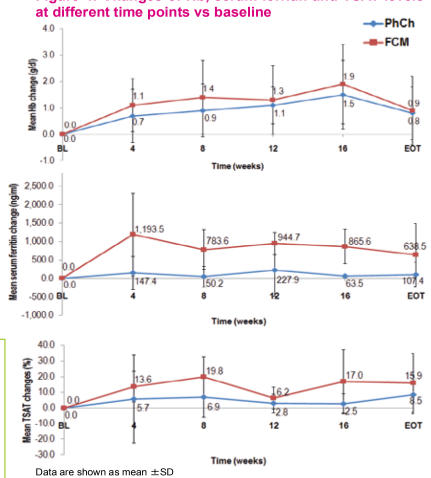
Parameter	PhCh N=63	FCM N=62	p-value
Continuous variables			
Age [years] median (range)	47 (30-66)	46 (26-64)	0.861
Hb [g/dl] at 1st anaemia episode median (range)	9.7 (8.0-9.9)	9.6 (8.7-9.9)	0.665
Hb [g/dl] at last assessment before randomisation median (range)	9.6 (7.9-11.8)	9.5 (7.6-11.1)	0.328
Serum ferritin [ng/ml] median (range)	199 (3.0-504)	201 (16.8-551)	0.851
TSAT [%] median (range)	14.0 (4.0-76.0)	14.0 (4.0-20.0)	0.705
Categorical variables			
Serum ferritin <300 ng/ml	51 (81.0)	52 (85.2)	0.634
Serum ferritin ≥300 ng/ml	12 (19.0)	9 (14.8)	
missing	0	1	

Figure 3: Time to achieve Hb ≥ 11g/dl



- Overall, 40 (32.0%) patients (35.5% in FCM and 28.6% in PhCh arm; p=0.447) reached Hb level of ≥11g/dl at 6 weeks.
- Median time to achieve Hb≥11g/dl was 9.0 weeks (95%CI 5.0–not reached) with FCM vs 10.6 weeks by PhCh (95%CI 5.9–14.3) corresponding to a hazard ratio (HR) 1.17 (95%CI 0.67–2.03) (Fig. 3).
- The mean Hb changes at different time points vs baseline were comparable in both arms whereas the mean serum ferritin and TSAT changes were increased in FCM as compared with PhCh arm at earlier time points (Fig. 4).
- Overall, in the PhCh arm 17 patients received oral iron substitution, 8 ESA, 2 both, 7 other treatment and 18 did not receive any anaemia treatment.
- During anaemia therapy, blood transfusion was performed in 2 patients in the FCM and 5 in the PhCh arm (p=0.246) whereas after 6 weeks of therapy 5 patients in the FCM and one in PhCh arm received blood transfusion (p=0.205).

Figure 4: Changes of Hb, serum ferritin and TSAT levels at different time points vs baseline



Conclusions

This is the first study investigating IV iron treatment for dose-dense CT-induced anaemia in BC. 32% of patients reached Hb≥11g/dl at 6 weeks, irrespective of anaemia therapy. FCM treatment increased ferritin and TSAT levels but did not improve anaemia in comparison to PhCh in this setting.

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Risk factors for locoregional recurrence (LRR) after neoadjuvant chemotherapy: pooled analysis of prospective neoadjuvant breast cancer (BC) trials

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Background

LRR after neoadjuvant chemotherapy (NACT) for BC may impact patient's outcome. This study aimed to evaluate the rates of LRR as first event after NACT and to identify independent predictors of LRR.

Patients and Methods

A total of 10,075 women with primary BC and available follow-up from 9 prospective neoadjuvant trials (GeparDuo, GeparTrio pilot and main study, GeparQuattro, PREPARE, TECHNO, GeparQuinto, GeparSixto and GeparSepto) were included in this pooled analysis. The main endpoint was cumulative incidence rates of LRR as first event after NACT; distant recurrence, secondary malignancy or death was defined as competing event. Cumulative incidence of LRR was estimated according to the Gray's competing risk model[1]. To identify predictors of LRR, surgery type, pathological complete response (pCR=ypT0 ypN0), BC subtypes (HR+/HER2-, HR+/HER2+, HR-/HER2+, TNBC) and other risk factors were evaluated using Fine-Gray's regression model[2]. All analyses according to pCR were performed using landmark (landmark setting)[3]. The two-sided significance level was set to α=0.05.

Results

Table 1. Baseline characteristics and response

Parameter	Category	N (valid %)	Parameter	Category	N (valid %)
Age, years	Median (range)	49 (21-80)	tumor grade	G1	336 (3.5)
cT	cT1	1195 (12.0)		G2	5037 (52.2)
	cT2	6277 (62.8)		G3	4279 (44.3)
	cT3	1425 (14.3)	BC subtypes	HR+/HER2-	3958 (45.8)
	cT4a-d	1102 (11.0)		HR+/HER2+	1458 (16.9)
cN	cN0	5098 (51.6)		HR-/HER2+	989 (11.5)
	cN1	4263 (43.2)		TNBC	2229 (25.8)
	cN2	385 (3.9)	Surgery type	BCS	6577 (68.1)
	cN3	133 (1.3)		Mastectomy	3080 (31.9)
Histological type	Ductal invasive	8150 (82.2)	pCR (ypT0 ypN0)	no	8020 (79.6)
	Lobular invasive	1039 (10.5)		yes	2055 (20.4)
	other	720 (7.3)			

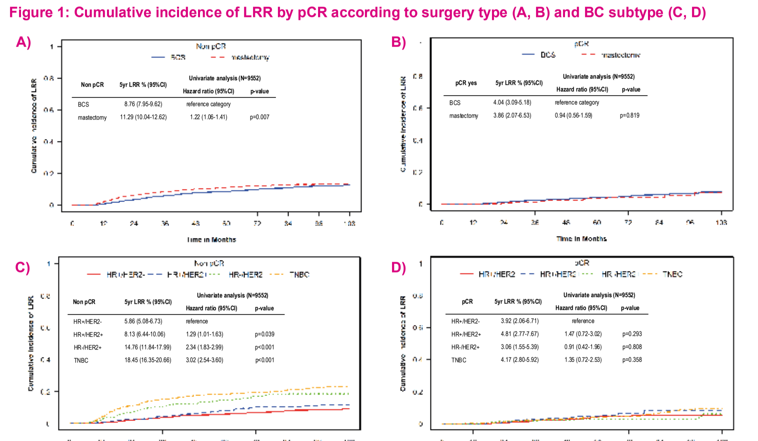
Table 2: Multivariate analysis of LRRs, overall

Parameter	Category	5-year LRR rate (95% CI)	Multivariate analysis (N=9552) Hazard ratio (95 % CI)	p-value
Age, years				<0.001
	>50	7.57 (6.77- 8.42)	reference category	-
	≤50	9.89 (9.07- 0.75)	1.35 (1.16-1.57)	<0.001
cT				0.077
	cT1-3	8.45 (7.85-9.08)		-
	cT4a-d	12.00 (10.06-14.12)	1.23 (0.98-1.55)	0.077
cN				<0.001
	negative	6.75 (6.04-7.51)	reference category	-
	positive	11.18 (10.24-12.15)	1.47 (1.26-1.71)	<0.001
tumor grade				0.001
	G1-2	6.91 (6.21-7.66)	reference category	-
	G3	11.38 (10.39-12.42)	1.33 (1.12-1.57)	0.001
Histological type				0.302
	Ductal invasive	9.36 (8.70-10.04)	reference category	-
	Lobular invasive	5.47 (4.13-7.07)	0.789 (0.58-1.08)	0.135
	Other	8.69 (6.67-11.04)	0.92 (0.68-1.25)	0.613
BC subtypes				<0.001
	HR+/HER2-	5.99 (5.23-6.81)	reference category	-
	HR+/HER2+	7.55 (6.13-9.15)	1.32 (1.04-1.67)	0.022
	HR-/HER2+	10.46 (8.51-12.63)	1.97 (1.50-2.59)	<0.001
	TNBC	14.41 (12.91-15.99)	2.72 (2.23-3.31)	<0.001
Surgery type				0.514
	BCS	7.82 (7.15-8.53)	reference category	-
	Mastectomy	11.28 (10.13-12.50)	1.06 (0.89-1.25)	0.514
pCR (ypT0 ypN0) (landmark)				<0.001
	yes	4.07 (3.21-5.08)	reference category	-
	no	9.52 (8.84-10.22)	3.33 (2.60-4.28)	<0.001

Table 3: Subgroup multivariate analysis by pCR

Parameter	Category	non-pCR patients HR (95 % CI)	non-pCR patients p-value	pCR patients HR (95 % CI)	pCR patients p-value
Age, years			0.001		0.099
	>50	reference	-	reference	-
	≤50	1.32 (1.12-1.55)	0.001	1.52 (0.92-2.52)	0.099
cN			<0.001		0.054
	negative	reference		reference	-
	positive	1.49 (1.27-1.74)	<0.001	1.61 (0.99-2.61)	0.054
tumor grade			<0.001		0.971
	G1-2	reference	-	reference	-
	G3	1.39 (1.16-1.65)	<0.001	1.01 (0.62-1.64)	0.971
BC subtypes			<0.001		0.314
	HR+/HER2-	reference	-	reference	-
	HR+/HER2+	1.23 (0.96-1.58)	0.097	2.12 (0.89-5.02)	0.089
	HR-/HER2+	2.05 (1.54-2.73)	<0.001	1.30 (0.56-3.03)	0.543
	TNBC	2.77 (2.27-3.39)	<0.001	1.65 (0.79-3.44)	0.180
Surgery type			0.143		0.464
	BCS	reference	-	reference	-
	Mastectomy	1.13 (0.96-1.33)	0.143	0.78 (0.41-1.51)	0.464

Figure 1: Cumulative incidence of LRR by pCR according to surgery type (A, B) and BC subtype (C, D)



- After a median follow-up in the entire cohort of 67 months (range 0-215 months), 959 (9.5%) LRRs as first event were observed.
- Age, clinical nodal status before NACT, tumor grade, pCR and BC subtypes but not surgery type were significant independent predictors of LRR in multivariate analysis (Table 2).
- Patients achieving a pCR have lower LRR rate compared to non-pCR. Patients treated with mastectomy and those with HR-/HER2+ or TNBC subtypes had higher LRR rates at 5 years in non-pCR subgroup only (Figure 1).
- In non-pCR subgroup age, tumor grade, HR-/HER2+ and TNBC subtypes were independent predictors of LRR whereas only cN+ showed a trend in predicting LRR in the pCR subgroup (Table 3).

Conclusions

- **Young age, node-positive and G3 tumors, non-pCR status, HER2+ and TNBC subtypes were found to significantly increase the risk of LRR as first event after NACT.**
- **Patients with HR-/HER2+ and TNBC not achieving pCR were at highest risk of LRR. Hence, there is a critical need to investigate better multimodality post-neoadjuvant therapies for this patients.**

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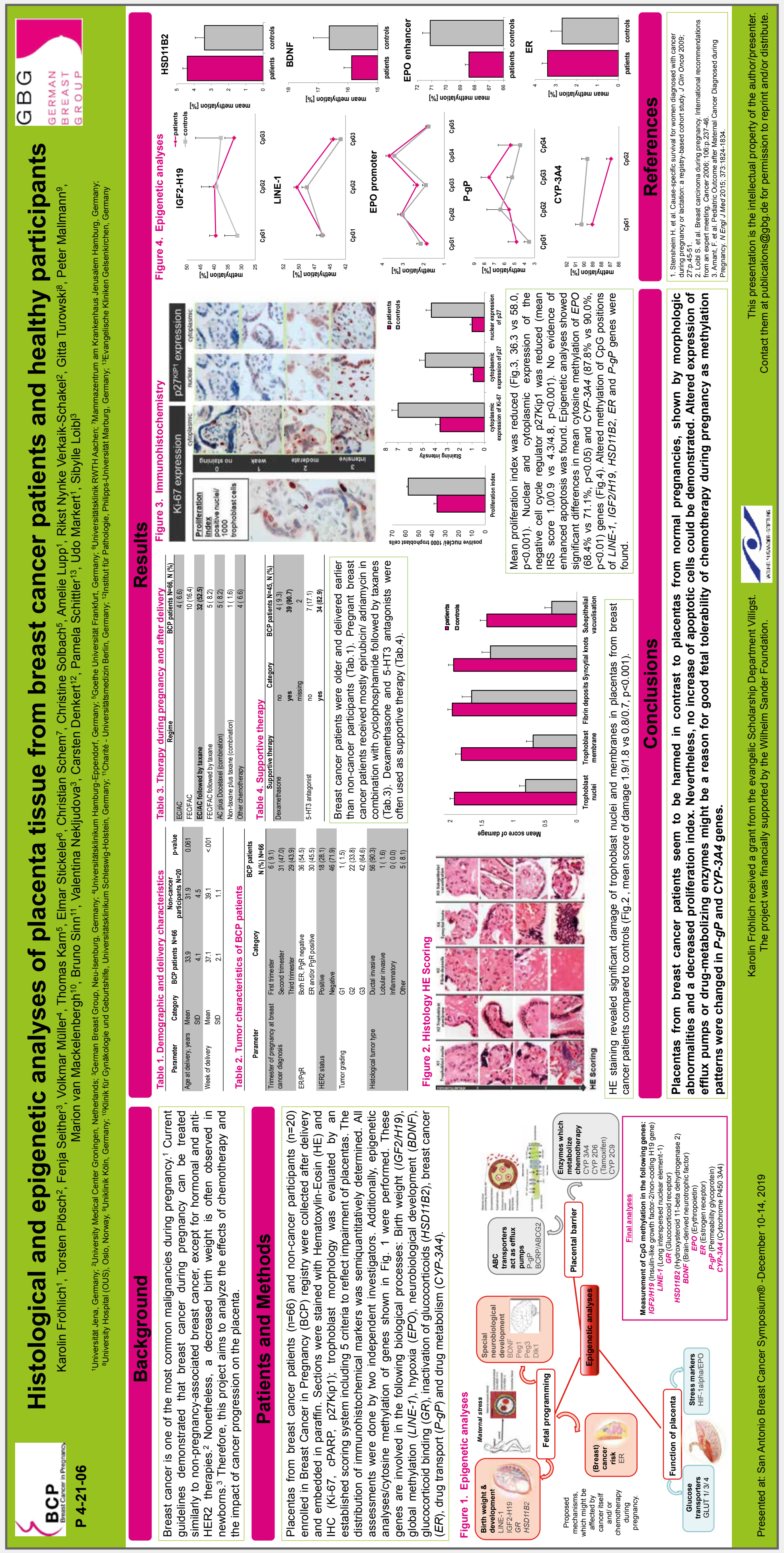
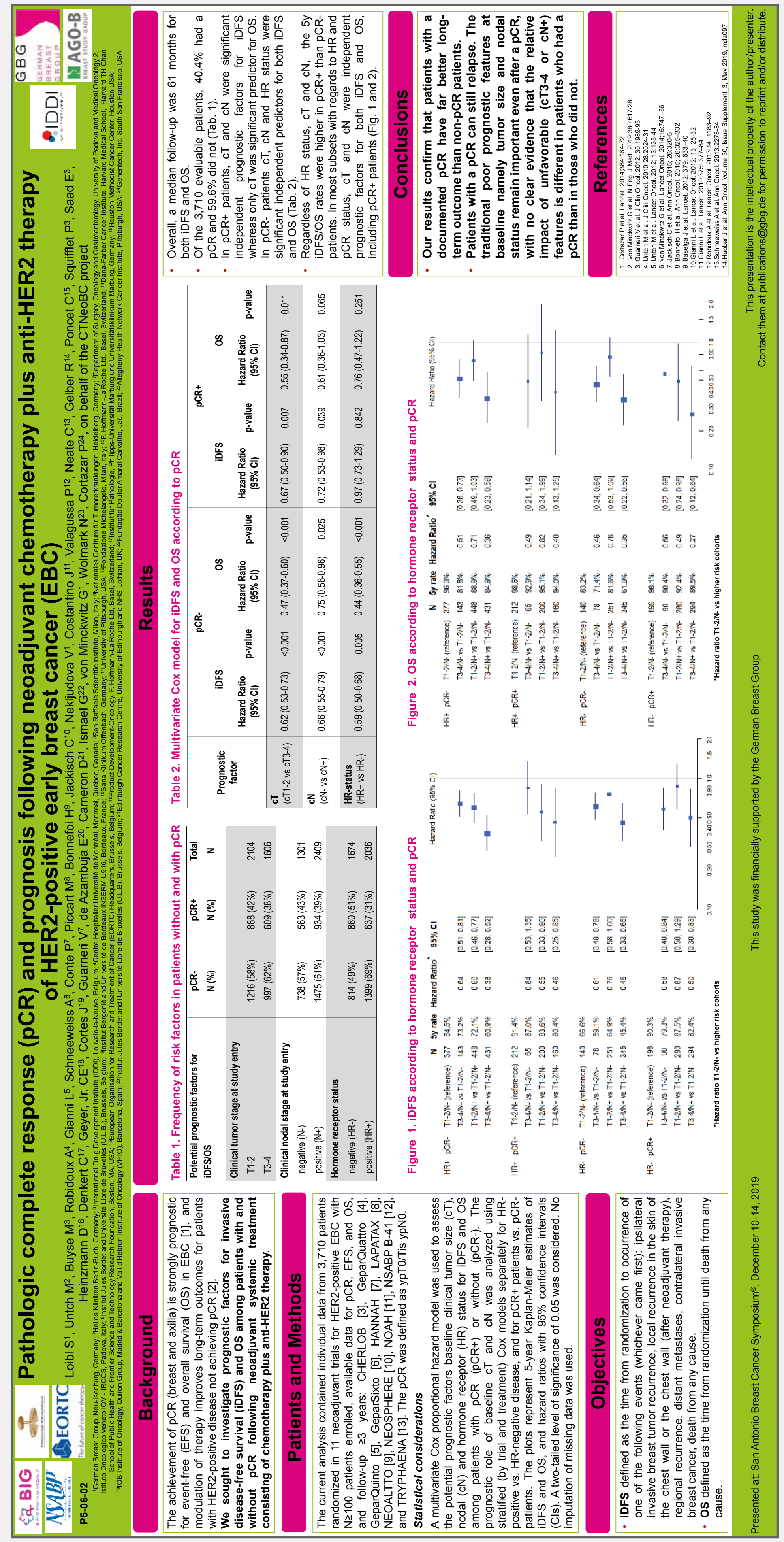

Histological and epigenetic analyses of placenta tissue from breast cancer patients and healthy participants


Pathologic complete response (pCR) and prognosis following neoadjuvant chemotherapy plus anti-HER2 therapy of HER2-positive early breast cancer (EBC)

P6-10-03

Germline (g) *BRCA1/2* mutations (m) and hematological toxicities in patients with triple negative breast cancer (TNBC) treated with neoadjuvant chemotherapy (NACT)

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GBG German Breast Group · AGO-B Breast Study Group

Background

BRCA1/2 genes play a central role in DNA repair. g*BRCA1/2* mutations cause a lack of expression and/or function of the corresponding proteins and consequently a homologous recombination deficiency.[1] Breast cancer patients harboring g*BRCA1/2*m treated with chemotherapy might be at higher risk of acute hematological toxicities, especially patients with TNBC who had a higher mutation rate (about 15%) among breast cancer subtypes.[2]
As available data are discordant and the role of taxane has not been analyzed so far, we investigated if patients with g*BRCA1/2*m experienced a higher rate of hematological toxicities compared to wildtype during anthracycline/taxane-based NACT and separately under taxane only.

Patients and Methods

Patients with early TNBC and known g*BRCA1/2*m treated with anthracycline/taxane-based NACT in the GeparQuinto[3], GeparSixto[4] and GeparOcto[5] studies were included. Primary G-CSF prophylaxis was foreseen for the intense dose-dense epirubicin-paclitaxel-cyclophosphamide (iddETC) arm in GeparOcto study. This analysis has been conducted in patients with g*BRCA1/2*m vs wildtype, in patients with g*BRCA1* vs wildtype and with g*BRCA2* mutation vs wildtype.
The multivariate models have been adjusted for age, BMI and treatment arm. The rate of toxicities under taxane has been investigated in the ETC arm of GeparOcto and in the EC-T +/- bevacizumab and weekly paclitaxel +/-everolimus arms of the GeparQuinto trial. The whole taxane treatment has been considered for the analysis.

Objectives

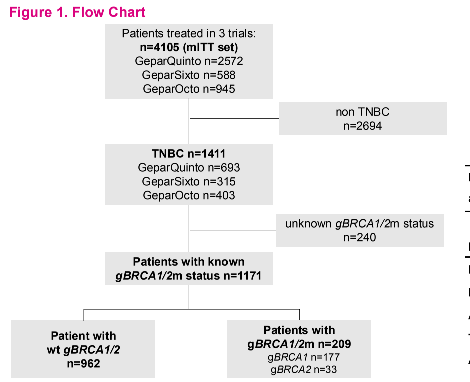
Primary objective was the rate of neutropenia grade (G) 3-4 after cycle 1 according to g*BRCA1/2*m.
Secondary objectives were:
- The rate of febrile neutropenia, leucopenia, anemia and thrombopenia G3-4 according to g*BRCA1/2* mutation status
- The overall toxicity rate G1-4 and G3-4 after cycle 1 according to g*BRCA1/2* mutation status
- The overall rate and the rate of each hematological toxicity G3-4 according to g*BRCA1/2* mutation status during the taxane part of chemotherapy.

Results

- 209 of 1171 (17.8%) evaluated patients had a g*BRCA1/2*m (177 g*BRCA1*m, 33 g*BRCA2*m) (Figure 1). Median age was 48 years [21-78] (Table 1).
- g*BRCA1/2* mutational status did not predict neutropenia G3-4 in univariate (OR=1.08, 95%CI 0.78-1.48, p=0.658) or multivariate analysis adjusted for age, BMI and treatment (OR=1.26, 95%CI 0.87-1.82, p=0.226).
- The rates of overall and other hematological toxicities are shown in Table 2.
- g*BRCA1/2* mutational status did also not predict for any other hematological toxicities G3-4 (univariate OR=0.94, 95%CI 0.64-1.40, p=0.773; multivariate OR=0.94, 95%CI 0.62-1.43, p=0.779).

Hematological toxicities under taxanes (Table 3):
- g*BRCA1/2* mutational status was a significant predictor of hematological toxicities G3-4 under taxane treatment (univariate OR=1.94, 95%CI 1.35-2.77, p<0.001; multivariate OR=2.91, 95%CI 1.55-5.45 p=0.001).

Figure 1. Flow Chart



Abbreviations: g, germline; mITT, modified intention to treat; TNBC, triple-negative breast cancer; wt, wildtype

Table 1. Baseline characteristics

Characteristic	Category	Wildtype N=962 N	%	g*BRCA1/2*m N=209 N	%
Age	Median [range]	49 [21-78]		41 [21-76]	
BMI	<30 kg/m²	781	81.2	176	84.2
	≥30 kg/m²	181	18.8	33	15.8
T stage	T1-2	814	84.8	181	86.6
	T3-4	146	15.2	28	13.4
N stage	N0	607	64.2	125	61.3
	N+	338	35.8	79	38.7
Grading	G1-2	228	23.8	50	23.9
	G3	731	76.2	159	76.1
CT regimen	PM	121	12.6	24	11.5
	PMCb	284	29.5	61	29.2
	iddETC	160	16.6	34	16.3
	EC-T	162	16.8	47	22.5
	EC-Pw	24	2.5	3	1.4
	EC-PwEv	21	2.2	1	0.5
	ECB-TB	170	17.7	37	17.7
	ECB-Pw	10	1.0	2	1.0
	ECB-PwEv	10	1.0	0	0.0

Abbreviations. B, Bevacizumab; BMI, Body Mass Index; C, Cyclophosphamide; Cb, Carboplatin; CT, Chemotherapy; E, Epirubicin; Ev, Everolimus; idd, intense dose-dense; M, Myocet; P, paclitaxel; T, Docetaxel.

Table 2. Hematological toxicity in patients without and with g*BRCA1/2* mutations

Hematological toxicities after cycle 1	Wildtype N	%	g*BRCA1/2*m N	%	p-value*	g*BRCA1*m N	%	p-value*	g*BRCA2*m N	%	p-value*
Neutropenia G3-4	326	35.7	74	37.4	0.683	61	35.9	1.000	13	44.8	0.330
Febrile neutropenia	17	1.8	3	1.4	1.000	1	0.6	0.337	2	6.1	0.130
Leucopenia G3-4	244	25.8	38	18.2	0.021	28	15.8	0.004	10	30.3	0.548
Anemia G3-4	2	0.2	0	0.0	1.000	0	0.0	1.000	0	0.0	1.000
Thrombopenia G3-4	11	1.2	1	0.5	0.705	1	0.6	0.704	0	0.0	1.000
Any toxicities G1-4	777	82.6	170	81.7	0.763	141	80.1	0.453	30	90.9	0.344
Any toxicities G3-4	428	46.3	88	43.6	0.533	72	41.9	0.317	16	51.6	0.587

*Fisher's exact test

Table 3. Hematological toxicity in patients with g*BRCA1/2* mutation under taxane treatment

Hematological toxicities during taxane treatment	Wildtype N=612 N	%	g*BRCA1/2*m N=148 N	%	p-value*
Neutropenia G3-4	219	35.8	73	49.3	**0.003**
Febrile neutropenia	37	5.9	7	4.6	**0.696**
Leucopenia G3-4	203	32.7	72	47.1	**0.001**
Anemia G3-4	16	2.6	5	3.3	0.584
Thrombopenia G3-4	9	1.4	7	4.6	**0.024**
Any toxicities G3-4	270	43.1	91	59.5	**<0.001**

*Fisher's exact test

Conclusions

- Overall, g*BRCA1/2* mutation status is not associated with a significantly higher risk of severe hematological toxicities.
- Under taxane therapy, patients with g*BRCA1/2* mutation demonstrate a higher rate of hematological toxicities G3-4, especially neutropenia, compared to wildtype patients, and should therefore be carefully monitored.

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Presented at: 42nd Annual San Antonio Breast Cancer Symposium, 10th-14th December 2019

P1-10-01

Caveolin Gene Expression Predicts for Response and Clinical Outcomes of Patients Treated with Preoperative Paclitaxel-based Chemotherapy Regimens in Early Stage Breast Cancer

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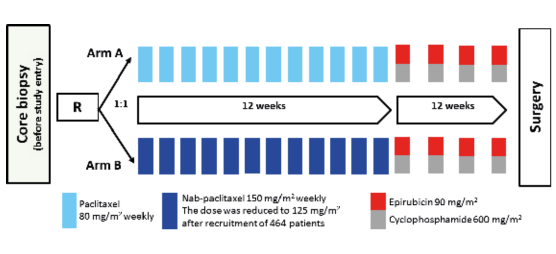
Background

Biomarkers are needed to prognosticate and predict efficacy of therapy for patients undergoing neoadjuvant chemotherapy for HER2-negative breast cancer (BC). Caveolin 1 and 2 (encoded by CAV1 and CAV2 genes) are responsible for formation of caveolae, which are 50-100 nanometer membrane invaginations implicated in endocytosis and transcytosis of nutrients and substances, including albumin. Overexpression of caveolin family genes has been implicated in driving BC progression, as well as in predicting response to nab-paclitaxel (albumin-bound paclitaxel) (1,2). GeparSepto (G7) phase III randomized trial compared neoadjuvant nab-paclitaxel with paclitaxel in early stage breast cancer, and showed improved pathological complete response (pCR) and disease-free survival (DFS) with nab-paclitaxel (3). We hypothesized that high CAV1/2 expression would correlate with poor clinical outcomes, but that patients with high CAV1/2 expression would have better outcomes with nab-paclitaxel-based chemotherapy.

Patients and Methods

We correlated tumor CAV1/2 RNA expression from available RNA-Seq data of HER2-negative patients (n=279) with pCR, DFS, and overall survival (OS) in the G7 trial (3) (**Figure 1**). CAV1/2 log-transformed values were analyzed as a continuous variable and dichotomized about the mean for each gene. Multivariable logistic regression models were generated, and included age, T-stage, N-stage, tumor histologic grade (G3 vs G1-2), Ki67 (continuous), and histology (non-ductal vs ductal). The primary objective of the G7 clinical trial was pCR, defined as ypT0/ypN0.

Figure 1. Study design GeparSepto



Results

- There was RNA-Seq data available for 279 out of 810 HER2-negative patients, of whom 26.5% were hormone receptor (HR)-negative (triple negative, TNBC). CAV1 and CAV2 expression values were directly correlated with each other (Pearson coefficient 0.452). (**Figure 2**)
- There was no difference in CAV1 expression between TNBC and HR-positive patients, but there was significant up-regulation of CAV2 expression (median) in TNBC patients (p=0.003) (**Figure 3**).
- With regard to prognostic effects, CAV2 expression was significantly associated with worse DFS (**Figure 4B**) and OS for all patients (**Figure 5B**). In particular, high CAV2 expression was associated with poor prognosis for TNBC patients in multivariate modeling but not for HR-positive patients (**Table 1**).
- Comparing the effects of CAV1/2 expression in the nab-paclitaxel vs the paclitaxel arm, high CAV1 expression was significantly associated with superior chance of obtaining pCR and improved OS (with a trend for improved DFS) in multivariate modeling (**Table 2**). For CAV2, higher expression was likewise associated with improved odds ratio of obtaining pCR, but no significant interactions in hazard ratios for DFS and OS were detected (**Table 2**). On Kaplan-Meier analysis, high CAV1 and CAV2 were associated with worse DFS in the paclitaxel-treated, but not the nab-paclitaxel- treated groups (**Figure 6**). Similarly, high CAV1 and CAV2 were associated with worse OS in the paclitaxel-treated, but not the nab-paclitaxel treated groups (**Figure 7**).

Table 1. Multivariate regression models with interaction test between CAV1/CAV2 and HR status

Endpoint	CAV-1 TNBC OR/HR (95%CI)	CAV-1 HR-positive OR/HR (95%CI)	P	CAV-2 TNBC OR/HR (95%CI)	CAV-2 HR-positive OR/HR (95%CI)	P
ypT0/ypN0	0.85 (0.31-2.33)	0.69 (0.28-1.70)	0.770	1.33 (0.48-3.68)	0.67 (0.26-1.70)	0.327
DFS	2.65 (0.95-7.41)	1.14 (0.61-2.14)	0.169	4.40 (1.44-13.46)	1.60 (0.84-3.05)	0.125
OS	3.10 (0.61-15.61)	1.80 (0.82-3.94)	0.551	9.38 (1.13-77.75)	2.05 (0.92-4.58)	0.186

Abbreviations: OR, Odds Ratio; HR, Hazard Ratio.

Table 2. Multivariate regression models with interaction test between arm (nab-paclitaxel vs paclitaxel) and CAV-1/CAV-2

Endpoint	CAV-1 low OR/HR (95%CI)	CAV-1 high OR/HR (95%CI)	P	CAV-2 low OR/HR (95%CI)	CAV-2 high OR/HR (95%CI)	P
ypT0/ypN0	0.94 (0.38-2.34)	4.92 (1.70-14.22)	**0.023**	0.95 (0.39-2.29)	5.39 (1.76-16.47)	**0.019**
DFS	1.37 (0.62-3.04)	0.53 (0.27-1.05)	0.077	0.96 (0.40-2.27)	0.70 (0.36-1.34)	0.575
OS	2.47 (0.78-7.80)	0.29 (0.11-0.77)	**0.005**	1.21 (0.36-4.06)	0.47 (0.20-1.10)	0.215

Abbreviations: OR, Odds Ratio; HR, Hazard Ratio.

Figure 2. Correlation between CAV1 and CAV2

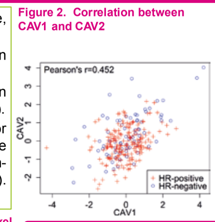


Figure 3. CAV1/CAV2 expression in HR-positive and TNBC patients

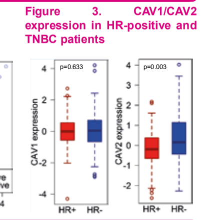


Figure 4. DFS according to CAV1 (A) and CAV2 (B)

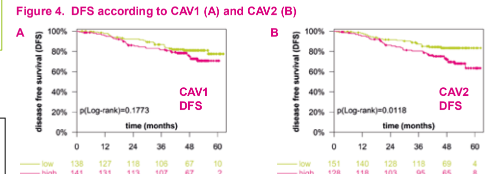


Figure 5. OS according to CAV1 (A) and CAV2 (B)

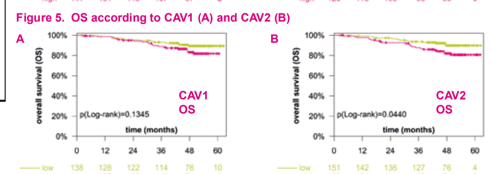


Figure 6. DFS with nab-paclitaxel vs paclitaxel according to CAV1 (A) and CAV2 (B) low vs high

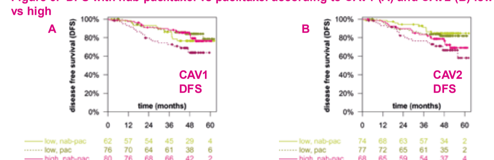
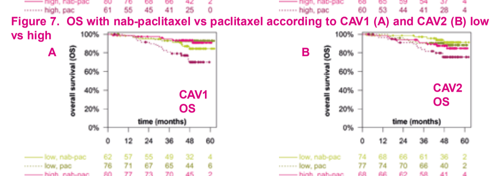


Figure 7. OS with nab-paclitaxel vs paclitaxel according to CAV1 (A) and CAV2 (B) low vs high



Conclusions

- CAV1 and CAV2 RNA expression are correlated in breast cancer.
- The odds of obtaining pCR with nab-paclitaxel treatment were improved for patients with high CAV1/2 expression.
- Higher CAV2 expression is associated with worse DFS and OS in all patients.
- For patients who receive paclitaxel-based treatment, high CAV1/2 expression is associated with worse DFS and OS.
- For patients who received nab-paclitaxel-based treatment, no significant differences in DFS and OS based on CAV1/2 expression were noted.
- **Taken together, these findings suggest that CAV1/2 expression may offset the negative prognostic factor associated with higher CAV1/2 expression in patients treated with nab-paclitaxel regimens by enhancing the efficacy of treatment, perhaps through increased nab-paclitaxel endocytosis/transcytosis. These results are hypothesis generating and further data are needed.**

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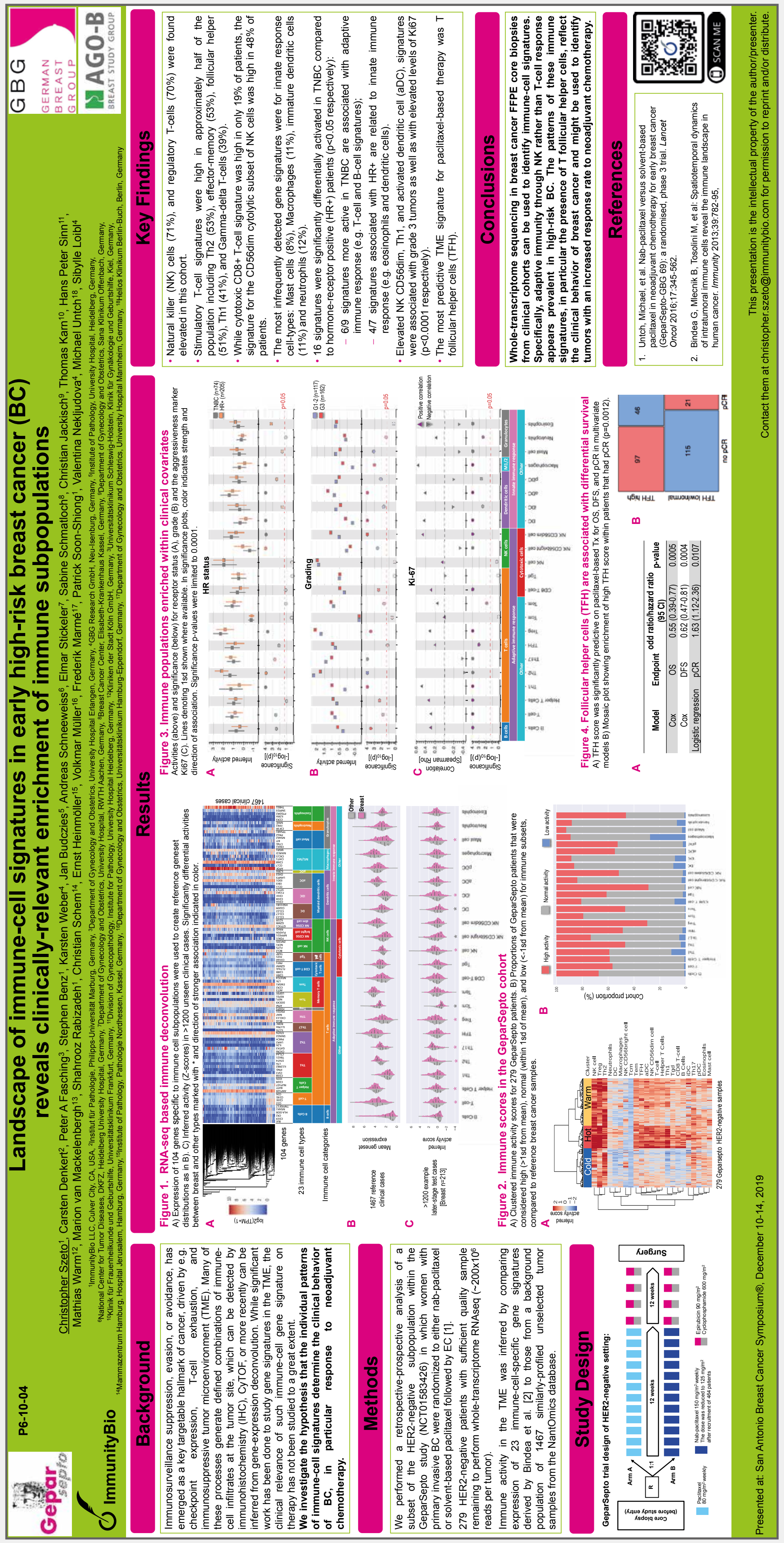
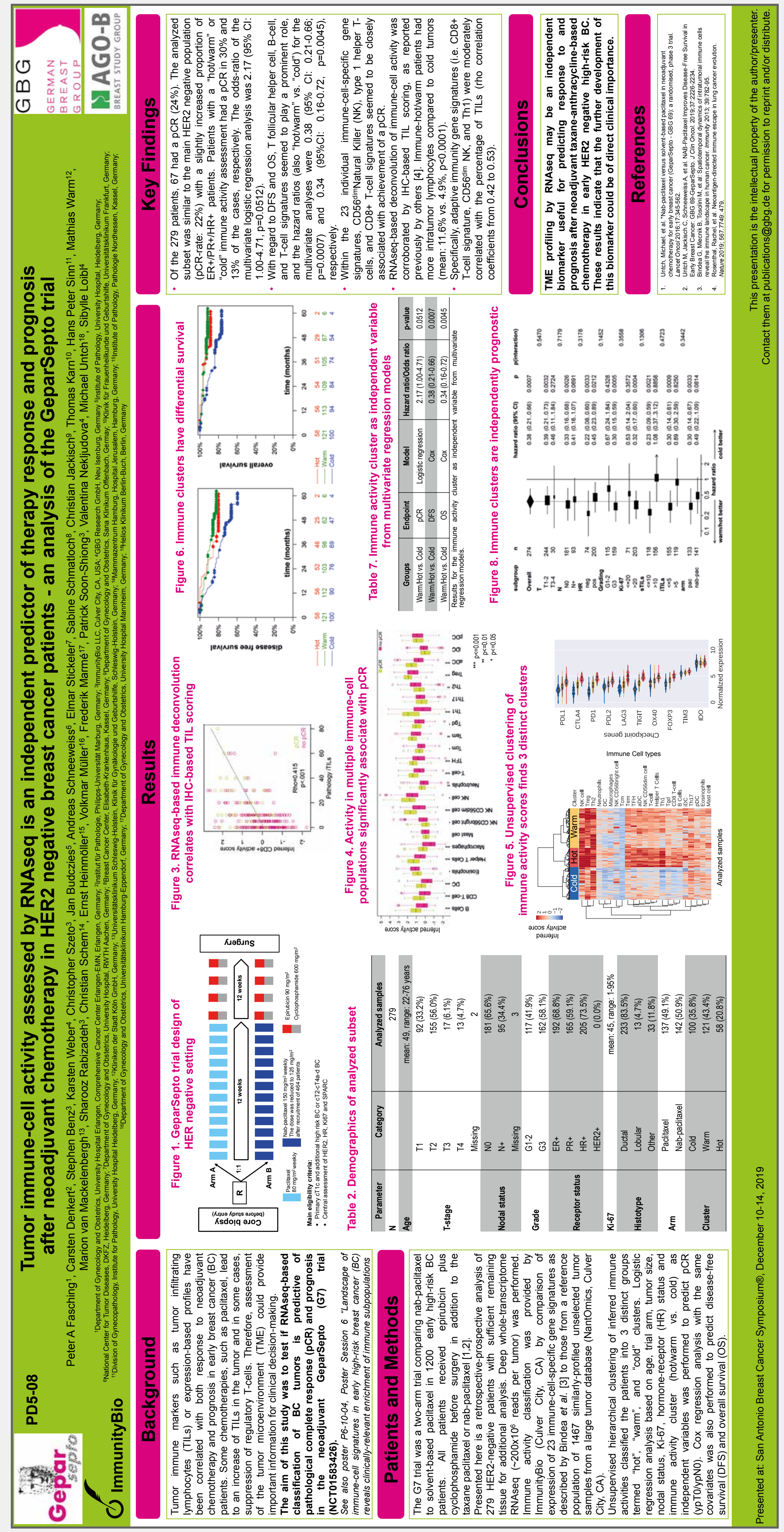
Presented at: San Antonio Breast Cancer Symposium, December 2019


P6-10-04
Landscape of immune-cell signatures in early high-risk breast cancer (BC) reveals clinically-relevant enrichment of immune subpopulations
Background
Methods
Study Design
Results
Key Findings
Conclusions
References
Presented at: San Antonio Breast Cancer Symposium®, December 10-14, 2019


PD5-08
Tumor immune-cell activity assessed by RNAseq is an independent predictor of therapy response and prognosis after neoadjuvant chemotherapy in HER2 negative breast cancer patients - an analysis of the GeparSepto trial
Background
Patients and Methods
Results
Key Findings
Conclusions
References
Presented at: San Antonio Breast Cancer Symposium®, December 10-14, 2019

New Study Concepts

Interview with Dr. Mattea Reinisch, coordinating investigator of the APPALACHES trial in Germany

A Phase II study of Adjuvant PALbociclib as an Alternative to CHemotherapy in Elderly patientS with high-risk ER+/HER2- early breast cancer (APPALACHES)

Dr. Mattea Reinisch
Kliniken Essen-Mitte

APPALACHES (EORTC 1745 ETF BCG) is a two-arm, open-label, multicenter, randomized phase II study in elderly patients with stage II/III, estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) early breast cancer for whom treatment with chemotherapy is indicated.

Primary objective: to assess the efficacy of the combination of at least 5 year endocrine therapy and 2 years of palbociclib as adjuvant systemic treatment instead of adjuvant chemotherapy followed by endocrine therapy in older patients with stage II-III ER+/HER2- early breast cancer.

1. What are the advantages of combining CDK4/6 inhibitors with endocrine therapy in patients with ER+ / HER2- breast cancer?

CDK4/6 inhibitors have fundamentally changed the therapy landscape of patients with advanced or metastatic hormone receptor (HR)-positive breast cancer. For example, the results from PALOMA-1 and PALOMA-2 trials demonstrated a significant improvement of progression-free survival (PFS) in patients receiving palbociclib plus letrozole compared with patients receiving letrozole alone. Based on these findings, the FDA and the EMA have approved the use of palbociclip in combination with letrozole for the treatment of postmenopausal women with ER-positive/HER2-negative advanced breast cancer as initial endocrine-based therapy for their metastatic disease. Recently, a significant benefit of CDK4/6 inhibitors on overall survival (OS) for patients with HR-positive/HER2-negative advanced breast cancer has been demonstrated (MONALEESA-3 and 7 and MONARCH 2). Therefore, the combination of CDK4/6 inhibitors with endocrine therapy could be a new standard therapy in this group of patients with an advantage in all subgroups. Furthermore, quality of life (QoL) substudies which accompanied the phase III studies (PALOMA, MONALEESA and MONARCH) showed that the addition of the CDK 4/6 inhibitors do not impair the QoL of the patients.

2. Could you further discuss the use of palbociclib in the treatment of advanced or metastatic ER+/HER2- breast cancer?

For many doctors and patients, OS is the most important endpoint. Therefore, we are happy that recent data from MONALEESA-3 plus MONALEESA-7 trials investigating the efficacy of ribociclib plus fulvestrant as well as from MONARCH 2 study evaluating abemaciclib plus fulvestrant for treatment of advanced or metastatic breast cancer has reported a significant improvement of this endpoint. Hence, these results provide more evidence for making a confident treatment choice in both, the first and second-line settings. Safety profiles in these studies were consistent with observations from previous clinical trials. The visceral crisis with an imminent organ failure is the only one reason to start with chemotherapy instead. However, patients with visceral metastasis also benefit from the use of CDK 4/6 inhibitors. The combination of palbociclib and adjuvant endocrine therapy could therefore be an alternative to adjuvant chemotherapy with comparable efficacy and less toxicity in older patients with high-risk ER+/HER2- early breast cancer.

3. What is the risk-benefit assessment for APPALACHES trial?

APPALACHES study will include patients ≥70 years old with a high risk of relapse in case of inadequate treatment. There is no published data documenting the tolerability of two years of palbociclib among older patients in the adjuvant setting. Therefore, a safety interim analysis will be conducted based on treatment discontinuation rate in the experimental arm. A risk of undertreatment for patients only being treated according to their chronological age should also be taken into consideration. Furthermore, recent data from the phase II CORALLEEN trial investigating letrozol plus ribociclib as neoadjuvant treatment for postmenopausal luminal B/HER2-negative breast cancer patients presented at the SABCS 2019 support the potential value of CDK4/6 inhibitors to help de-escalate chemotherapy in high-risk breast cancer. A significant risk of toxicity is expected in the control group with adjuvant chemotherapy that can be mitigated by the systematic use of granulocyte-colony stimulating factor (G-CSF) or Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) after each cycle of chemotherapy. In addition, the APPALACHES study offers a new and modern treatment approach in this hard to treat cohort of breast cancer patients.

4. Is there any way to predict which patients will benefit from targeted therapies with CDK4/6 inhibitors?

As far as we know, attempts to identify molecular biomarkers that predict response or resistance to CDK4/6 inhibitors in breast cancers have failed to identify clear candidates. More recently, analysis of circulating cell-free DNA samples from MONALEESA-2 study showed negative prognostic implications of PIK3CA and TP53 mutations in patients with advanced ER-positive breast cancer. As older patients have a higher risk of adverse events when receiving adjuvant chemotherapy compared to younger patients, the APPALACHES translational research program aims to evaluate biomarkers of aging during treatment and their correlation with treatment-related toxicity.

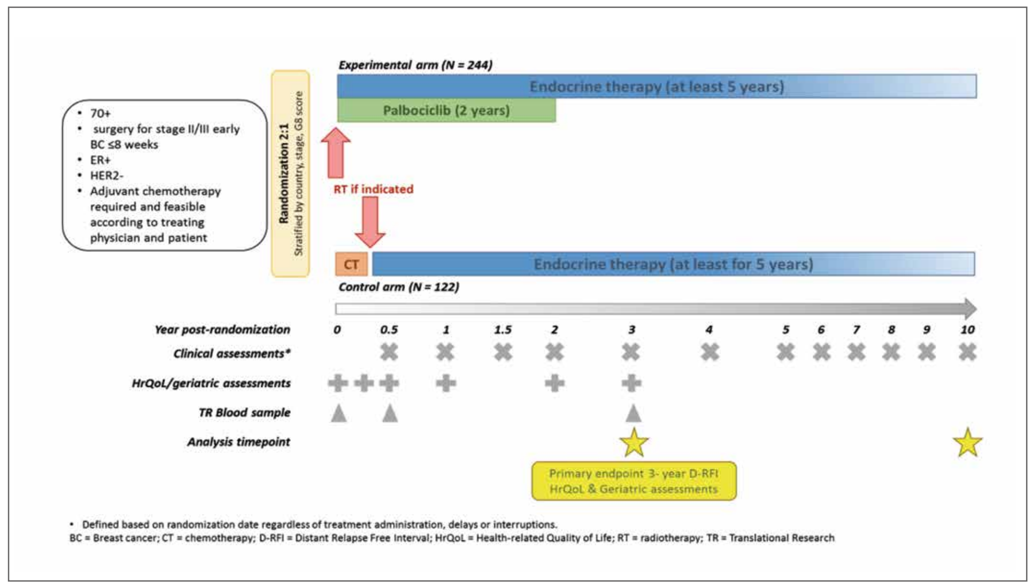


Figure 1: Study design of the APPALACHES study

Interview with Prof. Dr. Jörg Heil, coordinating investigator of the TAXIS trial in Germany

Tailored AXIllary Surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS)

Prof. Dr. Jörg Heil
Universitätsklinikum Heidelberg

TAXIS (SAKK 23/16/IBCSG 57-18/ABCSG-53) is an international, multicenter, randomized phase III trial to evaluate the optimal treatment for breast cancer patients with confirmed nodal disease at first diagnosis in terms of surgery and radiotherapy. In particular, it will investigate the value of tailored axillary surgery (TAS), a new technique that aims at selectively removing the positive lymph nodes – either before any systemic treatment or after neoadjuvant systemic treatment.

Primary objective: to show that TAS and axillary radiotherapy (RT) is non-inferior to axillary lymph node dissection (ALND) in terms of disease-free survival of breast cancer patients with positive nodes at first presentation.

1. What is the rationale of TAXIS trial for node-positive breast cancer patients in the era of effective systemic therapy and extended regional nodal irradiation?

In mean about 10 non-cancerous lymph nodes are removed while performing a classical axillary lymph node dissection in node positive patients. There is supporting evidence that the removal of non-cancerous lymph nodes during a classical axillary lymph node dissection is without benefit for the patient. Moreover, there is an increasing body of literature showing that leaving some cancerous lymph nodes behind will not decrease survival of the patients if adequate or even escalated adjuvant treatment regimes will be applied. The rationale of TAXIS is that surgery is efficient in macroscopic disease (what will be adequately removed by surgery) and radiotherapy is efficient in microscopic disease.

2. What needs special attention in the design of the TAXIS trial?

Special attention needs to be put on the fact that intensive collaboration between breast diagnostics, breast surgery and radiation oncology is necessary. Nodal status has to be defined exactly by imaging before treatment, clip marker placed and selectively removed by surgery. Moreover the trial design is "pragmatic", meaning that many routine procedures may be performed on every day basis.

3. What are the future perspectives for treatment of breast cancer patients with confirmed nodal disease at first diagnosis in terms of surgery and radiotherapy?

The majority of patients with confirmed nodal disease have 1-2 metastatic lymph nodes. For these patients we might assume that surgery can be more targeted and less invasive with adapted radiotherapy concepts.

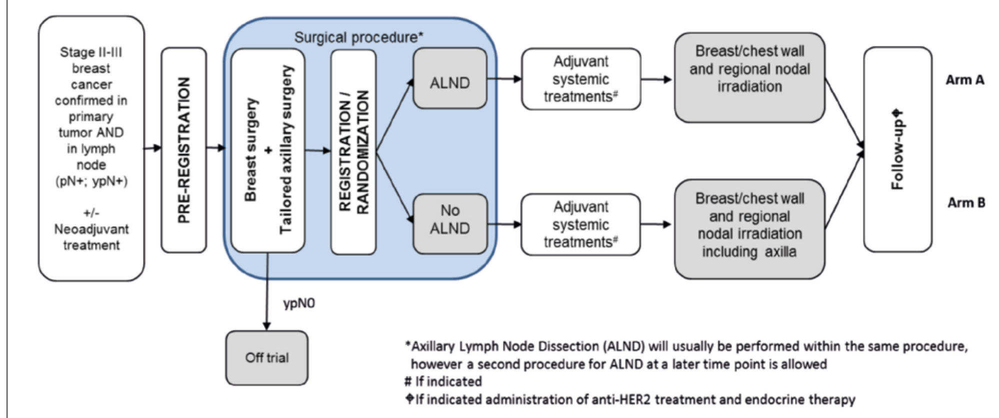


Figure 1: Study design of the TAXIS study

SASCIA

Interview with Prof. Dr. Frederik Marmé, coordinating investigator of the SASCIA trial in Germany

Phase III postneoadjuvant study evaluating Sacituzumab Govitecan, an Antibody Drug Conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment - SASCIA

Prof. Dr. Frederik Marmé
University Hospital Mannheim

SASCIA is a prospective, multicenter, randomized, open-label, parallel group, phase III study to evaluate the efficacy and safety of postneoadjuvant treatment with Sacituzumab govitecan compared to treatment of physician's choice with capecitabine or platinum-based chemotherapy or observation in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment.

Primary objective: to compare invasive disease free survival (iDFS) between patients treated with sacituzumab govitecan versus treatment of physician's choice.

1. Why is the postneoadjuvant approach in breast cancer patients so important?

The postneoadjuvant approach uses one of the most compelling advantages of neoadjuvant chemotherapy, which is the opportunity to observe response to therapy. It thereby allows identifying patients with an extremely good prognosis, for whom treatment might eventually be de-escalated, but also those with an extremely poor prognosis who require further novel therapeutic strategies. Thus, the postneoadjuvant approach offers therapy only to those who could really benefit, avoiding overtreatment. In turn, this provides an opportunity to design randomized clinical trials with a limited number of patients and therefore reaching the endpoints in a shorter period of time compared to the adjuvant setting.

2. Sacituzumab govitecan is a new antibody-drug conjugate, can you tell us what is the peculiarity of using such a drug?

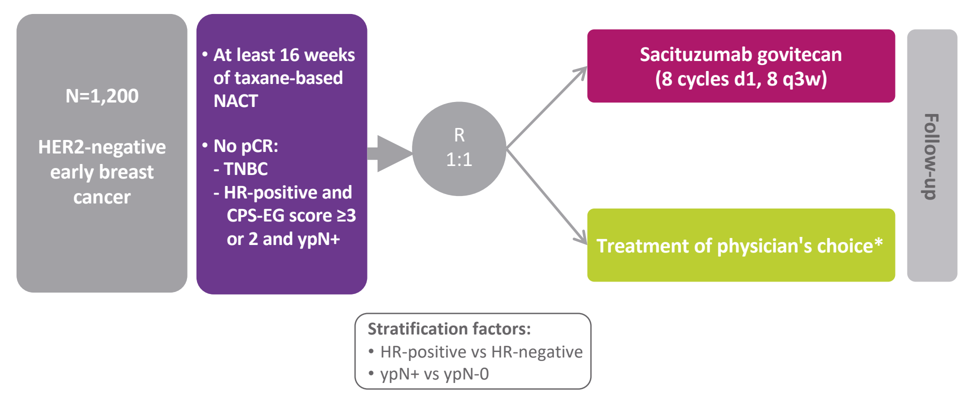
In general, antibody-drug conjugates (ADCs) are a new class of targeted biopharmaceutical drugs that combine monoclonal antibodies specific to surface antigens present on tumor cells with highly potent anti-cancer agents linked via a chemical linker. This allows delivering of cytotoxic agents in a targeted fashion into tumor cells whilst sparing systemic side effects of chemotherapy. Sacituzumab govitecan as an ADC is composed of the active metabolite of irinotecan, SN-38, linked with a therapeutic monoclonal antibody targeted against TROP-2, a self-surface glycoprotein that is differentially expressed on tumor cells with the highest expression in triple-negative and luminal breast cancer cells. In contrast, the TROP-2 expression is low in normal cells. The Sacituzumab govitecan has been demonstrated to provide compelling activity against both triple-negative and luminal breast cancer in heavily pretreated patient in clinical trials - even after immunotherapy and CDK4/6 inhibitors.

3. What is the study design of the SASCIA trial?

In the SASCIA, HER-2-negative patients at high risk of relapse after neoadjuvant chemotherapy will be randomized to either 8 cycles of sacituzumab govitecan or treatment of physician's choice, which can consist of 8 cycles of capecitabine or platinum-based chemotherapy as well as observation only. In addition, patients with ER-positive disease will receive standard of care endocrine therapy. The trial includes both, ER-negative (TNBC) as well as ER-positive patients. TNBC patients will be included on the basis of not having achieved a pCR whereas the ER-positive patients must not have achieved a pCR and in addition need to have a CPS+EG score of ≥ 3 or 2 with ypN+.

4. Are you going to investigate the tumor expression of potential biomarkers that may predict response to Sacituzumab govitecan?

Nowadays it is impossible to conduct clinical trials including targeted agents like ADCs without investigating potential predictive factors. Within the SASCIA we will investigate the role of TROP-2 expression as well as others mRNA and protein based biomarkers as potential predictive factors. In addition, the role of circulating tumor DNA (ctDNA) as an early response marker as well as polymorphisms which could predict efficacy and toxicity will be investigated to help to tailor this therapy further.



*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation.
Background therapy: in patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

Figure 1: Study design of the SASCIA study

Recruiting Studies

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A Phase III, Multicenter, Randomized, Open-label Study Comparing Atezolizumab (Anti PD-L1 Antibody) In Combination With Adjuvant Anthracycline/Taxane-Based Chemotherapy Versus Chemotherapy Alone In Patients With Operable Triple-Negative Breast Cancer

NCT03498716

ALEXANDRA/Impassion030 (BIG 16-05/AFT-27/WO39391) is an international, multicenter, randomized, open-label, controlled phase III trial that will recruit approximately 2,300 patients at approximately 370-450 sites globally within 4 years.

Background

Patients with TNBCs exhibit a poor clinical outcome, generally with rapid progression and a shorter time to local and distant relapse (Dent R et al. Clin Cancer Res 2007). Three-year invasive disease-free survival (iDFS) rates of 81 % have been reported for patients with TNBC who have received adjuvant anthracycline/taxane therapy (Sparano JA et al. J Clin Oncol 2015). Upon systemic relapse, patients with metastatic TNBC have poor outcomes, with rapid progression and decreased overall survival (OS) (Kassam F et al. Clin Breast Cancer 2009). Because TNBC does not currently have specific targeted agents approved for use in the early setting it is treated primarily with chemotherapy.

Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in an improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). TNBC may be more immunogenic compare to other breast cancer subtypes and promising clinical activity has been reported with atezolizumab in phase I/Ib metastatic TNBC trials (Adams S et al JAMA Oncol 2019). Furthermore, the results of the randomized phase III IMpassion130 study demonstrated enhanced anti-tumor activity when atezolizumab was co-administered with chemotherapy in the first line metastatic setting, with benefit mainly observed in PD-L-positive cohort. Atezolizumab has been generally well tolerated. Atezolizumab in combination with taxanes (including paclitaxel and nab-paclitaxel) has shown toxicities similar to those experienced with paclitaxel or nab-paclitaxel alone and have generally been manageable. The benefit-risk ratio for atezolizumab in combination with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide is expected to be acceptable in this setting.

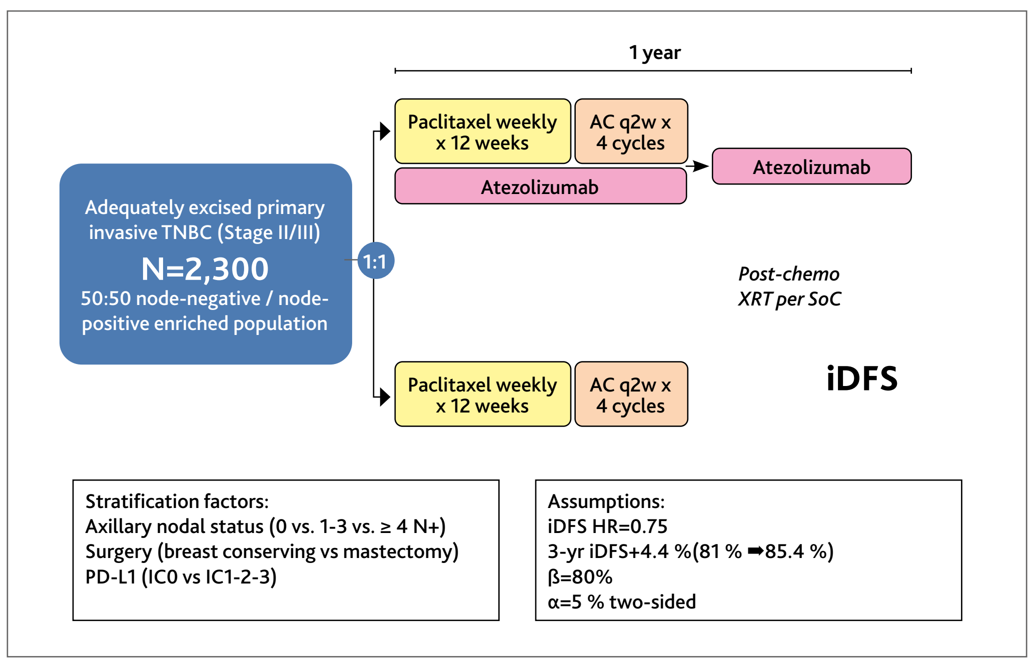

Figure1: Study design of the ALEXANDRA/IMpassion030 study

Study design and objectives:

ALEXANDRA/Impassion030 primarily aims to evaluate the efficacy, safety, and pharmacokinetic profile of adjuvant atezolizumab plus standard chemotherapy versus chemotherapy alone in early TNBC. Patients with operable stage II or III TNBC, confirmed by central pathology review, will be randomized to receive either adjuvant atezolizumab in combination with paclitaxel followed by atezolizumab, dose-dense doxorubicin or epirubicin (investigator's choice), and cyclophosphamide (atezolizumab+T-AC/EC) or paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide alone (T-AC/EC). Patients are stratified by type of surgery, nodal status, and centrally assessed PD-L1 status. Adjuvant treatment will consist of weekly paclitaxel 80 mg/m² for 12 weeks followed by dose dense anthracycline (epirubicin 90 mg/m2 or doxorubicin 60 mg/m²) and cyclophosphamide 600 mg/m² for 4 doses every 2 weeks or the same chemotherapy regimen (T-AC/EC) given concomitantly with atezolizumab 840 mg every 2 weeks followed by maintenance atezolizumab 1,200 mg every 3 weeks until completion of 1 year of atezolizumab. The primary endpoint is to evaluate iDFS of adjuvant atezolizumab+T-AC/EC compared with T-AC/EC alone in patients with TNBC. Secondary endpoints include iDFS by PD-L1 and lymph node status, overall survival, safety, patient functioning and health related quality of life (HRQoL). Furthermore, tumor tissue and blood samples will be collected for biomarker research.

Study report:

ALEXANDRA/Impassion030 worldwide recruitment started in July 2018 and in Germany in June 2019, respectively. As of 31st December 2019, there are 5 patients enrolled in the study at the German sites [1-2]. Enrollment is targeted to be completed at QIV 2021.

Publications:

1. McArthur HL, Ignatiadis M, Guillaume S et al. ALEXANDRA/IMpassion030: A phase III study of standard adjuvant chemotherapy with or without atezolizumab in early-stage triple negative breast cancer. J Clin Oncol 2019; 37, no.15_suppl, TPS598.
2. Ignatiadis M, McArthur HL, Bailey A et al. ALEXANDRA/IMpassion030: A phase III study of standard adjuvant chemotherapy with or without atezolizumab in early stage triple negative breast cancer. Ann Oncol 2019; Volume 30, Issue Supplement_5, 289TiP.

We are thanking all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients and by providing biomaterial in a timely manner.

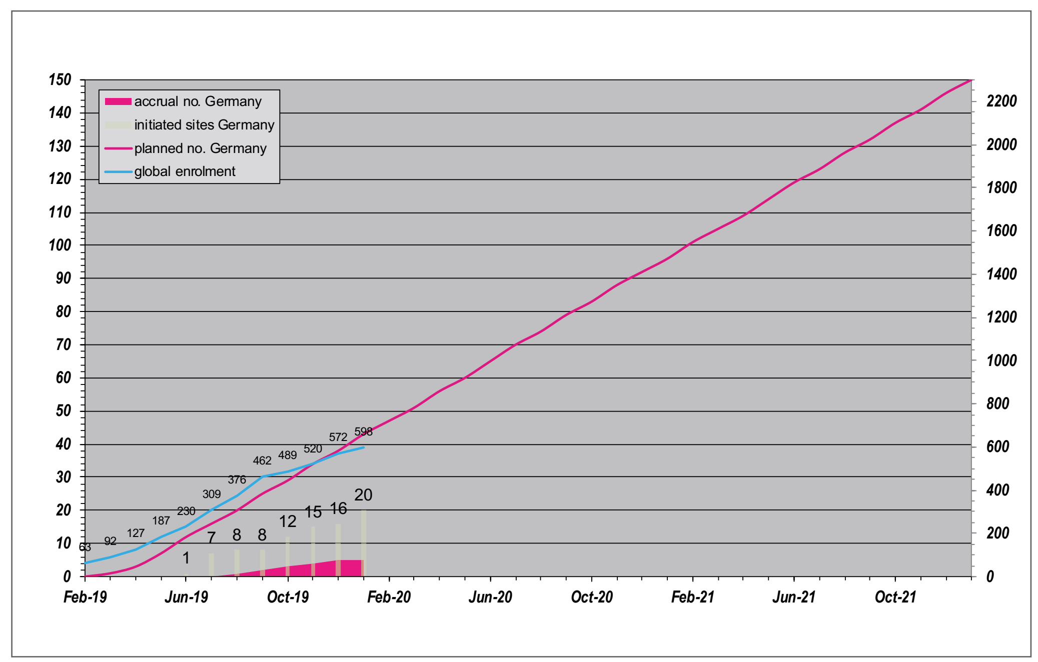

Figure 2: ALEXANDRA/Impassion030 recruitment as of 31st December 2019

COLLABORATING STUDY GROUPS:

SPONSOR:
Hoffmann-La Roche

STUDY CHAIR GERMANY:
Prof. Dr. Marcus Schmidt
Universitätsfrauenklinik
Mainz

TAMENDOX

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GBG 91: TAMENDOX

Genotype and phenotype guided supplementation of TAMoxifen standard therapy with ENDOXifen in breast cancer patients

NCT03931928

TAMENDOX (IKP275) is a prospective, multicenter, single-blind, three treatment arms, placebo-controlled, pharmacogenetics/pharmacokinetic phase II study that will recruit 504 patients from approximately 40 sites in Germany.

Background

The selective estrogen receptor modulator tamoxifen is a non-steroidal antiestrogen which was approved for the treatment of hormone-receptor positive breast cancer in the 1970s. Today tamoxifen is the sole labelled treatment for premenopausal patients but postmenopausal patients have the choice of an aromatase inhibitor (AI) for the inhibition of peripheral estrogen synthesis. Despite widespread use of AIs in postmenopausal patients and high-risk premenopausal patients (in combination with ovarian function suppression), tamoxifen remains a standard-of-care due to its high efficacy, tolerable toxicity profile and potential AI contraindications. While adjuvant endocrine therapy with tamoxifen reduces recurrences risk by half, approximately one third of patients will suffer from disease relapse (Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Lancet 2011).

By integrating the new knowledge of the variable tamoxifen bioactivation into an individualized tamoxifen treatment scheme, improved efficacy could be gained by the supplementation of standard tamoxifen with individualized doses of (Z)-endoxifen (Z-4-hydroxy-N-desmethyl-tamoxifen), the major active metabolite of tamoxifen. Of note, the formation of (Z)-endoxifen is mainly catalyzed by the highly polymorphic CYP2D6 enzyme and depends on genetic variation of the encoding gene. About 8 % of the European population are CYP2D6 poor metabolizers (PM) due to the lack of functional alleles; heterozygous non-functional allele carriers and those homozygous for reduced-function alleles are termed intermediate metabolizers (IM) and make up ~40 % (Saladores et al. Expert Rev Mol Diagn 2013; Zanger et al. Pharmacol Ther 2013).

Independent clinical studies demonstrated that genetically determined low (Z)-endoxifen levels predict higher relapse rates in pre- and postmenopausal women (Madlensky et al. Clin Pharmacol Ther 2011; Saladores et al. Pharmacogenomics J 2015; Helland et al. Breast Cancer Res 2017). The available evidence has recently been addressed by the Clinical Pharmacogenetics Implementation Consortium (CPIC®) (Goetz et al. Clin Pharmacol Ther 2018). The concept TAMENDOX study is based on a different novel approach which pursues the supplementation of standard adjuvant tamoxifen (20mg/d) with only low doses of (Z)-endoxifen (up to 3 mg/d). In collaboration with Bayer, the doses used in this study have been calculated and validated by physiology-based pharmacokinetic (PBPK) modeling (Dickschen et al. Front Pharmacol 2012; Dickschen et al. Springerplus 2014). (Z)-endoxifen concentrations as found in normal metabolizers (EM) can be attained by IM and PM patients in this way. Evidence from in vitro modeling experiments of a premenopausal setting have already demonstrated that breast cancer cell killing can be improved by adding endoxifen to standard tamoxifen (Maximov et al. J Natl Cancer Inst 2014).

(Z)-Endoxifen is the major active metabolite of tamoxifen with an approximately 100 times higher affinity to the estrogen receptor α (ER-α) than tamoxifen itself. The primary pharmacodynamic mode of action is the antagonization of estrogen-bound ER, leading to the inhibition of estrogen-dependent genomic signalling and inhibition of tumor cell proliferation. A direct effect on the ER in humans has been demonstrated by PET/CT imaging in a phase I trial of (Z)-endoxifen dose escalation (40-300mg for 28 days) in patients with refractory ER-positive solid tumors, including breast: an average decline of 33 % radioactive-liganded ER has been found upon (Z)-endoxifen hydrochloride administration compared to baseline. These findings supported the strong binding of endoxifen to the ER and the feasibility of PET-based imaging as a pharmacodynamic biomarker for (Z)-endoxifen/ER binding in vivo.

Tamoxifen remains an important endocrine treatment option for premenopausal patients and those postmenopausal patients with contraindications for AI. Nonetheless, the high long-term relapse rate presents a severe limitation in current treatment. Compromised bioactivation of tamoxifen to its active metabolite (Z)-endoxifen in patients with reduced CYP2D6 activity likely contributes to this limitation, as a 2-fold and 1.4-fold increased risk for disease recurrence for PM and IM patients compared to EM patients has been observed. Thus, effective therapeutic (Z)-endoxifen levels can be achieved by supplementation of standard tamoxifen therapy with a low dose of (Z)-endoxifen.

The TAMENDOX trial is designed to show that (Z)-endoxifen supplementation in IM and PM patients will increase their steady state plasma

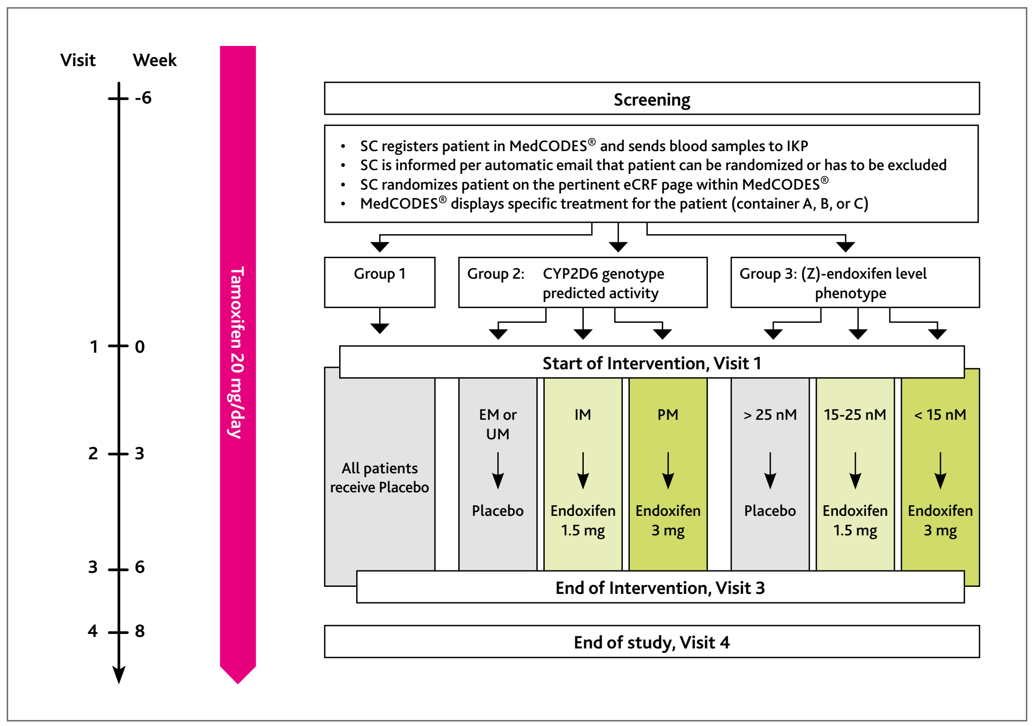

Figure 1: TAMENDOX study design

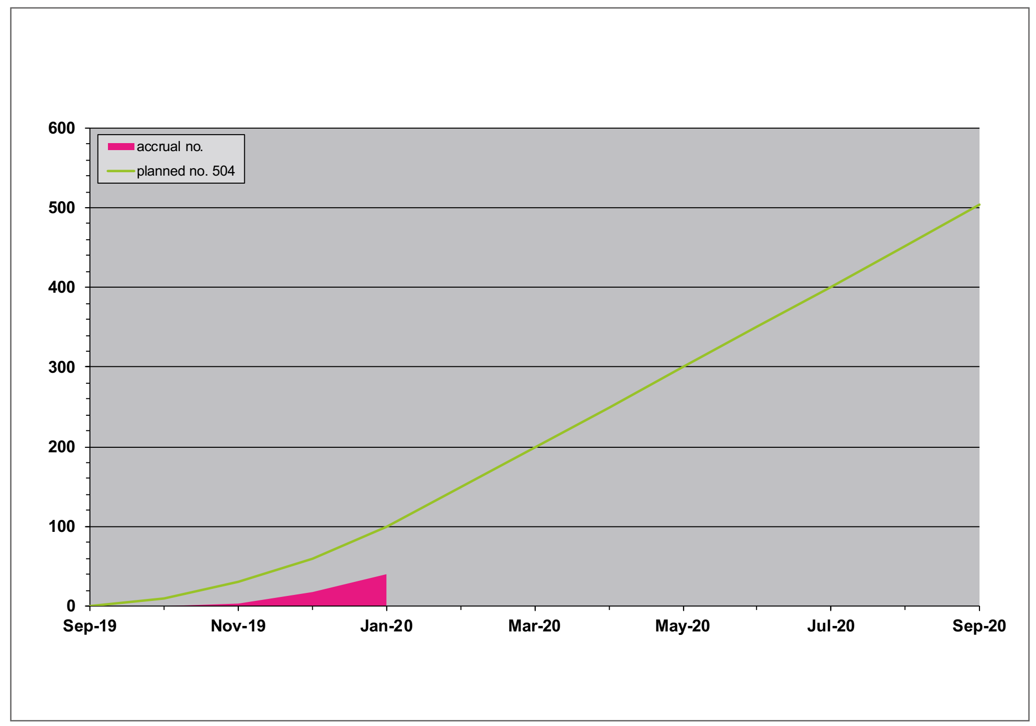

Figure 2: TAMENDOX recruitment as of 31st December 2019

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

IKP STUTTGART

SPONSOR:
Robert Bosch Gesellschaft für Medizinische Forschung mbH

COORDINATING INVESTIGATOR:
Prof. Dr. Matthias Schwab
Dr. Margarete Fischer-Bosch-Institut für Klinische Pharmakologie, Stuttgart

concentrations of (Z)-endoxifen to the level found in patients without compromised metabolism, i.e. EM or ultrarapid metabolizers (UM). The trial is not designed to evaluate outcome measures of (Z)-endoxifen supplementation in tamoxifen treated patients.

Study design and objectives

TAMENDOX aims to evaluate the supplementation of tamoxifen with low dose (Z)-endoxifen to overcome the impaired bioactivation of tamoxifen to its active metabolite (Z)-endoxifen in patients with compromised CYP2D6 activity. Pre- and postmenopausal women with ductal carcinoma in situ (DCIS) or Stage I, IIA, IIB or IIIA invasive BC who have received at least three months standard tamoxifen treatment before baseline visit are eligible.
Tamoxifen treatment (20 mg/day) for at least three months in premenopausal and postmenopausal patients is mandatory prior to the start of the study, and will be continued during intervention period without change of dosage. During the intervention, a daily oral dose of (Z)-endoxifen or placebo will be given according to CYP2D6 genotype or (Z)-endoxifen plasma concentrations (phenotype): group 1 (control group) will receive placebo independent of CYP2D6 genotype or (Z)-endoxifen plasma concentration; group 2 will receive (Z)-endoxifen dosed according to CYP2D6 "genotype" (i.e. genotype predicted IM or PM activity) or placebo (genotype predicted EM / UM), and group 3 will receive (Z)-endoxifen dosed according to (Z)-endoxifen steady state plasma concentrations (phenotype) at screening (i.e. ≤ 15 nM or > 15 and ≤ 25 nM) under tamoxifen treatment with 20 mg/day or placebo (> 25 nM). The intervention period will be 6 weeks to assure steady-state levels.
Primary objective is to increase (Z)-endoxifen steady-state concentrations in patients with compromised CYP2D6 activity to levels observed in patients with full CYP2D6 activity. The target concentration is > 32 nM.
Secondary objectives are 1) to increase (Z)-endoxifen steady state concentrations in patients with CYP2D6 genotype predicted PM activity to levels observed in patients with full CYP2D6 activity by supplementation with 3 mg/day (Z)-endoxifen (> 32 nM); 2) to increase (Z)-endoxifen steady state concentrations in patients with CYP2D6 genotype predicted IM activity to levels observed in patients with full CYP2D6 activity by supplementation with 1.5 mg/day (Z)-endoxifen (> 32 nM); 3) to increase (Z)-endoxifen steady state concentrations in patients with basal (Z)-endoxifen plasma levels ≤ 15 nM to levels observed in patients with full CYP2D6 activity by supplementation with 3 mg/day (Z)-endoxifen (> 32 nM); 4) to increase (Z)-endoxifen steady state concentrations in patients with basal (Z)-endoxifen plasma levels > 15 nM and ≤ 25 nM to levels observed in patients with full CYP2D6 activity by supplementation with 1.5 mg/day (Z)-endoxifen (> 32 nM); 5) to assess safety of low dose (Z)-endoxifen supplementation; 6) to assess and compare steady state plasma levels of tamoxifen, desmethyltamoxifen, 4-hydroxtamoxifen, and possible other tamoxifen metabolites between the intervention groups and control group.

Study report:

The TAMENDOX study started recruitment on 4th of September 2019 and the first patient was randomized on 1st of October 2019. As of 31st December 2019, there are 40 patients enrolled in the study. The duration of the total study period from inclusion (screening visit) until end of study (visit 4) will be up to 14 weeks per patient. Patient recruitment is anticipated to last one year.

GBG 96: GeparDouze

A randomized, double-blind, phase III clinical trial of neoadjuvant chemotherapy with atezolizumab or placebo in patients with triple-negative breast cancer followed by adjuvant continuation of atezolizumab or placebo

NCT03281954

GeparDouze (NSABP B-59) is an international, multicenter, prospective, randomized, double-blind, phase III trial that will recruit 1,520 patients from up to 300 sites in approximately 11 countries within about 38 months.

Background

Triple-negative breast cancer (TNBC) is associated with relatively higher pathologic complete response (pCR) rate following neoadjuvant chemotherapy (NACT) and patients who achieved a pCR have a favorable prognosis (Liedtke C et al. J Clin Oncol 2008; Hahnen et al. JAMA Oncol 2017). However, women with residual TNBC following NACT have higher risk for recurrence than those with other subtypes of breast cancer (BC) (Cortazar P et al. Lancet 2014). Therefore, there is a compelling need to identify additional therapies to increase the percentage of patients with pCR and improve long term outcomes.
A relatively mature avenue of research has been the incorporation of additional agents such as carboplatin to standard anthracycline-based regimens in patients with stage II and III TNBC. In the neoadjuvant GeparSixto study, the pCR rate among patients with TNBC was increased from 36.9 % (95 % CI, 29.4-44.5) in patients not receiving carboplatin to 53.2 % (95 % CI 54.4-60.9) in patients receiving carboplatin (p=0.005) (von Minckwitz et al. Lancet Oncol 2014). In addition, the germline *BRCA*1/2 mutations and RAD mutations as well as family history of breast and/or ovarian cancer could not identify patients most likely to benefit from carboplatin (Hahnen et al. JAMA Oncol 2017). Long-term survival analysis of GeparSixto study showed that after a median follow-up of 47.3 months, TNBC patients treated with carboplatin had a significantly longer disease-free survival than those without (HR 0.56; 95 %CI [0.34-0.93]; p=0.024 (Untch et al. Ann Oncol 2017). In the BrighTNess study a significant improvement of pCR was demonstrated in patients treated with carboplatin, veliparib and paclitaxel compared to patients receiving paclitaxel alone (53 % vs 31 %, p < 0.001) but not to those receiving paclitaxel plus carboplatin (53 % vs 58 %, p=0.36) (Loibl S et al. Lancet Oncol 2018).
More recent approaches have been evaluating immune therapy with inhibitors of the programmed death–1 (PD-1)/programmed death–ligand 1 (PD-L1) interaction in combination with chemotherapy. One of these PD-1/PD-L1 inhibitors is atezolizumab, a humanized immunoglobulin (Ig) G1 monoclonal antibody. It targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7.1 (also known as CD80), both of which function as inhibitory receptors expressed on T-cells. Atezolizumab is being studied as a single agent as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy. Results of the I-SPY2 trial (Nanda et al. J Clin Oncol 2017) demonstrated that the PD-1/PD-L1 inhibitors co-administered with chemotherapy can increase pCR over chemotherapy alone. The phase 1b study of atezolizumab and nab-paclitaxel in patients with metastatic TNBC also reported a very high response rate (Adams S et al. J Clin Oncol 2016).
Given these results, the GeparDouze trial aims to explore the efficacy and safety of neoadjuvant and adjuvant administration of atezolizumab/placebo in patients with high-risk TNBC. It is hypothesied that the cohort receiving atezolizumab will have a higher pCR rate, and this increased activity will result in improved event-free survival (EFS).

Study design and objectives:

GeparDouze aims to evaluate efficacy and safety of neoadjuvant/adjuvant administration of atezolizumab/placebo in TNBC patients with a sequential regimen of neoadjuvant atezolizumab/placebo administered with weekly paclitaxel and with every-3-week carboplatin followed immediately by neoadjuvant administration of atezolizumab/placebo with epirubicin or doxorubicin/cyclophosphamide (EC/AC). Patients will then undergo surgery. Following surgery, determination of pCR status and recovery from surgery, patients who did not discontinue atezolizumab/placebo due to toxicity during neoadjuvant therapy will resume the original randomized investigational therapy assignment and continue the therapy as adjuvant treatment until 1 year after initial dose of atezolizumab/placebo. Since activity of radiation therapy may also be augmented by inhibition of PD-1/PD-L1, radiation therapy, if indicated, should be co-administered with atezolizumab/placebo.

GeparDouze

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Dr. Stephan Hofmann
Clinical Project Management
gepardouze@GBG.de

This will allow for collection of safety data related to co-administration of atezolizumab with radiation therapy on a blinded, placebo-controlled trial. Adjuvant atezolizumab/placebo may be delayed until after completion of radiation therapy per investigator discretion.

Patients are randomized in a 1:1 ratio to receive either neoadjuvant chemotherapy + atezolizumab 1200 mg or placebo IV every 3 weeks followed by surgery and continuation of atezolizumab 1200 mg or placebo IV as adjuvant therapy for 6 months. Stratification factors are group (NSABP Inc; GBG), tumor size (1.1-3.0 cm; >3.0 cm), EC/AC (q2w; q3w), nodal status (positive; negative) and PD-L1 status (positive; negative or indeterminate). Patients with primary cT1c-cT3 TNBC and centrally assessed hormone receptor-status, HER2-status, Ki-67, and stromal tumor-infiltrating lymphocytes (sTILs) on core biopsy can be enrolled.

Co-primary objectives are 1) to determine whether the addition of atezolizumab to chemotherapy (weekly paclitaxel plus carboplatin followed by AC or EC) improves pCR in the breast and axilla (ypT0/Tis ypN0) and 2) to determine whether the addition of atezolizumab to chemotherapy followed by adjuvant atezolizumab improves EFS. Secondary objectives include assessment of other pCR definitions (ypT0/Tis and ypT0 ypN0); positive nodal status conversion rate; recurrence-free interval; overall survival; distant disease-free survival; brain metastases-free survival and safety. Tertiary objectives are assessment of pCR (ypT0/Tis ypN0) and EFS in patients with deleterious germline *BRCA* mutation status. Furthermore, the GeparDouze study will also address translational research questions such as to evaluate the expression of PD-L1 and percentage of TILs as predictors for pCR and EFS; to evaluate percentages of TILs in patients with residual BC at surgery as a predictor for EFS; to investigate potential new biomarkers of response and resistance using baseline and on-therapy specimens; to evaluate serial circulating tumor DNA (ctDNA) as a predictive biomarker for pCR and EFS as well as an early predictor of recurrence; to evaluate the microbiome of breast cancer patients and to explore potential new biomarkers, toxicity, immune markers, tumor antigens.

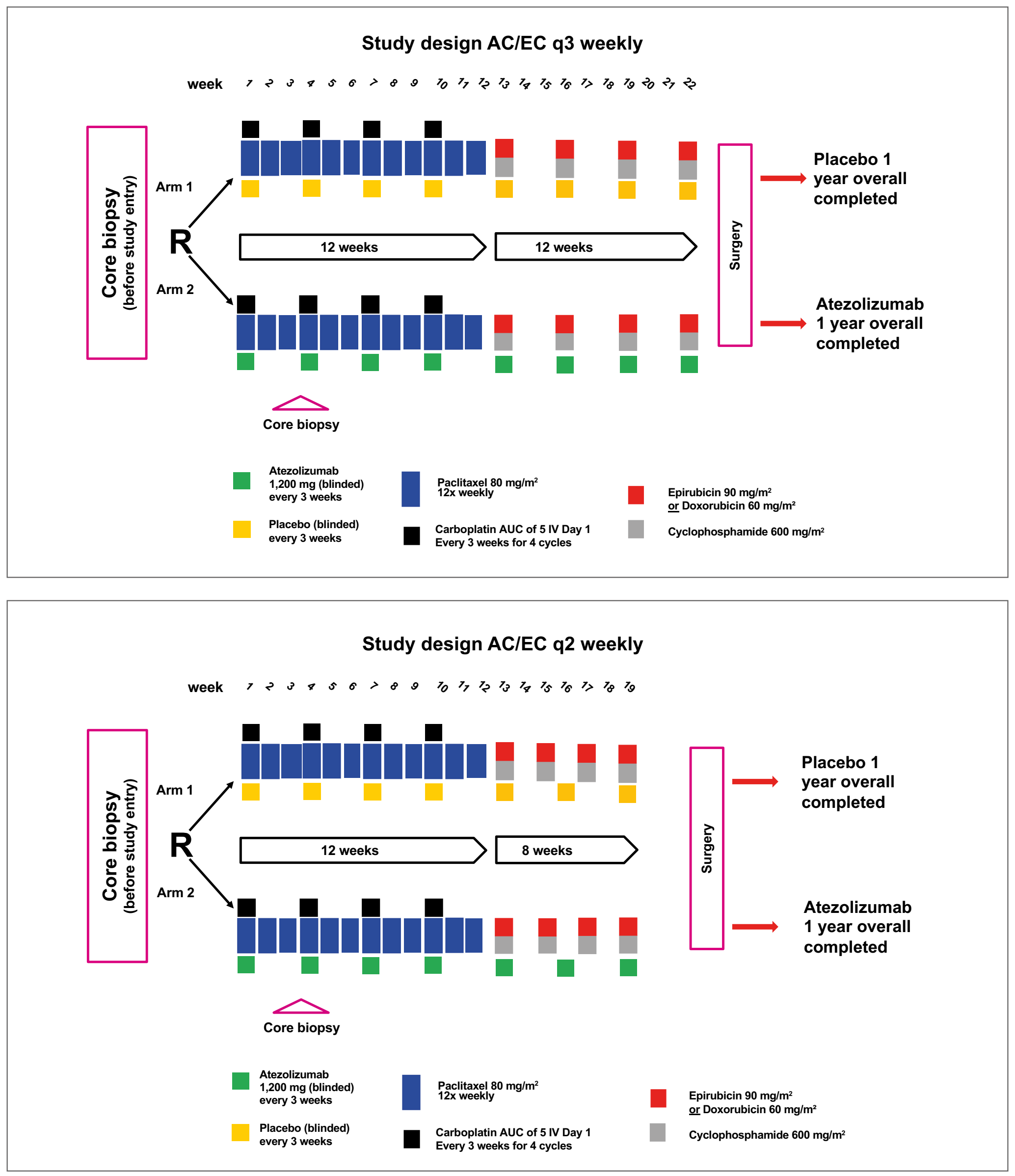

Figure 1: GeparDouze study design

Study report:

GeparDouze recruitment started in December 2019. As of 31st December, there are 253 patients enrolled in the study. Follow-up of an additional 39 months after completion of accrual is planed to obtain 298 EFS events. The expected study duration is approximately 72 months [1-3].

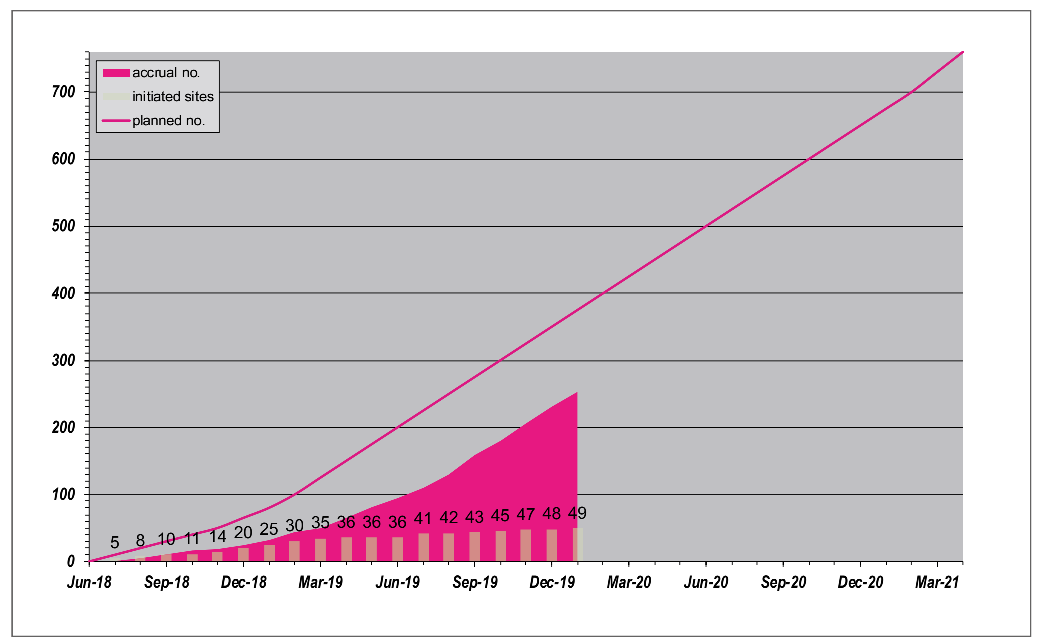

Figure 2: GeparDouze recruitment as of 31st December 2019

We are thanking all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients and by providing biomaterial in a timely manner.

Publications

1. Loibl S, Jackisch C, Rastogi P et al. GeparDouze/ NSABP B-59: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy with atezolizumab or placebo in patients with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. Ann Oncol 2019; 30 (suppl_3): iii34-iii38; TIP-poster.
2. Geyer CE, Loibl S, Rastogi P et al. NSABP B-59/GBG 96-GeparDouze: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with triple-negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. J Clin Oncol 2019;37.15_suppl. TPS605.
3. Geyer CE Jr, Loibl S, Rastogi P et al. A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo: NSABP B-59/GBG 96-GeparDouze. SABCS 2019; OT2-04-08, TIP.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

NSABP

SPONSOR:
NSABP Foundation Inc

STUDY CHAIR:
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GBG 97: AMICA

Anti-hormonal maintenance treatment with or without the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in hormone receptor positive / HER2-negative metastatic breast cancer: A phase II trial

NCT03555877

AMICA is a multicenter, prospective, randomized open-label, controlled phase II study that will recruit 150 patients from 20-30 sites in Germany.

Background
Dysregulation of the cell cycle is one of the hallmarks of cancer. The cyclin dependent kinases are a large family of serine / threonine kinases that have a crucial role in regulating cell cycle progression. For example, the cyclin dependent kinases 4 and 6 (CDK4/6) and their partner d-type cyclins control transition from G1 to S phase of the cell cycle by phosphorylating the retinoblastoma protein. Preclinical evidence demonstrated a synergistic inhibitory effect of CDK4/6 inhibitors and antiestrogens in hormone-receptor (HR) positive breast cancer (BC) cell lines. Ribociclib, a CDK4/6 inhibitor, is currently evaluated in various disease settings including phase III trials in metastatic breast cancer.
While guidelines recommend endocrine therapy as a 1st line treatment in patients with HR-positive/HER2-negative metastatic BC, about 30 % of patients will receive chemotherapy.
A meta-analysis of 11 randomized trials has shown that longer duration of therapy is associated with PFS and overall survival (OS) (Gennari A. et al. J Clin Oncol. 2011). However, the duration of chemotherapy is frequently determined either by toxicities or by patients and physicians' preferences, resulting in treatment periods of less than 6 months. Moreover, although 1st line chemotherapy is effective in women with HR-positive/HER2-negative BC, PFS is around 6-8 months and 2nd or 3rd line treatments are by far less effective. Therefore, well tolerated maintenance treatments with the potential to prolong PFS and even OS are urgently needed. The phase III MONALEESA-2 trial has reported a significant improvement in PFS in 1st line metastatic BC when the CDK4/6 inhibitor ribociclib was added to letrozole (25.3 vs. 16.0 months; hazard ratio=0.57) (Hortobagyi GN et al. N Engl J Med. 2016). Maintenance treatment with anti-hormonal drugs is an accepted treatment strategy in everyday clinical practice (Sutherland S et al. Eur J Cancer. 2016; Rossi S et al. Future Oncol. 2016) but prospective data are lacking. Therefore, the AMICA study evaluates the impact of the addition of a CDK4/6 inhibitor to an anti-hormonal maintenance treatment of physicians´ choice.

Study design and objectives
After at least 4 cycles of chemotherapy of physician´s choice, patients with at least stable disease will be randomized in a 2:1 ratio to receive endocrine maintenance therapy ± open-label treatment with ribociclib therapy. Endocrine therapy, at the discretion of the investigator, could have already been started up to 4 weeks before randomization but not later than with first dose of ribociclib. Stratification factors for randomization will be: 1) previous endocrine treatment for metastatic disease (yes vs no); 2) involved sites (≤ 2 vs > 2); 3) best response under chemotherapy (response vs stable disease). In both study arms, treatment will be given until disease progression, unacceptable toxicity, or withdrawal of consent of the patient. AMICA primarily aims to evaluate the impact on PFS of an anti-hormonal maintenance therapy after 1st line chemotherapy at the discretion of the investigator (e.g. taxanes, capecitabine, vinorelbine, anthracycline) with or without the CDK4/6 inhibitor ribociclib. Secondary objectives are to evaluate the impact on OS and clinical benefit rate; to compare safety between the two arms; to compare treatment compliance between the two arms and to evaluate patient reported outcomes. Tertiary objectives are to evaluate biomarkers which might predict response to CDK inhibition and endocrine therapy using formalin-fix paraffin embedded (FFPE) metastatic tissue samples and blood (e.g. cyclines, RB expression, p27, p16 expression) as well as to assess the role of mutations, e.g. PIK3CA and ESR1 in circulating tumor DNA (ctDNA) [1].
An amendment of the study protocol (approved on 5th November, 2018) included the following changes: a) inclusion of patients who had previously received a CDK4/6 inhibitor; b) permission of using herbal medication during study therapy; c) permission of surgery for primary tumor at the discretion of the investigator; d) exclusion of tamoxifen, one of the possible endocrine therapies, due to new data reported from the MONALEESA-7 trial [2].

Study report:
AMICA recruitment started in March 2018. As of 31st December 2019, there were 29 patients enrolled in the study. The expected study duration initially was 21 months, increased to 40 months via amendment 1 of the study protocol. Due to low recruitment another amendment to reduce the sample size to approximately 100 and to change the study design to one-arm study is in preparation.

Publications:
1. Decker T, Barinoff, J, Furlanetto J et al. Anti-hormonal maintenance treatment with/without the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in HR+/HER2- metastatic breast cancer: a phase II trial (AMICA) GBG 97. 38. Jahrestagung Deutsche Gesellschaft für Senologie 2018; TIP-poster.
2. Decker T, Denkert C, Lübbe K et al. Antihormonal maintenance treatment with or without the CDK4/6 inhibitor ribociclib after first line chemotherapy in hormone receptor positive/HER2 negative metastatic breast cancer: A phase II trial (AMICA) GBG 97. Ann Oncol 2018; 29 (suppl_8): 364TiP.

We are thanking all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients and by providing biomaterial in a timely manner.

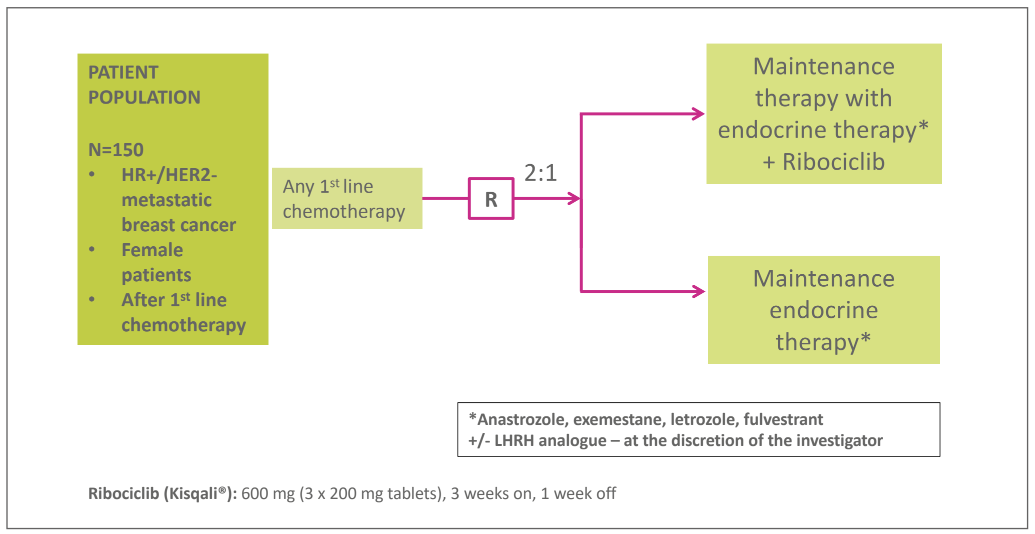

Figure 1: AMICA study design

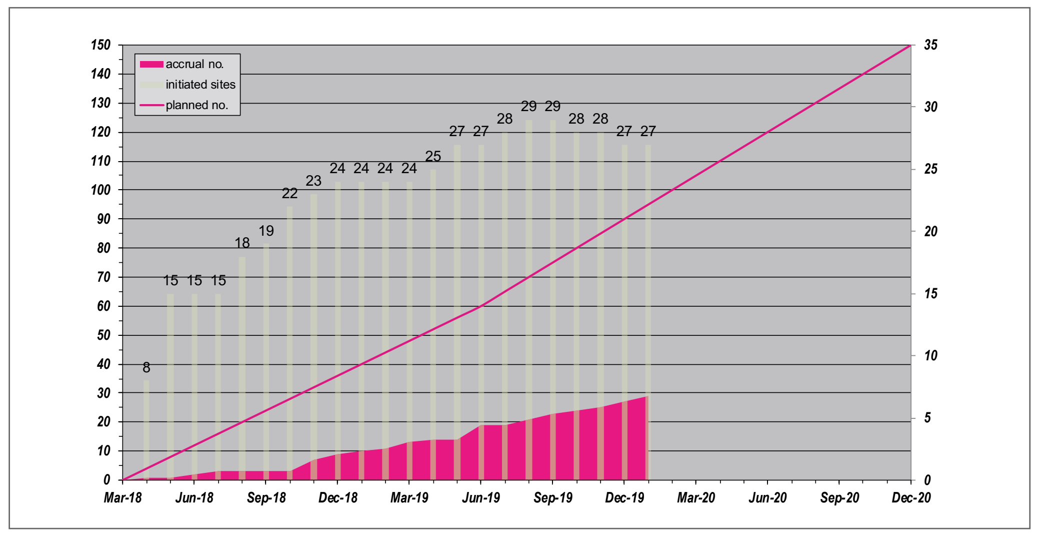

Figure 2: AMICA recruitment as of 31st December 2019

COLLABORATING STUDY GROUPS:
GBG German Breast Group

SPONSOR:
GBG Forschungs GmbH

COORDINATING INVESTIGATOR
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Onkologie Ravensburg

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GBG 93: PADMA

A randomized, open-label, multicenter phase IV study evaluating palbociclib plus endocrine treatment versus a chemotherapy-based treatment strategy in patients with hormone receptor positive / HER2-negative metastatic breast cancer in a real world setting

NCT03355157

PADMA is an international, prospective, randomized, open-label, multicenter, controlled phase IV low intervention trial to test whether endocrine treatment with palbociclib is better than mono-chemotherapy +/- endocrine maintenance therapy as per treating physician´s choice as first line therapy in advanced/ metastatic breast cancer (MBC) that will be conducted in approximately 70 sites in Europe within approximately 36 months.

Background

Endocrine therapy is the recommended option for estrogen receptor (ER) positive / human epidermal growth factor receptor 2 (HER2) negative MBC as first-line therapy in the majority of patients except those with rapidly progressing, life-threatening disease, also known as visceral crisis (Cardoso F et al. Ann Oncol 2014; Gradishar et al. Natl Compr Canc Netw 2016; AGO guidelines 2016, www.ago-online.de). With the novel CDK4/6 inhibitors in addition to either an aromatase inhibitor (AI) or fulvestrant the treatment landscape is changing rapidly. However, the data comparing endocrine therapy (ET) alone with chemotherapy (CT) are scarce and less convincing. Since palbociclib improves the efficacy of ET alone by about 50 %, the hypothesis is that palbociclib + ET is superior to mono-chemotherapy of physician´s choice with or without ET maintenance therapy in time to treatment failure. However, due to rigid inclusion and exclusion criteria, limited number of treatment options, and strictly prescribed monitoring intervals the majority of clinical trials are done in an "artificial environment" and often do not mirror real world situation. Therefore, this trial is planned as low intervention real world trial to compare two treatment strategies that are commonly used options in real-world practice: a combination of palbociclib with ET versus a pre-planned CT strategy with or without ET maintenance until treatment failure. In real world, the majority of patients with MBC receive CT to obtain a quick response, although it has not been proven that a quick response achievement will be translated into a patients benefit (e.g., longer TTF). Therefore, a pre-planned analysis will investigate the association between investigator- assessed response assessed 3 months after randomization and patient benefit (measured by TTF).

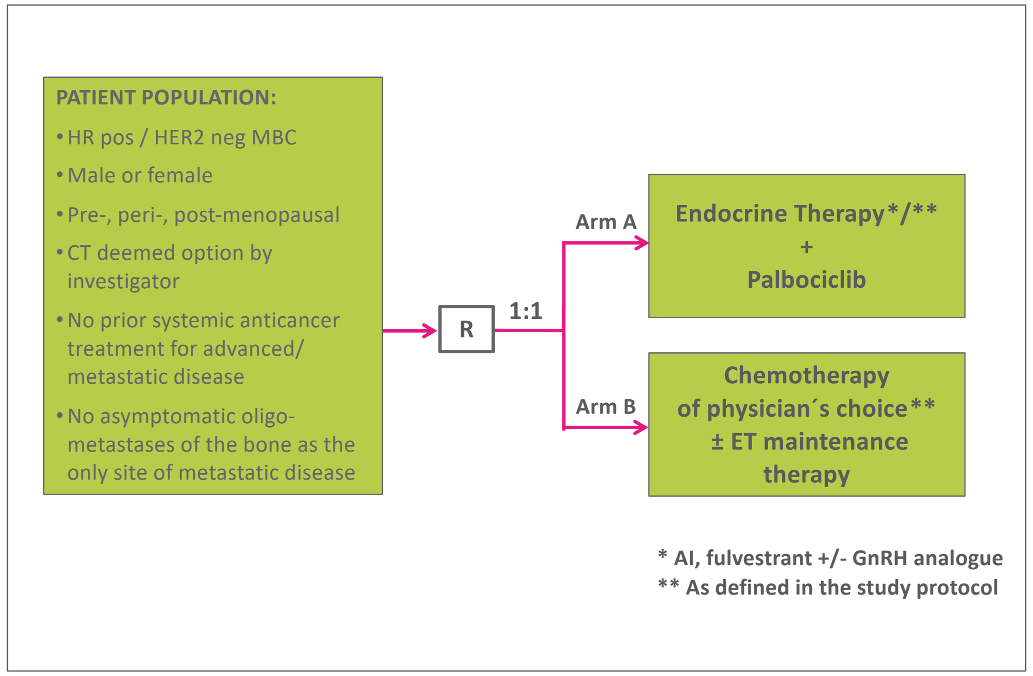

Figure 1: PADMA study design

The hypothesis of the study is that palbociclib + ET can show a significant improvement in time-to-treatment failure (TTF) over CT regimen (mono-chemotherapy with or without ET maintenance therapy). This will provide level 1 evidence from real world that palbociclib + ET is the first choice in MBC patients needing first-line therapy compared to CT with or without ET maintenance therapy. In addition, we assume that patient reported outcome (PRO) as measured by FACT-B, and a novel composite endpoint of well-being and healthcare utilization as measured by daily monitoring treatment impact (DMTI) will be improved with palbociclib + ET vs. CT regimen.

Study design and objectives:

Patients will be randomized in a 1:1 ratio to receive either ET with palbociclib or CT with or without endocrine maintenance therapy. Stratification factors for randomization will be: 1) hormone resistant (relapse on or within 12 months of end of adjuvant endocrine therapy) versus hormone sensitive (relapse beyond 12 months after end of endocrine therapy or de-novo metastatic HR-positive / HER2-negative breast cancer); 2) symptomatic (as defined per investigator) vs. asymptomatic (as defined by investigator). In both study arms, treatment will be given until disease progression, unacceptable toxicity, or withdrawal of consent of the patient or change of initial treatment plan (either approximately six chemotherapy cycles followed by maintenance endocrine therapy or chemotherapy until disease progression).
PADMA primarily aims to compare the time-to-treatment failure (TTF) for patients randomized to receive pre-defined chemotherapy treatment strategy versus those randomized to receive palbociclib and endocrine therapy. The TTF is defined as time from randomization until discontinuation of treatment due to disease progression, treatment toxicity, patient's preference, or death. Secondary objectives are to compare progression free survival (PFS), time to first subsequent treatment (TFST), time to first subsequent chemotherapy (TFSCT) and time to second subsequent treatment regimen (TSST) between treatment arms; to compare the overall survival between treatment arms 36 months after the first patient was randomized; to compare patient well-being and health care utilization (number and duration of phone calls, and patient visits to investigator sites), content with Quality of Life (QoL) and degree of bother by side-effects; to assess PRO measured by FACT-B; to compare time-to-deterioration in Trial Outcome Index-Physical/Functional/Breast (TOI-PFB derived from FACT-B); to compare safety, tolerability and treatment compliance

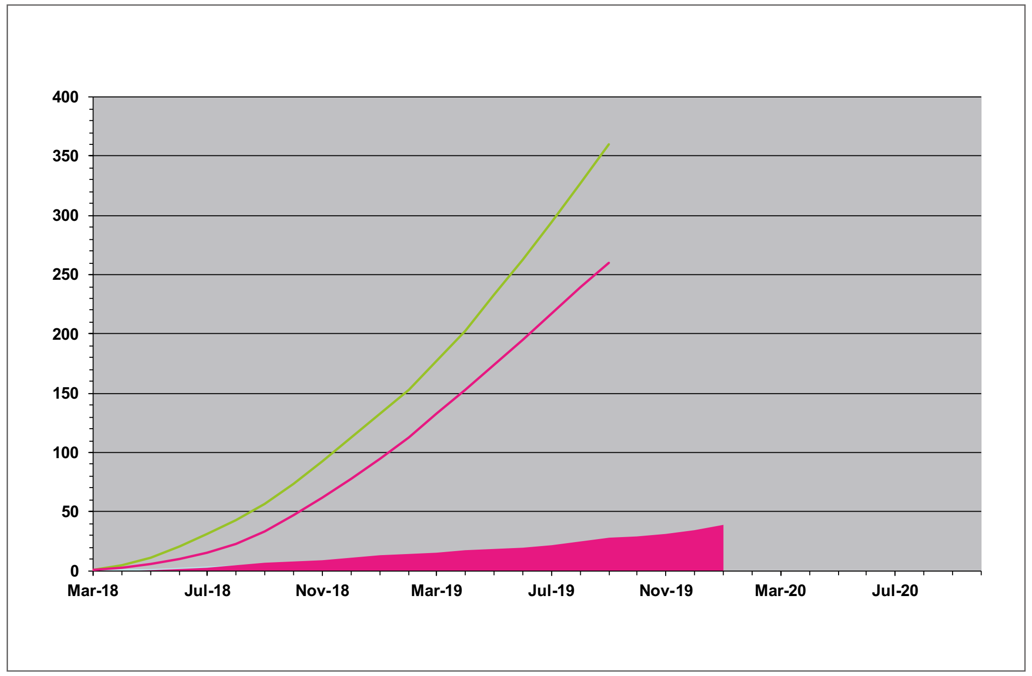

Figure 2: PADMA recruitment as of 31st December 2019

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

SOLTI

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between the two arms. Exploratory objectives include comparison of time to response as assessed by the investigator; comparison of duration of first subsequent treatment (DFST); investigation of association between investigator- assessed response measured 3 months after randomization and patient benefit (measured by TTF) [1].
Furthermore, the PADMA study will also address translational research questions such as an investigation of biomarkers (e.g., cyclines, RB expression, p27, p16 expression) which might predict the response to CDK inhibition in MBC as well as evaluation of circulating tumor DNA (ctDNA) at various time points (at start of therapy, throughout treatment and at end of treatment) to monitor tumor progression.
The protocol has been amended in July 2018. The main changes of this protocol amendment 1 were a reduction of the number of planned patients, and the removal of the initially planned interim analysis and of an activity tracker monitoring sleep and activity levels, respectively.

Study report:
The PADMA recruitment started in March 2018 in Germany. As of 31st December 2019, there are 39 patients enrolled in the study. The study will also be opened for sites in Spain. The end of the study (i.e. last visit of the last patient randomized) is estimated for 2021 [1-3].

Publications:

1. Loibl S, Barinoff J, Decker T, et al. A randomized, open-label, multicentre, phase IV study evaluating palbociclib plus endocrine treatment versus a chemotherapy based treatment strategy in patients with hormone receptor positive/HER2-negative metastatic breast cancer in a real world setting. J Clin Oncol 2017;35 15_suppl. TPS1115).
2. Loibl S, Barinoff J, Seiler S, et al. A randomized, open-label, multi-center phase IV study evaluating Palbociclib plus endocrine treatment versus a chemotherapy-based treatment strategy in patients with hormone receptor-positive, HER2-negative metastatic breast cancer in a real world setting (PADMA). Cancer Res 2018;78(4 Suppl):OT3-05-04.
3. Thill M, Seiler S, Decker T et al. A randomized, open-label, phase IV study evaluating palbociclib plus endocrine treatment versus a chemotherapy-based treatment in patients with hormone receptor-positive, HER2-negative metastatic breast cancer (PADMA). 38. Jahrestagung Deutsche Gesellschaft für Senologie 2018; TIP-poster.

We are thanking all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients and by providing biomaterial in a timely manner.

GBG 94: PATINA

A randomized, open-label, phase III trial to evaluate the efficacy and safety of palbociclib + Anti-HER2 therapy + endocrine therapy vs. Anti-HER2 therapy + endocrine therapy after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer

NCT02947685

PATINA (AFT-38) is an international, multicenter, randomized, open-label, phase III trial testing the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy vs. anti-HER2 therapy + endocrine therapy after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer that will recruit 496 patients worldwide (120 patients from approximately 30 sites in Germany) within 36 months.

PATINA is a collaborative study conducted by Alliance Foundation Trials (AFT), LLC in partnership with the German Breast Group (GBG) and supported by AFT, LLC.

Background
In light of the evolving breast cancer (BC) classification, HER2-positive BC has emerged as a separate disease entity and the development of therapies targeting the HER2 receptor has dramatically improved patient outcomes. During the first decade of trastuzumab use for advanced HER2-positive BC, a significant improvement in the understanding of the biology of HER2-positive disease led to the development and approval of novel anti-HER2 agents. In order to improve beyond the current standards, it is important to highlight the major limitations of available therapies: 1) patients with advanced disease inevitably develop resistance to anti-HER2 therapies; 2) tumor heterogeneity within HER2-positive BC is now evident and can be divided into two major subtypes according to the expression of hormone receptor (HR) status; 3) specific subsets of HER2-positive disease (e.g. somatic PIK3CA mutation) have a particularly unfavorable outcome when treated with conventional chemotherapy. Taken together these factors point to the need for clinical studies dedicated to specific subsets of HER2-positive BC.
The PATINA study is built on strong preclinical and clinical rationale demonstrating the benefits of palbociclib, a selective CDK4/6 inhibitor, when given in combination with endocrine therapies (ET) and anti-HER2 therapies. The expectation is that the addition of palbociclib to the first-line treatment of HER2-positive/HR-positive disease will delay the onset of therapeutic resistance and ultimately prolong patient survival.

Study design and objectives:
PATINA primarily aims to demonstrate that the combination of palbociclib with anti-HER2 therapy plus endocrine therapy is superior to anti-HER2-based therapy plus endocrine therapy in prolonging progression-free survival (PFS) in participants with HR+/HER2-positive metastatic BC who have not received any prior treatment beyond induction treatment in this setting. Secondary objectives are to compare measures of tumor control (including PFS, overall response, clinical benefit rate, duration of response) between the treatment arms; to compare median overall survival (OS) at 3-years and 5-years between the treatment groups; to compare safety and tolerability between the treatment arms; to compare the incidence of central nervous system metastasis between the treatment arms; to compare patient reported time to symptom progression as assessed by the FACT-B TOI-PFB; to compare patient reported BC specific health related quality of life (HRQoL) and general health status. In addition, PATINA includes translational research objectives which will investigate the benefits of palbociclib in subsets of HER2-positive disease (e.g. *PIK3CA* mutant) [1].
The protocol has been amended in February 2018. Essential points of this amendment were (1) to clearly delineate between preliminary screening vs. randomization process, (2) a more detailed description of the specimen collection and storage for the Mastering Breast Cancer (MBC) Initiative, and (3) updates of the in- and exclusion criteria, respectively.
The next protocol amendment (anticipated for December 2019) includes the following essential points: (1) updates of the in- and exclusion criteria; (2) IMP will change from capsules to tablets; (3) modification of drug handling (including drug dispensation and accountability, drug administration and dose modification); (4) administrative changes.

Translational research
Translational research will be performed to compare progression-free survival based upon

PATINA
A COLLABORATIVE STUDY SPONSORED BY ALLIANCE FOUNDATION TRIALS, LLC

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investigator assessment of progression between patients in the two treatment arms in the subset of patients with tumors bearing a *PIK3CA* mutation. *PIK3CA* genotype will be assessed in circulating cell-free DNA (cfDNA). The exploratory objectives are to evaluate PFS and OS in genomically-defined BC subgroups based on pre-specified genomic assays; to evaluate baseline tumor- and blood-based markers as predictors of benefit from the addition of palbociclib to anti-HER2 therapy plus ET; to evaluate tumor- and blood-based markers at the time of disease recurrence for mechanisms of resistance to therapy; to compare serial levels of cfDNA in patients receiving anti-HER2 therapy plus ET versus anti-HER2 therapy plus ET plus palbociclib; to compare mutational profile/copy number variants obtained from tumor tissue to those measured in cfDNA; to determine the trough concentrations of palbociclib when given in combination with trastuzumab plus ET or trastuzumab plus pertuzumab plus ET; to determine trastuzumab and pertuzumab trough concentrations when given in combination with palbociclib plus ET; to explore correlations between palbociclib exposure and efficacy/safety findings in this patient population.

Study report:

The PATINA worldwide recruitment started in July 2017 and in Germany in July 2018, respectively. As of 31st December 2019, there are 12 patients enrolled in the study at the German sites. Enrollment is targeted to be completed by December 2020 and the last patient last visit is expected for December 2025 [1-4].

Publications

1. Metzger O, Mandrekar S, Ciruelos E, et al. PATINA: A randomized open label phase III trial to evaluate the efficacy and safety of palbociclib 1 anti HER2 therapy 1 endocrine therapy vs anti HER2 therapy 1 endocrine therapy after induction treatment for hormone receptor positive, HER2-positive metastatic breast cancer. Ann Oncol 2017; 28 (suppl.5): 324 TiP.
2. Metzger O, Mandrekar S, Loibl S, Ciruelos E, Gianni L, et al. PATINA: A randomized open label phase III trial to evaluate the efficacy and safety of palbociclib + anti HER2 therapy + endocrine therapy vs anti HER2 therapy + endocrine therapy after induction treatment for hormone receptor positive, HER2 positive metastatic breast cancer. Cancer Research 2018; 78(4 Supplement):OT3-05-07.
3. Loibl S, Metzger O, Mandrekar SJ et al. PATINA: A randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + Anti-HER2 therapy + endocrine therapy (ET) vs. anti-HER2 therapy + ET after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer (MBC). Ann Oncol 2018; 29 (suppl_8):369 TiP.
4. Metzger O, Mandrekar S, Ciruelos E PATINA: A randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy (ET) vs. anti-HER2 therapy + ET after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer (MBC). Cancer Res 2019;79(4 Suppl): Abstract nr OT3-02-07.

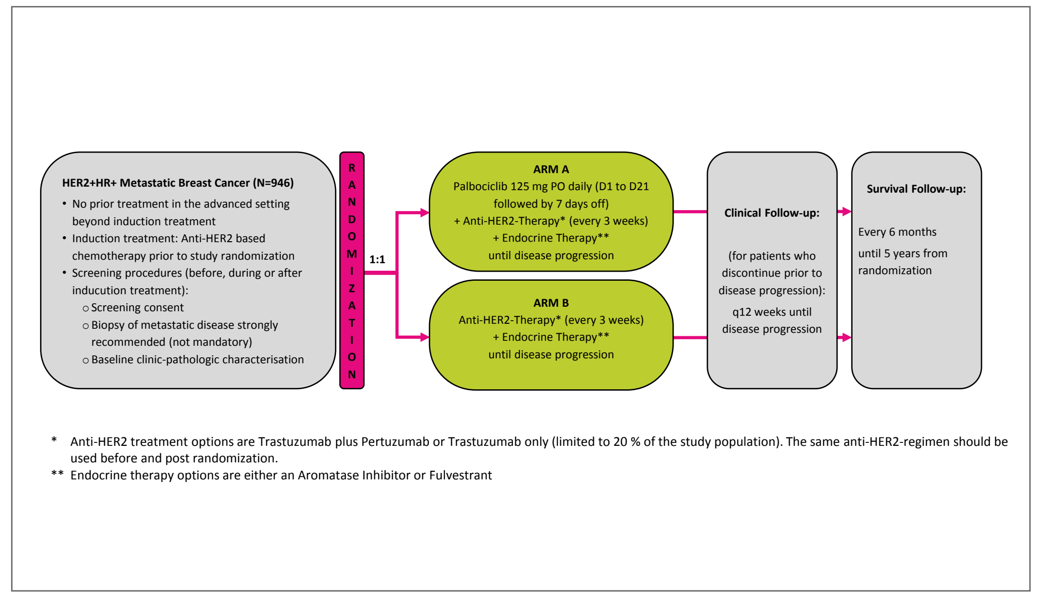

Figure 1: PATINA study design

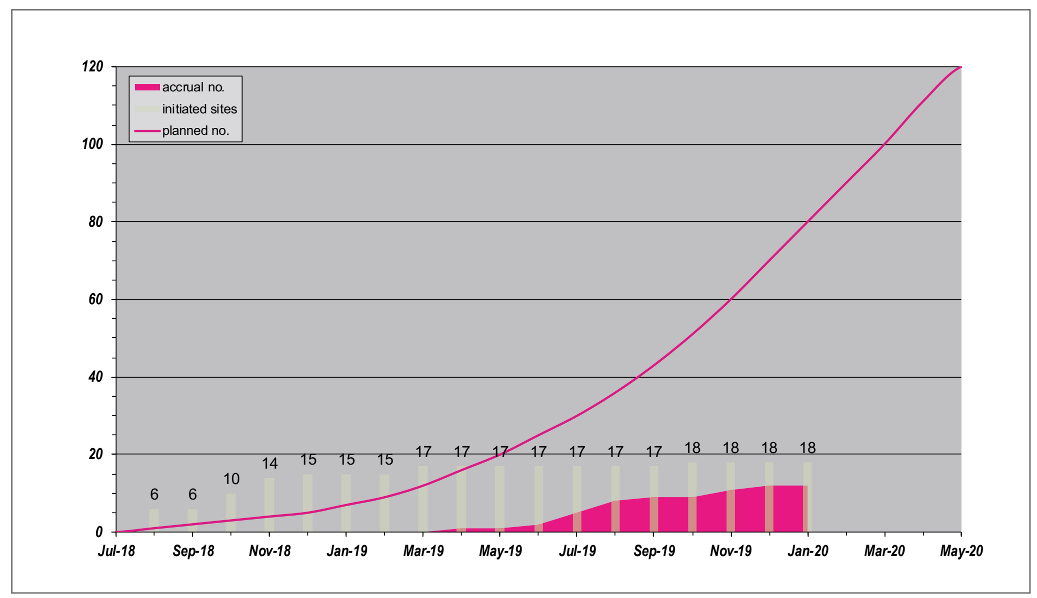

Figure2: PATINA recruitment as of 31st December 2019

COLLABORATING STUDY GROUPS:

SPONSOR:
Alliance Foundation Trials

INTERNATIONAL STUDY CHAIR:
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BCP
Breast Cancer in Pregnancy

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GBG 29: Breast Cancer in Pregnancy (BCP)

Prospective and retrospective registry study of the German Breast Group (GBG) for diagnosis and treatment of breast cancer in pregnancy compared to young non-pregnant women

NCT00196833

BCP (BIG 03-02) is a long time retrospective/ prospective multicenter, international registry that will recruit pregnant breast cancer patients and non-pregnant young women.

Background

Breast cancer in pregnancy is regarded as a rare coincidence. However, about 7 % of the women diagnosed with breast cancer are younger than 40 years with a small increase in the incidence in the last years (Eisemann et al. Geburtsh Frauenheilk 2013; De Santis et al. CA Cancer J Clin 2011). The median age of first pregnancy in Germany is 30 years (according to the federal statistical office). Since the incidence of breast cancer under the age of 40 is rising and women tend to delay pregnancy into later reproductive years the coincidence of pregnancy and breast cancer is increasing. Little is known about the incidence of breast cancer in pregnancy in Germany and Western Europe.

Therefore, in 2003 the German Breast Group launched a registry which was extended throughout Europe and worldwide (Breast International Group), to systematically investigate breast cancer during pregnancy and to increase the evidence for treatment options.
With an amendment of the original study protocol, it is now possible to also include a non-pregnant control cohort of women diagnosed with breast cancer at or below the age of 40 years. Those can be matched to the pregnant breast cancer patients as controls treated in everyday clinical practice.
All patients with histologically confirmed breast cancer who are pregnant, as well as patients of 40 years or younger with histologically confirmed breast cancer who are not pregnant and have given informed consent for data collection and biomaterial collection can be entered into the registry. Retrospective participants can be entered without an informed consent as long as the data are captured anonymously.

Study objectives

The BCP study primarily aims to assess the fetal outcome 4 weeks after delivery. Secondary endpoints will include maternal outcome of pregnancy, tumor stage at presentation and biological characteristics, breast cancer therapy, type of surgery, mode of delivery (vaginal vs. caesarean), outcome of the new-born 5 years after diagnosis, and outcome of breast cancer 5 years after diagnosis.
In addition, the registry allows investigation of translational research questions, using tumor specimen as well as placenta tissue from patients with breast cancer during pregnancy.

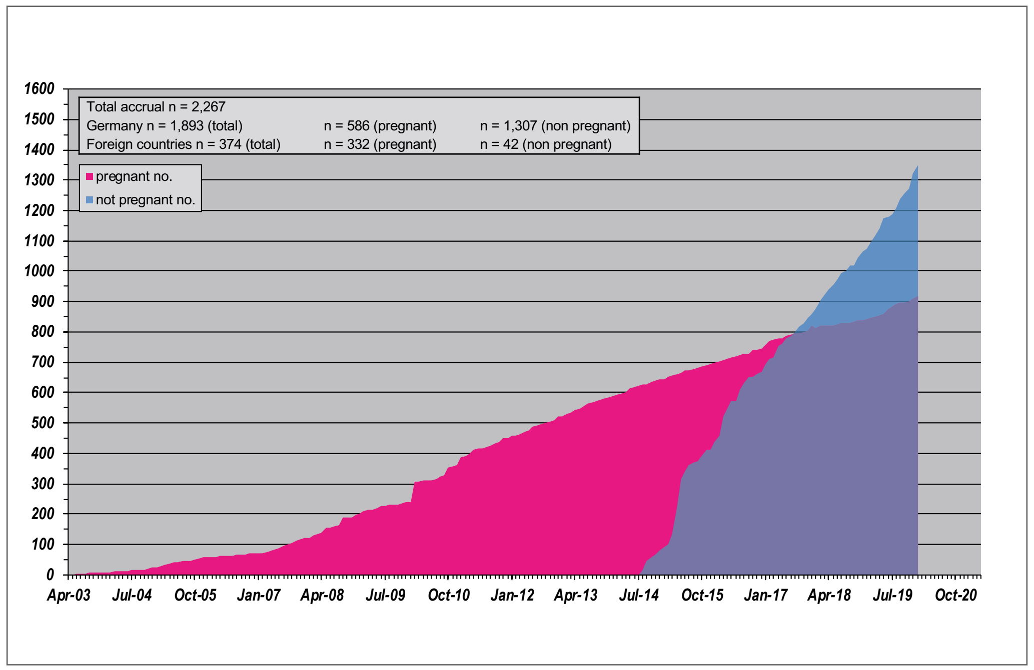

Figure 1: BCP recruitment as of 31st December 2019

Study report

As of 31st December 2019, a total of 2,267 patients have been registered, 1,893 in Germany (586 pregnant and 1,307 non pregnant women).
A first analysis of registry data looking at fetal health for up to 4 weeks after delivery included 447 patients and showed that although infants exposed to chemotherapy in utero had a lower birth weight and reported more complications compared to their unexposed counterparts, these differences were not clinically significant. Since none of the infants was exposed to chemotherapy in the first trimester, the differences were most likely related to premature delivery. This led to the conclusion that preterm birth was strongly associated with adverse events and a full-term delivery seems to be of paramount importance. Moreover, a delay of cancer treatment did not significantly affect disease-free survival for mothers with early breast cancer [1].
In a combined analysis of our data with data form the Cancer in Pregnancy registry, Leuven, Belgium, we were able to demonstrate that overall survival was similar for patients diagnosed with breast cancer during pregnancy compared with non-pregnant patients. This information is important for counseling patients and supports the option to start treatment with continuation of pregnancy [2].
We were also able to demonstrate that neoadjuvant chemotherapy for patients with breast cancer during pregnancy results in the same pCR rate if given during pregnancy or after delivery and as in non-pregnant controls. Disease free and overall survival was not different between the three cohorts [3].
The general recommendation derived from the registry data so far is that patients with breast cancer during pregnancy can and should be treated as closely as possible according to patients diagnosed outside pregnancy. Up-to-date guidelines on breast cancer during pregnancy, which also incorporated outcomes from the BCP registry, have been published in 2015 [4].
Little is known about the impact of pregnancy on breast cancer biology at the genomic level. It is believed that breast cancer during pregnancy is biologically not different from breast cancer diagnosed outside pregnancy [5]. Current translational research project aims to compare the mutational pattern as well as the gene expression profile between pregnant and non-pregnant patients with breast cancer. In our preliminary results we showed that overall the mutational landscape does not seem to be different between pregnant patients enrolled in BCP study and no-pregnant controls obtained from The Cancer Genome Atlas (TCGA) database [6,7]. Further analyses using other datasets are currently conducted.
Data from the BCP registry including oncological management, toxicity and survival of young non-pregnant patients with breast cancer diagnosed at the age of 40 years or younger has been analyzed. From February 2014 until June 2018, 969 non-pregnant patients ≤ 40 years have been registered. The median age at diagnosis was 35 years (range 19-40). Overall, 90.1 % of patients had a stage T1-2 at diagnosis and 67.1 % of patients had negative lymph nodes; 86.7 % of tumors were invasive ductal carcinomas and 4.1 % lobular carcinomas. Grade (G) 3 was reported in 55.5 %; 26.6 % of tumors were luminal A-like (ER- and/or PgR-positive, HER2- negative, G1-2), 40.0 % luminal B-like (ER- and/or PgR-positive, HER2-negative, G3 or ER- and/or PgR-positive, HER2-positive, any G), 7.7 % HER2 positive non-luminal-like, and 25.7 % triple negative breast cancers. 3.8 % of young non-pregnant patients had metastatic disease at primary diagnosis [8].
Recently, a histologic and epigenetic analysis of placenta tissue from breast cancer patients (N=66) and non-cancer participants (N=20) enrolled in the BCP registry demonstrated morphologic abnormalities and a decreased proliferation index without increase of apoptotic cells in placenta from breast cancer patients as compared with placenta from normal pregnancies. Altered expression of efflux pumps or drug-metabolizing enzymes might be a reason for good fetal tolerability of chemotherapy during pregnancy as methylation patterns were changed in P-gP and CYP-3A4 genes [9].

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

BIG Breast International Group

SPONSOR:
The project was initially supported by the BANSS-Foundation and German Cancer Consortium (DKTK)

STUDY CHAIR:
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Publications

1. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012; 13(9):887-96.
2. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol 2013; 31(20):2532-9.
3. Loibl S, Han S, Mayer K, et al. Neoadjuvant chemotherapy for patients with breast cancer during pregnancy (BCP). J Clin Oncol 2014; 32:5s (suppl; abstr 1071).
4. Loibl S, Schmidt A, Gentilini O, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol 2015; 1(8):1145-53.
5. Loibl S, Han SN, Amant F. Being Pregnant and Diagnosed with Breast Cancer. Breast Care (Basel). 2012; 7(3):204-209.
6. Loibl S, Pfarr N, Weber K, et al. Comparison of the mutational landscape of breast cancer during pregnancy and non-pregnant controls. Ann Oncol 2017; 28(suppl_1):Abstract nr 10P.
7. Loibl S, Pfarr N, Weber K, et al. Comparison of the mutational landscape of breast cancer during pregnancy and non-pregnant controls. Cancer Res 2017;77(4 Suppl):Abstract nr P2-03-09.
8. Seiler S, Schmatloch S, Reinisch M et al. Cancer Management and Outcome of very young non-pregnant patients with breast cancer diagnosed at 40 years or younger – GBG 29. Cancer Res 2019;79(4 Suppl): Abstract nr P1-17-07.
9. Froehlich K, Plösch T, Seither F et al. Histological and epigenetic analyses of placenta tissue from breast cancer patients and healthy participants. SABCS 2019;Abstract nr P4-21-06.

Thanks to all participating sites and practices that have entered their patients into the registry and have contributed to this important research so far. We would kindly like to remind all study centers to provide biomaterial which is urgently needed to answer translational research questions. More information and CRF forms are available on the GBG website:
http://www.germanbreastgroup.de/de/studien/bcp.php

GBG 79: Brain Metastases in Breast Cancer (BMBC)

BMBC

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BMBC (Brain Metastases in Breast Cancer) is a long-time retrospective and prospective multicenter registry designed to collect tumor characteristics of the primary and metastatic tumor as well as treatment data from patients diagnosed with brain metastases of breast cancer treated in German hospitals.

Background

Brain metastases of breast cancer reduce quality of life and prognosis in breast cancer patients. Their incidence has increased during the last years (Frisk et al. Br J Cancer 2012). 10-40 % of patients with metastatic breast cancer will develop brain metastases during the course of disease depending on the biological subtype of the primary tumor. The prognosis for patients with brain metastases is generally poor. Good performance status and a limited number of brain metastases are factors that can prolong survival (Ogawa et al. J Neurooncol 2008). Therapeutic approaches in treating metastases of the central nervous system include surgery, radiotherapy, and systemic chemotherapy and the combination of these options.

Due to the analysis of small and heterogeneous patient cohorts, risk factors for the development of brain metastases and the impact of early detection of brain metastases have been analyzed insufficiently. Improvement of treatment strategies are required as the number of brain metastases will increase over the next years due to the better control of visceral disease. A multidisciplinary approach with rapid integration of new treatment strategies is required for the treatment of patients developing brain metastases, aiming to prolong survival, preserve neurologic function and improve quality of life.

The BMBC registry was initiated to include patients with brain metastases and a history of breast cancer that were diagnosed for brain metastases since the year 2000. Registration of patient data is allowed prospectively after obtaining an informed consent. Retrospective participants can be entered without an informed consent if the patient is not able to sign the informed consent and as long as the data are anonymously captured.

The registry study is performed in collaboration with Prof. Dr. Volkmar Müller, Priv. Doz. Dr. Isabell Witzel, and Dr. Elena Laakmann from the Universitätsklinikum Hamburg-Eppendorf.

Study objectives

The BMBC registry aims to collect data to determine the incidence of brain metastases, the number and size of brain metastases, location, histopathological characteristics of the primary tumor and brain metastases, sensitivity of diagnostic tools (cranial computed tomography (CT) and magnetic resonance imaging (MRI)), performance status, prognosis, quality of life, and the influence of treatment strategies on prognosis and neurological function. In addition, the registry allows investigation of translational research questions, using tumor specimen of the primary and metastatic tumor.

Planned analyses include treatment patterns in Germany, patient outcome, as well as validation of prognostic scoring systems in a multicenter setting and in the context of new targeted therapies. Planned translational research projects include the impact of glycosylation, resistance mechanisms against HER2-targeted therapies, the role of the blood brain barrier, evaluation of markers of radioresistance and specific genomic alterations associated with brain tropism of breast cancer cells.

Study report

The study was opened for documentation in April 2014 with more than 50 participating centers. As of 31st of December 2019, 2,864 patients have been registered and 404 tissue samples have been received. Registration of patients is ongoing. First analysis of treatment patterns and clinical outcome in 1,105 breast cancer patients with brain metastases (BM) from the BMBC registry has confirmed our previous findings [1,2] and has shown that HER2-positive patients had the longest median survival with 12.1 months (95 % CI, 10.2–13.7) compared to 5.5 months (95 % CI, 4.1–7.1) for luminal primary tumors and 4.1 months (95 % CI, 3.1–4.8) for triple-negative patients ($p < 0.001$) [3]. Median overall survival (OS) of patients with BM diagnosed between 2000 and 2006 was 7.2 months (95 %CI, 5.3-9.6) compared to 6.7 months (95 % CI, 5.5-8.1) of patients diagnosed between 2007 and 2012 ($p=0.848$). However, we could not observe improvement of survival over the study period and the time intervals in any tumor subtype. Hence, larger patient cohorts are needed to detect the survival difference.

A subproject has retrospectively analyzed clinical data, CT and MRI scans obtained from 300 breast cancer patients with BM in 4 centers participating in the BMBC registry in Germany [4]. Patients with hormone receptor (HR)-positive or HER2-positive status had a significantly lower number of BM at diagnosis. HER2-positive patients treated with trastuzumab before the diagnosis of BM demonstrated a lower incidence of intracranial metastases. Patients with HER2-positive breast cancer had a higher number of cerebellar metastases compared to HER2-negative patients, whereas patients with triple-negative breast cancer developed more often leptomeningeal disease. These findings suggest a different tumor cell homing to different brain regions depending on molecular subtype and treatment.

An update of the first clinical data of patients participating in the BMBC registry has recently been published [5]. A total of 1,712 breast cancer patients who developed BMs between January 2000 and December 2016 at 80 institutions in Germany were retrospectively analyzed. Median age at diagnosis of BMs was 56 years (22-90 years). About 47.8 % (n=732) of patients had HER2-positive, 21.4 % (n=328) had triple-negative and 30.8 % (n=471) had HR-positive, HER2-negative (luminal-like) primary tumors. The proportion of patients with HER2-positive BMs decreased when the years 2000-2009 are compared with 2010-2015 (51 % vs 44 %), whereas the percentage of patients with luminal-like tumors increased (28 % vs 34 %), (p=0.033). Patients with BMs in the posterior fossa were more often HER2-positive (53.8 %) compared to those with triple-negative (20.7 %) or luminal-like primary breast cancer (25.5 %), (p<0.0001). Median overall survival (OS) after development of BMs for the entire cohort was 7.4 months (95 % CI 6.7-8.0 months). One-year survival rate was 37.7 % (95 % CI, 35.2-40.1). Patients with HER2-positive tumors had the longest median OS of 11.6 months (95 % CI, 10.0-13.4) compared with 5.9 months (95 % CI, 5.0-7.2) for patients with luminal-like and 4.6 months (95 %CI 3.9-5.4) for patients with triple-negative tumors. Patients with HER2-positive tumors who received anti-HER2 treatment had longer median OS than those without (17.1 vs 7.2 months, p<0.0001). Thus, the analysis of this large cohort of breast cancer patients with BMs demonstrated that the subtype of the primary tumor can influence the location of BMs and has a high impact on prognosis. In addition, a validation of the prognostic value of the disease-specific breast-graded prognostic assessment (breast-GPA) score in breast cancer patients with BM from the BMBC registry has been presented at the SABCS 2018. The breast-GPA score included age, Karnofsky performance score and tumor subtype of breast cancer patients (Sperduto et al. Int J Radiation Oncology Biol Phys 2012). The breast-GPA score has been further demonstrated to better identify patients with a bad prognosis (Laakmann E, et al. J Cancer Res Clin Oncol 2016) as compared with other prognostic indices which were developed to stratify patients with BM in groups according to their outcome. Therefore, this analysis aimed to validate the breast-GPA in breast cancer patients with BMs from the BMBC registry. A total of 613 patients were categorized into 4 groups according to the breast-GPA scores: 0-1: 11.9 % (n=73), 1.5-2: 22.3 % (n=137), 2.5-3: 47.8 % (n=293), and 3.5-4: 18 % (n=110). Median overall survival (OS) within the breast-GPA subgroups varied between 2.4 (95 %CI 2.0-3.4); 4.8 (95 %CI 3.6-6.9); 9.2 (95 %CI 7.2-11.3) and 12.3 (95 %CI 8.9-18.0) months, respectively and was significantly shorter compared to the OS published by Sperduto et al. [6].

Publications

1. Witzel I, Laackman E, Fehm T, et al. Brain Metastases in Breast Cancer Network Germany (BMBC, GBG 79): Multicentric, retro- and prospective collection of patient data and biomaterial from breast cancer patients with brain metastases. Cancer Res 2015; 75 (9 Suppl): Abstract OT2-5-01.
2. Witzel I, Loibl S, Laakmann E, et al. Brain Metastases in Breast Cancer Network Germany (BMBC, GBG 79): First analysis of 1004 patients from the multicenter registry. Cancer Res 2016;76(4 Suppl): Abstract nr P6-17-08.
3. Mueller V, Loibl S, Laakmann E et al. Doris Augustin, Brain Metastases in Breast Cancer Network Germany (BMBC, GBG 79): Treatment patterns and clinical outcome of more than 1000 patients with brain metastases from breast cancer. J Clin Oncol 34, 2016 (suppl; Abstract 2070).
4. Laakmann E, Witzel I, Scriba V et al. Radiological Patterns of Brain Metastases in Breast Cancer Patients: A Subproject of the German Brain Metastases in Breast Cancer (BMBC) Registry. Int J Mol Sci. 2016 23;17(10).
5. Witzel I, Laakmann E, Weide R, et al. Treatment and outcomes of patients in the Brain Metastases in Breast Cancer Network Registry. Eur J Cancer. 2018; 102:1-9.
6. Witzel I, Riecke K, Laakmann E et al. Validation of different prognostic scores in breast cancer patients with brain metastases of the BMBC registry (GBG-79). Cancer Res 2019; 79(4 Suppl):Abstract nr P4-08-26.

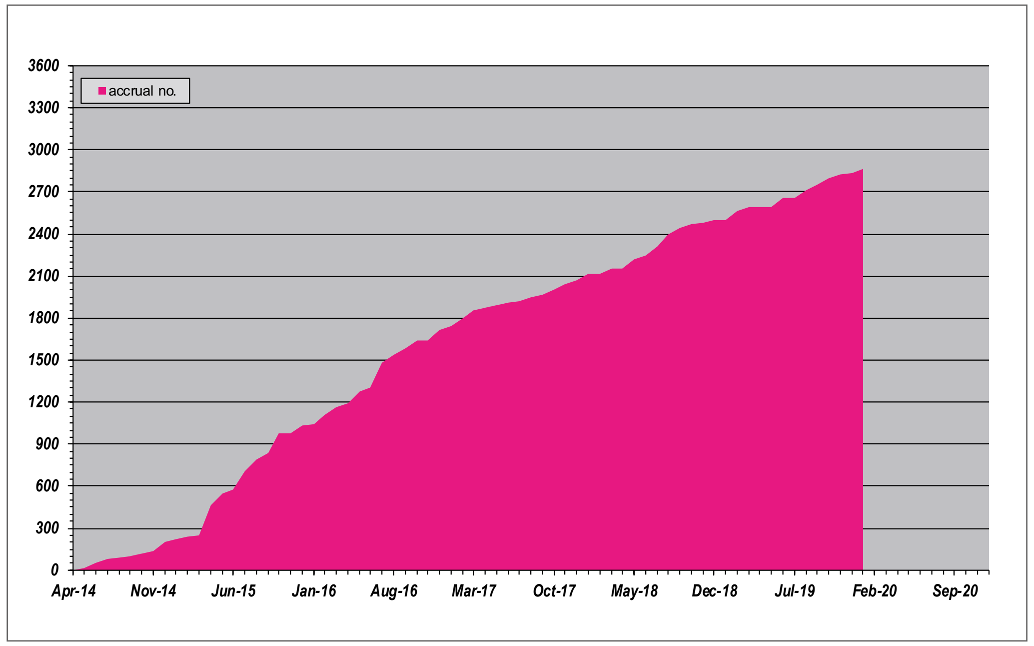

Figure 1: BMBC recruitment as of 31st December 2019

We encourage all study centers and practices to enter eligible patients into the registry.
We thank all participating sites that have entered their patients into the registry and have contributed to this important research so far.
We would like to kindly remind all sites to provide biomaterial which is urgently needed to answer translational research questions.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

Universitätsklinikum Hamburg-Eppendorf

TRAFO

SPONSOR:
GBG Forschungs GmbH

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GBG 86: DESIREE

A multicenter, randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer

NCT02387099

DESIREE is a multicenter, double-blind, randomized phase II trial that will recruit 156 patients from 60 sites in Germany within approximately 24 months.

Background

The BOLERO-2 study demonstrated an enormous benefit for patients who received everolimus in addition to exemestane and who progressed during/after a non steroidal aromatase inhibitor (NSAI) (Baselga N Engl J Med 2012), which led to approval of everolimus in this indication. However, experience from routine use has shown a high rate of intolerability of this innovative treatment approach especially during the first 12 weeks of treatment. Most common side effect is mucositis/stomatitis which is considered the leading cause for treatment discontinuation not related to tumor progression. This outside clinical trial experience is contrary to findings from BOLERO-2, where the number of patients still taking full-dose (10 mg) of everolimus at 4, 8, and 12 weeks is 77.8 %, 75.6 %, and 75.6 %, respectively. These findings are in concordance with non-interventional studies.

In the non-responder part (setting III) of the neoadjuvant GeparQuinto study, everolimus was given as salvage treatment in combination with paclitaxel for patients without response to 4 cycles epirubicin/cyclophosphamide +/- bevacizumab. A dose-escalation schema was successfully used to improve tolerability of everolimus together with the cytotoxic agents (von Minckwitz Ann Oncol 2011; von Minckwitz Ann Oncol 2014).

The palliative DESIREE study compares the cumulative rate of mucositis/stomatitis grade 2-4 (WHO's oral toxicity scale (OTS) at 12 weeks after start of treatment using a conventional and a dose-escalating schema of everolimus in combination with exemestane in patients with metastatic breast cancer and progression or relapse after non-steroidal aromatase-inhibitor treatment.

Study design and objectives

DESIREE primarily aims to assess the cumulative rate of mucositis/stomatitis grade 2-4 (OTS) at 12 weeks after start of treatment using a conventional and a dose-escalating schema of everolimus in combination with exemestane.

Secondary objectives are: the cumulative rate of mucositis/stomatitis grade 2-4 (OTS), cumulative rate of mucositis/stomatitis grade 1 and any grade (OTS) at 12 and 24 weeks after start of treatment, rate of patients on 10 mg daily at 12 weeks and 24 weeks, clinical benefit rate at 24, safety with regard to other organ signs and symptoms, time to grade ≥ 2 mucositis/stomatitis, cumulative dose at 4 weeks, relative dose intensity for everolimus and quality of life using the FACT-B questionnaire and the QSDQ. Potential biomarkers predicting safety and compliance will be determined after completion of study treatment.

Study report

DESIREE started recruitment in June 2015. As of 31st December 2019, a total of 142 patients have been included. The end of the study (i.e. last visit of the last patient randomized) was initially estimated for October 2017, but due to the very slow accrual it was recently extended to QIV/2020.

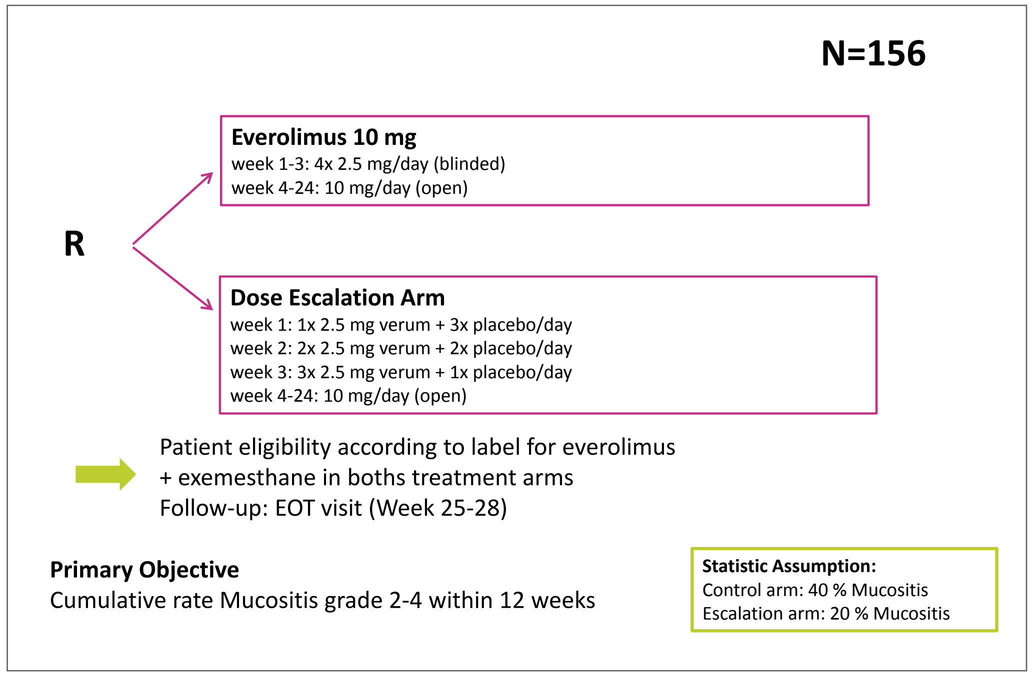

Figure 1: DESIREE study design

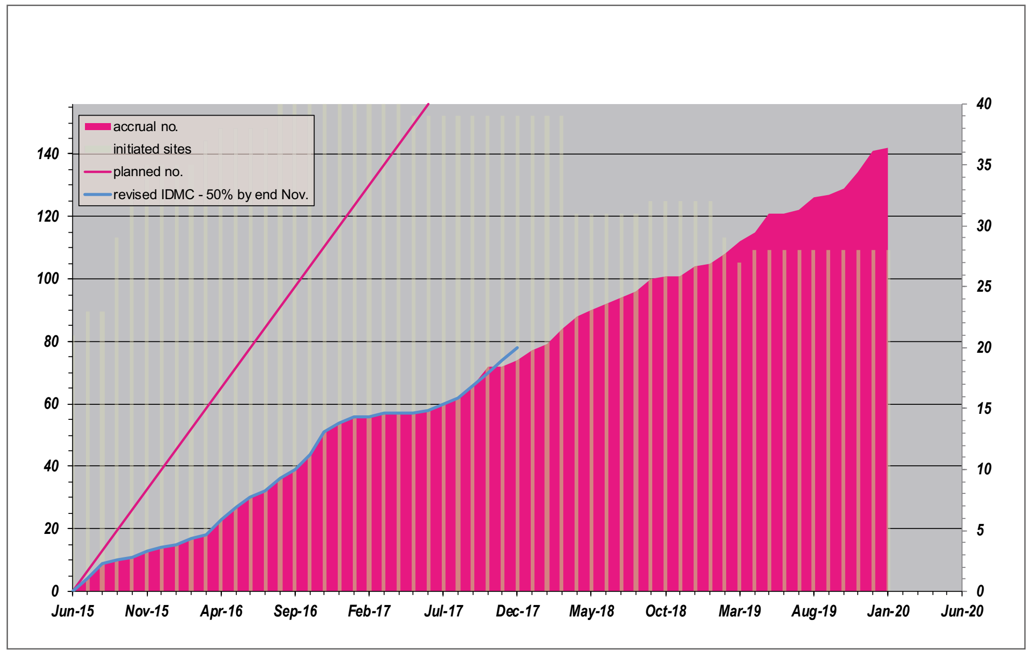

Figure 2: DESIREE recruitment as of 31st December 2019

We are thanking all participating centers for their commitment and efforts so far. We would like to encourage all sites to continue to support the DESIREE study by recruitment of patients and provision of biomaterial in a timely manner.

COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

STUDY CHAIR:
Prof. Dr. Sibylle Loibl
German Breast Group,
Neu-Isenburg

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GBG 85: AURORA

Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer

NCT02102165

AURORA is an exploratory, multinational, collaborative molecular screening program aiming to recruit and collect biomaterial from 1,000 metastatic breast cancer patients from 69 sites (7 in Germany) within approximately 4 years.

Background

The current era of molecular oncology offers the technology to characterize, at the base pair level, the complete molecular landscape of cancer. This heralds great promise with regards to understanding driving genetic aberrations, elucidating tumor genetic heterogeneity, discovering new therapeutic targets, and ultimately improving outcomes for cancer patients. For breast cancer in particular, recent studies using massively parallel sequencing have uncovered a large number of candidate "driver" mutations that occur at a low frequency. In some cases, these driver mutations and/or other molecular aberrations are potentially targetable by agents currently approved in the clinical settings or in various stages of clinical development.

There is increasing evidence to demonstrate that breast cancer metastases often acquire new molecular aberrations compared to their matched primary tumors, and that different treatment-resistant clones may emerge over time. While the clinical relevance of these phenomena is not yet well understood, obtaining biopsies from the metastatic lesions could help uncover mechanisms of resistance and thus help refine treatment decisions. There is currently an exponential growth of molecular screening initiatives, at the national, single hospital or even at the private laboratory level, aimed at sequencing tumor DNA from breast cancer patients in order to identify "actionable mutations" that could be targeted in the clinical setting. However, such isolated approaches have major limitations as they generate fragmented results that might lose their potential and impact if not contextualized in a proper, structured clinical setting. Moreover, the use of modern techniques is likely to result in breast cancer being further reclassified into smaller molecular subpopulations. Clinical trials for these molecularly defined small subpopulations are likely to require international collaboration in order to meet recruitment objectives. Ultimately, the aim of AURORA is to improve the outcomes of all patients diagnosed with metastatic breast cancer.

Study design and objectives

Patients are eligible if they are 18 years or older, either female or male, and have not received more than 1 type of treatment from the time metastases were discovered, metastasi(e)s has just been diagnosed or their disease has come back (disease relapse). Biopsy samples from both the primary and metastatic (or relapsed) tumor will be collected for central analyses, together with blood, serum and plasma samples. Any samples not analyzed immediately will be stored in an independent bio-repository to enable future (not yet defined) research aimed at better understanding metastatic breast cancer.

In summary, the main objectives of AURORA are to better understand the genetic aberrations in metastatic breast cancer and to discover the mechanisms of response or resistance to therapy, in order to ultimately identify the "right therapy for each individual patient". At the same time, patients with genetic aberrations that are being targeted by new drugs in development will be offered the possibility to participate in clinical trials, when approved and available in their countries.

Study report:

First results from the AURORA study were presented at the ESMO 2019. A total of 381 patients recruited until November 2017 and with assessable data were included in the molecular analyses. The pathological subtype distribution included 228 hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, 51 HER2-positive and 71 triple-negative (TNBC) tumors; for 31 cases the information was not available. 292 (77%) patients were treatment naïve in the metastatic setting including 76 patients (20%) with de novo metastatic disease. The analysis focused on patients with paired samples (primary and metastases) and showed increased number of mutations in the metastatic samples. Hence, the findings shed light on the molecular makeup of several clinically-relevant metastatic breast cancer categories [1]. The patients will be followed up for 10 years.

Reference:
Aftimos PG, Antunes De Melo e Oliveira AM, Hilbers F et al. First report of AURORA, the breast international group (BIG) molecular screening initiative for metastatic breast cancer (MBC) patients (pts). Ann Oncol 2019; 30 (suppl_3): iii47-iii64.

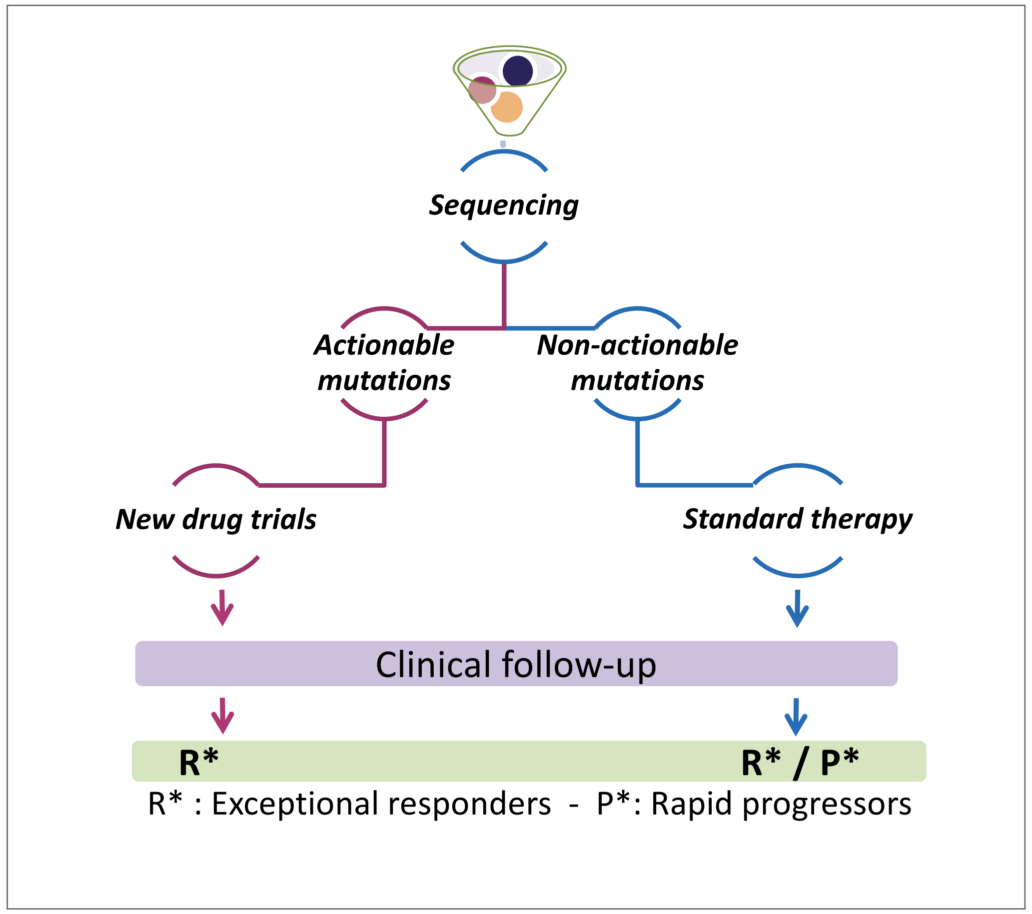

Figure 1: AURORA study design

We are thanking all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients and by providing biomaterial in a timely manner.

COLLABORATING STUDY GROUPS:

SPONSOR:
Breast International Group (BIG)

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COORDINATING INVESTIGATOR (GERMANY)
Benjamin Schnappauf
Sana Klinkum Offenbach, Germany

Studies in Follow-up

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GBG 78: Penelope^{B}

Phase III study evaluating palbociclib (PD-0332991), a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor in patients with hormone-receptor-positive, HER2-normal primary breast cancer with high relapse risk after neoadjuvant chemotherapy

NCT01864746

PENELOPE^{B} is a prospective, international, multicenter, randomized, double-blind, placebo-controlled, post-neoadjuvant phase III study that has recruited 1,250 patients from approximately 300 sites in 11 countries.

Background

About one third of hormone receptor (HR)-positive, HER2-normal breast cancer patients with residual disease after neoadjuvant chemotherapy have a substantial risk of relapse (von Minckwitz et al. J Clin Oncol 2012). Those patients can be identified using the validated clinical-pathologic stage–estrogen/grade (CPS-EG) scoring system (Figure 1A), ranging from 0-6 (Jeruss et al. J Clin Oncol 2008; Mittendorf et al. J Clin Oncol 2011).
Palbociclib is an oral, highly selective inhibitor of CDK4/6 kinase activity that prevents cellular DNA synthesis by inhibiting cell cycle progression (Finn et al. Breast Cancer Res 2009). Luminal tumors have shown sensitivity to palbociclib. In a phase II study, palbociclib extended progression free survival in combination with letrozole as first-line hormonal treatment for advanced breast cancer (Finn et al. Cancer Res 2012). Palbociclib has also shown single agent activity in patients with relapsed HR-positive advanced breast cancer (DeMichele et al. Cancer Res 2011). Based on the recent results from the PALOMA-2 (Finn et al. N Engl J Med 2016) and PALOMA-3 trials (Turner et al. N Engl J Med 2015), palbociclib was approved by European Medicines Agency (EMA) for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in combination with fulvestrant in pretreated patients.

In the Penelope^{B} study we aim to demonstrate that one year of post-neoadjuvant treatment with palbociclib, in addition to standard anti-hormonal therapy, provides a superior invasive disease free survival and an acceptable safety profile compared to placebo in women with HR-positive, HER2-normal early breast cancer who did not obtain a pathological complete response after taxane-containing neoadjuvant chemotherapy and are at high risk of relapse (CPS-EG score ≥3 or 2 if ypN+) (Marmé et al. Eur J Cancer 2015).

Study design and objectives

Penelope^{B} primarily aims to compare invasive disease-free survival (iDFS) between the two treatment arms.
In addition, iDFS excluding second non-breast cancers, overall, distant disease-free and local recurrence-free survival, iDFS per treatment group in patients with luminal-B tumors, compliance and safety, patient reported outcomes (quality of life), health economics, drug-drug interaction-potential for the palbociclib – endocrine combination therapy (in a subset of this patient population) as well as correlations between drug exposure and efficacy and safety findings will be analyzed. The study includes post- as well as premenopausal women and allows the use of different endocrine therapies. Furthermore, the Penelope^{B} study will also address translational research questions, such as the role of biomarkers involved in the CDK4/6 pathway.
Based on the outcome of the first efficacy interim analysis (April 2017), the Independent Data Monitoring Committee (IDMC) has recommended to adapt the patient's number of the trial to a total of 1,250 patients.

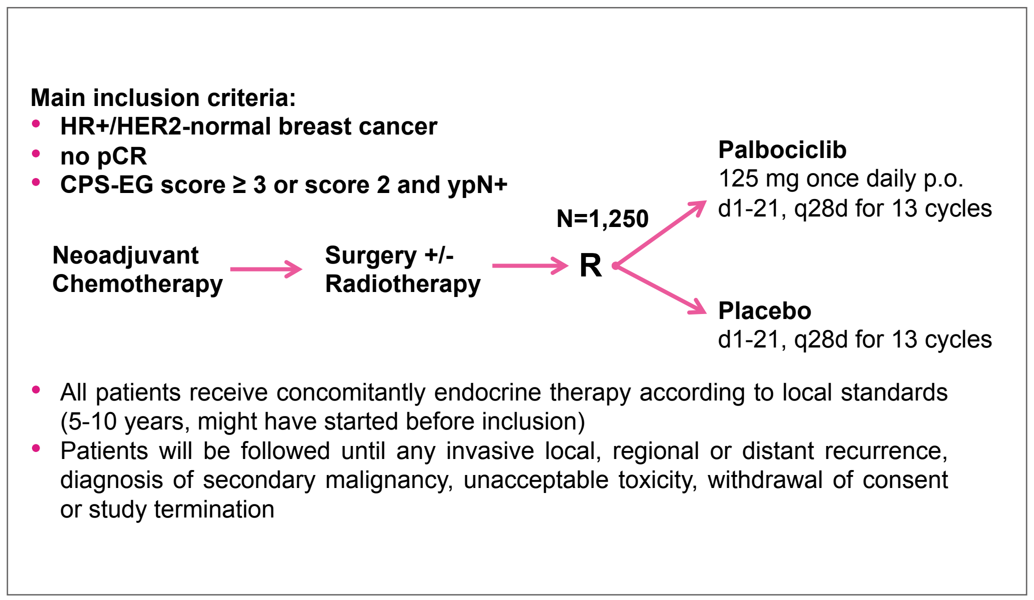

Figure 1: Penelope^{B} study design

Study report

Penelope^{B} started recruitment with the first randomized patient in Germany in February 2014. The first international patient was randomized in Spain in October 2014. The recruitment was closed in December 2017. An efficacy interim analysis was recently performed. Final analysis on the primary endpoint and secondary efficacy endpoints (except for OS) will be conducted when 290 iDFS events have been observed, which is estimated to occur about 6.5 years after first patient in.

We are thanking all participating centers for their commitment and efforts so far. We would like to encourage all sites to continue to support the Penelope^{B} study by timely provision of the biomaterial and the documentation of the patients.

COLLABORATING STUDY GROUPS:

GBG German Breast Group
BIG Breast International Group
AGO-B Breast Study Group
NSABP Partners in Cancer Research

SPONSOR:
GBG Forschungs GmbH

INTERNATIONAL STUDY CHAIR:
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GBG 68: GAIN-2

Neo-/adjuvant phase III trial to compare intense dose-dense chemotherapy to tailored dose dense chemotherapy in patients with high-risk early breast cancer

NCT01690702

GAIN-2 is a neo-/ adjuvant, prospective, multicenter, randomized, open-label phase III trial that has recruited 2,887 patients from 136 sites in Germany.

Background

Combined chemotherapy regimens always require compromises regarding the doses of each drug and the treatment intervals due to acute and cumulative toxicities. The sequential administration of monotherapies, however, allows the administration of high doses of single substances and dose-dense intervals. Such intense, dose-dense chemotherapy regimens have shown to improve the survival in early breast cancer patients with high risk of recurrence when compared to conventional dosed chemotherapy (Möbus et al. J Clin Oncol 2010; Citron et al. J Clin Oncol 2003). However, both of these dose-dense regimens tested so far used solvent-based taxanes (paclitaxel and docetaxel) and nowadays outdated comparators.
Nab-paclitaxel, the nanoparticle albumin-bound form of paclitaxel, has shown a better toxicity profile and higher efficacy compared to solvent-based taxanes and might thus be preferred in an intense dose-dense regimen.
It is long known from the NSABP-B18 trial and others that neoadjuvant chemotherapy is as effective as adjuvant chemotherapy in preventing recurrences (Wolmark et al. J Natl Cancer Inst Monogr 2001).
The hypothesis studied by GAIN-2 is that in patients with early node-positive or high-risk node-negative breast cancer, a pre-defined, intense, dose-dense, regimen (EnPC – epirubicin followed by nab-paclitaxel followed by cyclophosphamide) is more effective compared with a dose-dense regimen, where single doses are adjusted depending on individual hematological and non-hematological toxicities (dtEC-dtD - dose-dense, dose-tailored epirubicin and cyclophosphamide followed by dose-dense, dose-tailored docetaxel).
The maximum dose of nab-paclitaxel in this setting has been explored in a run-in phase included in the study design. It has been shown that patients can safely be treated with a biweekly dosage of 330 mg/m² nab-paclitaxel (Möbus et al. J Clin Oncol 2013) which is now used for the main phase of the study.

Study design and objectives

GAIN-2 primarily aimed to compare invasive disease-free survival after neo-/adjuvant chemotherapy with EnPC or dtEC-dtD in patients with primary node-positive or high risk node negative breast cancer. In addition, overall, distant disease-free, locoregional relapse-free, local relapse-free, regional relapse-free and brain metastasis-free survival, compliance and safety, side-effects of taxanes, pCR rate in patients treated with neoadjuvant therapy and treatment effects by intrinsic subtypes, number of involved nodes and Ki-67 are compared between the two treatment arms. Breast conservation rate between adjuvant and neoadjuvant patients as well as the survival endpoints by pCR will be also assessed.
In addition, GAIN-2 offers the opportunity to address a range of translational research questions, which are summarized bellow.
An amendment of the study protocol (effective as of 1st August 2016) allowed treatment of patients with the same regimens in the neoadjuvant setting. All neoadjuvant patients with HER2-positive disease received trastuzumab and optional pertuzumab at doses and duration in concordance with current treatment guidelines.

Substudies

Substudy subcutaneous trastuzumab

In addition to the main protocol, 226 HER2-positive patients of the GAIN-2 trial were randomized to receive further trastuzumab subcutaneously (s.c.) instead of intravenously (i.v.) after completion of the chemotherapy according to current guidelines. The patients were randomized between trastuzumab application into thigh or abdominal wall and the preference of the patients is determined. In addition, pharmacokinetic measurements were performed in 36 patients (18 per group).

Substudy biology of lymph node metastases

The substudy on biology of lymph node metastases examines primary tumors and corresponding axillary lymph nodes for biologically relevant factors involved in lymphogenic and distant tumor cell spread. Written informed consent and the availability of primary tumor and axillary lymph node tissue are crucial for this translational substudy.

Substudy on SNP (Single Nucleotide Polymorphisms)

This observational substudy aims to associate the germline genotype of the patient with the treatment response, long-term prognosis and the molecular profile of the tumors in both randomization arms.

Substudy on ovarian function

To define the risk of premature ovarian failure and loss of fertility with modern regimens, the hormone levels of estradiol, Follicle-Stimulating Hormone (FSH) and Anti-Müllerian Hormone (AMH) in addition to antral follicle counts measured by ultrasound are assessed.

Study report

Between October 2012 and July 2017, a total of 2,887 patients have been enrolled in the main study (2,289 in the adjuvant setting and 598 in the neoadjuvant setting from 136 recruiting sites in Germany) [1,2]. The trastuzumab substudy has enrolled 226 patients between November 2013 and August 2017.
Pharmacokinetic analysis of a s.c. injection of trastuzumab into the thigh or into the abdominal wall in patients with HER2-positive primary breast cancer (BC) treated within the neo-/adjuvant GAIN-2 study showed that bioavailability of s.c. trastuzumab as reflected by peak and total exposure measured in cycle 7 was approximately 30 % higher if the antibody was administered into the thigh; no increased toxicity was observed. Study limitations were that no cross-over design was used and the number of patients who satisfied criteria for per-protocol-set was different in the arms [3].
Results of the pCR rates within the breast (ypT0/is ypN0+) for the neoadjuvant setting demonstrated that the pCR rates for patients treated with iddEnPC were statistically significantly higher compared to those receiving dtEC-dtD as neoadjuvant chemotherapy (53.3 % [95 %CI 52.4 %-64.0 %] vs 49.7 % [95 %CI 43.8 %-55.5 %]; p=0.043). No significant difference for pCR was found within the breast cancer subtypes [4].
The first results of the ovarian substudy were presented at the SABCS 2017. The pooled analysis of 740 breast cancer patients aged ≤45 years treated with anthracycline or taxane-based chemotherapy (CT) within the GeparSixto, GeparSepto, GENEVIEVE and Gain-2 trials showed that nearly 70% of women regained premenopausal hormone levels of FSH and E2 within 2 years after the end of CT. Despite that, less than one third of the women maintain their fertility potential as predicted by AMH, indicating that AMH is a very sensitive marker for the prediction of fertility function after CT for early breast cancer [5]. Recently, an impact of chemotherapy-induced ovarian failure on long-term outcomes in young women with early

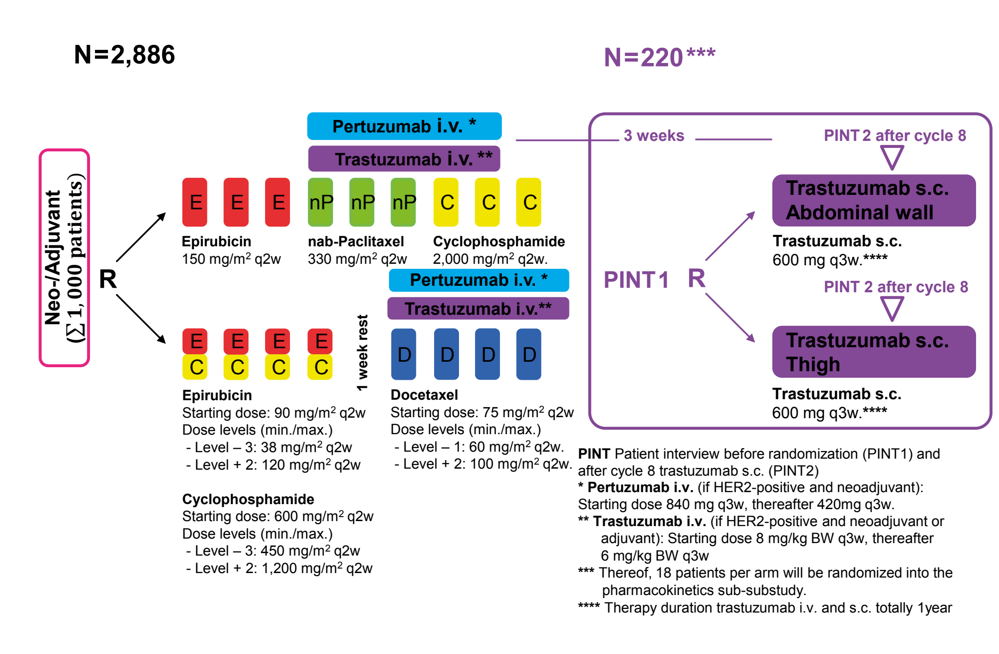

Figure 1: Study design of the GAIN-2 main study and the subcutaneous trastuzumab substudy

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

SPONSOR:
GBG Forschungs GmbH

STUDY CHAIR:
Prof. Dr. Volker Möbus
Universitätsklinikum Frankfurt, Frankfurt am Main

breast cancer was presented at the ESMO 2019. Patients with chemotherapy-induced ovarian failure after anthracycline/taxane-based CT showed a better disease-free survival, especially in women with hormone-receptor positive tumors or younger than 30 years. The improvement in disease-free survival translates into a survival advantage in patients with hormone-receptor positive early breast cancer [6].

Publications

1. Noeding S, Forstbauer H, Wachsmann G, et al. GAIN2: Adjuvant phase III trial comparing an intensified dose-dense adjuvant therapy with EnPC compared to a dose-dense, dose-adapted therapy with dtEC dtDocetaxel in patients with primary breast cancer and a high risk of recurrence. Ann Oncol 2014, 25 (suppl_4): iv90.
2. Möbus V, Lück H-J, Forstbauer H, et al. GAIN-2: Adjuvant Phase III Trial to Compare Intense dose-dense (idd) Treatment with EnPC to Tailored dose-dense (dt) Therapy with dtEC-dtD for Patients with high-risk Early Breast Cancer: Results of the Second Safety Interim Analyses. Cancer Res 2016;76(4 Suppl): Abstract nr P1-13-05.
3. Möbus V, Mahlberg R, Janni W, et al. Pharmacokinetic results of a subcutaneous injection of trastuzumab into the thigh versus into the abdominal wall in patients with HER2 positive primary breast cancer (BC) treated within the neo-/adjuvant GAIN-2 study. Cancer Res 2018;78(4 Suppl):Abstract nr P5-20-09.
4. Moebus V, Noeding S, Ladda E, et al. Neo-/adjuvant phase III trial to compare intense dose-dense (idd) treatment with EnPC to tailored dose-dense (dt) therapy with dtEC-dtD for patients with high-risk early breast cancer: results on pathological complete response (pCR) for patients treated within the neoadjuvant setting. J Clin Oncol 2018; 36.15_suppl.568.
5. Furlanetto J, Thode C, Huober J, et al. Changes in hormone levels (E2, FSH, AMH) and fertility of young women treated with neoadjuvant chemotherapy (CT) for early breast cancer (EBC) [abstract]. Cancer Res 2018;78(4 Suppl):Abstract nr PD7-09.
6. Furlanetto J, Nekljudova V, Schneeweis A, et al. Impact of chemotherapy-induced ovarian failure (CIOF) on disease-free survival (DFS) and overall survival (OS) in young women with early breast cancer (EBC). Ann Oncol 2019;30 (Suppl_5), 180PD.

We are thanking all participating centers for their commitment and efforts so far. We would like to encourage all sites to continue to support the GAIN-2 study by transferring participants to the General Follow-up and to the self-reported outcome registry.

GBG 87: PALLAS

PALLAS

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PALLAS: PALbociclib CoLlaborative Adjuvant Study

A randomized phase III trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer

NCT02513394

PALLAS (ABCSG 42, AFT-05, BIG 14-3) is a multicenter, prospective, international, randomized, open-label, adjuvant phase III study that has recruited 5,795 patients worldwide.

Background

Although many patients with HR-positive (HR+)/HER2-negative (HER2-) breast cancer may be cured of their disease with optimal local and systemic therapy, a significant number of patients with stage II and III disease will experience disease recurrence. Adjuvant endocrine therapy for breast cancer can be extremely effective, particularly with extension beyond 5 years, however disease recurrence can occur, with risk distributed over the decades following initial diagnosis. Methods to improve the efficacy of endocrine therapy, and delay the onset of resistance, are needed.
HR+ breast cancer biologically may demonstrate features suggestive of sensitivity to CDK4/6 inhibition with agents such as palbociclib. Given the demonstrated activity and safety of palbociclib in the first-line treatment of metastatic HR+/HER2- breast cancer, supporting FDA approval, there is interest in whether the benefits of CDK4/6 inhibition may translate into the adjuvant setting. The purpose of the PALLAS study is to determine whether the addition of palbociclib to adjuvant endocrine therapy will improve outcomes over endocrine therapy alone for HR+/HER2- early breast cancer. Assessment of a variety of correlative analysis, including evaluation of the effect of palbociclib in genomically defined tumor subgroups, is planned.

Study design and objectives

PALLAS primarily aims to compare invasive disease-free survival (iDFS) for the combination of at least 5 years endocrine therapy and 2-year palbociclib treatment versus at least 5 years endocrine therapy alone in patients with histologically confirmed HR+/HER2- invasive early breast cancer. Secondary objectives are to compare iDFS excluding second primary cancers of non-breast origin, distant recurrence-free survival (DRFS), locoregional recurrences-free survival (LRRFS), overall survival (OS) and safety between the two arms. The principal translational research objective is to compare baseline tumor tissue to determine whether there is prognostic or predictive utility for defined genomic subtypes (luminal A, luminal B and non-luminal) with respect to iDFS and OS.
Clinical science objectives are to evaluate adherence to oral therapy in patients receiving palbociclib and endocrine therapy, to determine the association of body mass index (BMI) and race with the efficacy of palbociclib and endocrine therapy. Patient reported outcomes objectives are to compare patient-reported quality of life, fatigue, arthralgia, and endocrine symptoms between the two arms overall and by subgroups defined by age at randomization (≤ 50 and > 50) and initial endocrine therapy (tamoxifen and AI) at multiple pre-specified time points. Multiple tissue- and blood-based correlative studies are scheduled throughout the course of the PALLAS trial to evaluate potential markers of response and/or resistance in patients receiving endocrine therapy with palbociclib versus endocrine therapy alone. These sample analyses will be outlined in the TRANS-PALLAS manuals and guidelines, developed with the dedicated TRANS-PALLAS committee. The German Breast Group acts as a local study group for Germany and is responsible for the biobanking organization of the PALLAS study for non-US samples.

Study report

PALLAS recruited 5,795 patients worldwide (110 in Germany) between October 2015 and November 2018. Two interim efficacy analyses were planned for monitoring the futility and superiority, and are scheduled to occur when 33 % and 67 % of the total number of iDFS events are observed. The first interim efficacy analysis has already been carried out. The study participants are currently in the treatment or follow-up phase, depending on the time of randomization [1,2].

Publications

1. Mayer E.L, Demichele A.M, Pfeiler G, Barry W, Metzger O, et al. PALLAS: PALbociclib CoLlaborative adjuvant study: A randomized phase 3 trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant

COLLABORATING STUDY GROUPS:
GBG German Breast Group
BIG Breast International Group
ABCSG Austrian Breast & Colorectal Cancer Study Group
ALLIANCE Foundation Trials, LLC

SPONSOR:
AFT (US), ABCSG (Non-US Sites)

INTERNATIONAL STUDY CHAIRS:
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Dr. Angela DeMichele
Abramson Cancer Center (US)
Prof. Dr. Michael Gnant
ABCSG (AT)

STUDY CHAIRS GERMANY:
Dr. Sabine Schmatloch
Elisabeth Krankenhaus, Kassel

endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol 2017;28: 215TiP.

2. Mayer E, DeMichele A, Gnant M, Barry W, Pfeiler G, et al. PALLAS: PALbociclib CoLlaborative Adjuvant Study: A randomized phase 3 trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+/HER2- early breast cancer. Cancer Res 2018; 78(4 Suppl): OT3-05-08.

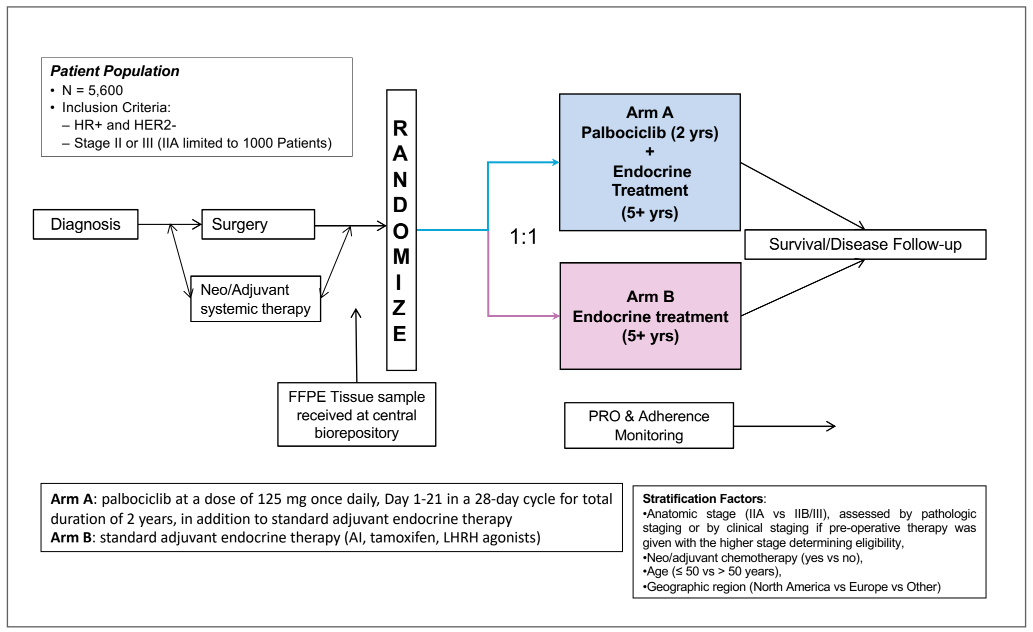

Figure 1: PALLAS study design

We are thanking all participating centers for their commitment and efforts so far. We would like to encourage all sites to continue to support the PALLAS study by transferring participants to the General Follow-up and to the self-reported outcome registry in a timely manner.

GBG 82: OLYMPIA

A randomized, double-blind, parallel group, placebo-controlled multi-center Phase III study to assess the efficacy and safety of olaparib versus placebo as adjuvant treatment in patients with germline *BRCA*1/2 mutations and high-risk HER2-negative primary breast cancer who have completed definitive local treatment and neoadjuvant or adjuvant chemotherapy

NCT02032823

OLYMPIA (BIG 6-13, NSABP B-55, D081CC0006) is a multicenter, double-blind, parallel group, placebo-controlled, randomized phase III trial that has recruited approximately 1,800 patients from 650 sites in 22 countries within approximately 4 years.

Background

Approximately 5 % of breast cancers are associated with a *BRCA* mutation, with approximately 60 % of those being associated with the *BRCA*1 gene (generally presenting with triple negative phenotype) and approximately 40 % being associated with the *BRCA*2 gene (generally estrogen/progesterone positive phenotype) Mutations in either gene result in tumors that are deficient in homologous recombination. Currently, there are no approved treatments specific for germline *BRCA*1/2 mutated breast cancer patients and these patients are treated according to their hormone receptor and HER2 status.
Polyadenosine 5'diphosphoribase [poly (ADP ribose)] polymerisation (PARP) inhibition is a novel approach to targeting tumors with deficiencies in DNA repair mechanisms. PARP enzymes are essential for repairing DNA single strand breaks. Inhibiting PARP leads to the persistence of single strand breaks, which can then, during the process of DNA replication, be converted to the more serious DNA double strand breaks. Tumors with homologous recombination deficiencies, such as breast cancers in patients with germline *BRCA*1/2 mutations, cannot accurately repair the DNA damage, leading to cancer cell death.
Olaparib is a potent PARP-1, -2 and -3 inhibitor, that is being developed as an oral therapy, for use as monotherapy (including maintenance) and for combination with chemotherapy and other anti-cancer agents. Olaparib has been shown to inhibit selected tumor cell lines in vitro and in xenograft and primary explant models as well as in genetic *BRCA* knockout models, either as a stand-alone treatment or in combination with established chemotherapies. Clinical studies have shown that olaparib monotherapy in patients with germline *BRCA* mutations offers potentially efficacious and less toxic cancer treatment compared with currently available chemotherapy regimens (Fong et al. N Engl J Med 2009; Tutt et al. Lancet 2010; Gelmon et al. Lancet Oncol 2011; Kaufman et al. J Clin Oncol 2015).
The OLYMPIA study investigates for the first time the efficacy of olaparib compared with placebo in an adjuvant/post-neoadjuvant approach in patients with germline *BRCA*1/2 mutations and high-risk HER2-negative disease.

OlympiA – Olaparib in Adjuvant BRCAm breast cancer

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olympia@GBG.de

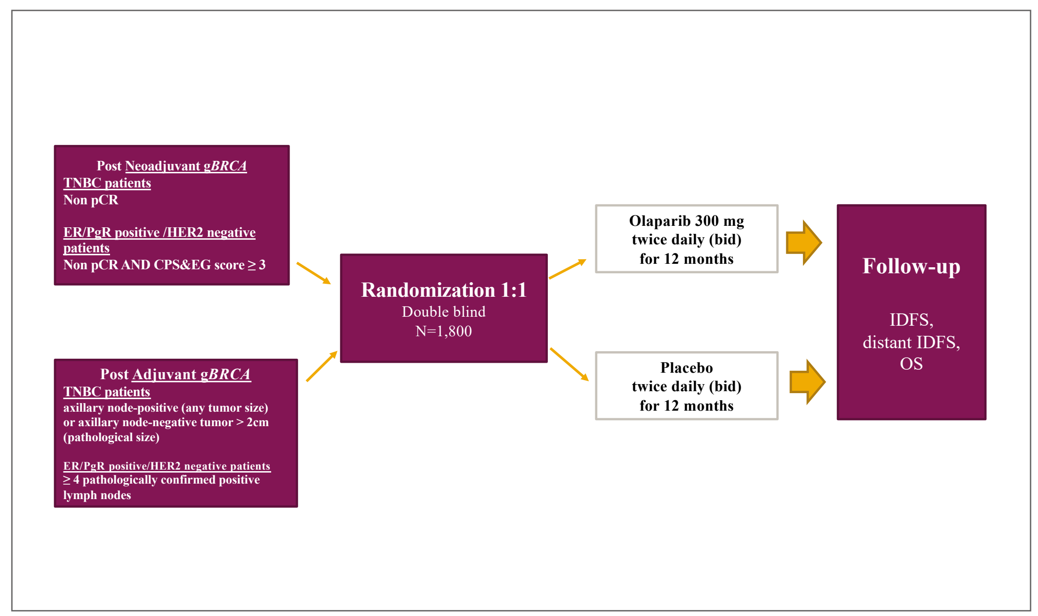

Figure 1: OLYMPIA study design

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

BIG Breast International Group

NRG ONCOLOGY Advancing Research. Improving Lives.

frontier science

SPONSOR:

AstraZeneca

INTERNATIONAL PRINCIPAL INVESTIGATOR:
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King's College,
London (UK)

STUDY CHAIR GERMANY:
Prof. Dr. Elmar Stickeler
Universitätsklinikum Aachen

Study design and objectives
OLYMPIA primarily aims to assess the effect of adjuvant treatment with olaparib on invasive disease-free survival (IDFS). In addition, the safety and tolerability of adjuvant treatment with olaparib is a key objective. Secondary objectives are to assess the effect of adjuvant treatment with olaparib on overall survival (OS), distant disease-free survival (DDFS), the incidence of new primary cancers (contralateral invasive breast cancer, contralateral non-invasive breast cancer, ovarian cancer, fallopian tube cancer and peritoneal cancer), and patient reported outcomes (according to the FACIT- Fatigue and EORTC QLQ-C30 questionnaires). Moreover, the efficacy of olaparib will be assessed in patients identified as having a deleterious or suspected deleterious variant in either of the *BRCA* genes using variants identified with current and future germline *BRCA* mutation assays (gene sequencing and large rearrangement analysis) and the exposure to olaparib (in plasma) will be determined.
Translational research components include the exploration of methods for estimating OS adjusting for the impact of confounding by subsequent therapies, the investigation whether resistance mechanisms to olaparib can be identified through analysis of tumor and blood sample derivatives, and the determination of the frequency and nature of *BRCA* mutation/s in tumor samples and comparison with germline *BRCA* mutation status. With an amendment of the study protocol, patients with HER2-negative/HR-positive disease are allowed to take part in the study.

Study report
OLYMPIA recruited a total of 1,836 patients worldwide (198 patients in Germany) between QII 2014 and QI 2018. Two interim analyses are planned for superiority and are scheduled to occur when 165 and 330 of the total number of iDFS events are observed [1, 2]. The end of the study (last patient out in the clinical follow-up) is estimated for 2028.

Publications

1. Tutt J, Kaufmann B, Gelber R et al. OlympiA: A randomized phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAm). J Clin Oncol 2015; 33.15_suppl.TPS1109.
2. Tutt A, Kaufmann B, Garber J et al. OlympiA: A randomized phase III trial of olaparib as adjuvant therapy in patients with high-risk HER2-negative breast cancer (BC) and a germline BRCA1/2 mutation (gBRCAm). Ann Oncol 2017; 28 (suppl_5): v43-v67; TIP216.

We are thanking all participating centers for their commitment and efforts so far. To facilitate timely analysis of the iDFS events we would like to encourage all sites to continue to support the OLYMPIA study by transferring participants to the General Follow-up and to the self-reported outcome registry.
Please also ensure that the biomaterial required is provided in a timely manner.
A high degree of censoring, which becomes necessary when iDFS assessment outcomes are not promptly entered, will negatively impact data quality.

GBG 75: INSEMA

INSEMA

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Clinical Project Management
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Comparison of axillary sentinel lymph node biopsy versus no axillary surgery in patients with early-stage invasive breast cancer and breast-conserving surgery: a randomized prospective surgical trial

NCT02466737

INSEMA is a prospective, multicenter, randomized trial that has recruited 5,505 patients from approximately 150 sites in Germany and approximately 20 sites in Austria.

Background
Although there is no doubt that the presence of lymph node metastases worsens prognosis of a patient, there is a lack of unambiguous evidence to support lymph node dissection. Axillary surgery for breast cancer is now considered as a staging procedure that does not seem to influence breast cancer mortality, since the risk of developing metastases depends mainly on the biological behavior of the primary tumor (seed-and-soil model). Women with breast cancer have benefitted greatly from a series of carefully conducted randomized controlled trials focusing on axillary surgery. Each successive trial showed that less surgery was better, as outcomes were the same and less surgical intervention resulted in fewer surgical complications (Fisher et al. N Engl J Med 2002; Rudenstam et al. J Clin Oncol 2006; Martelli et al. Ann Surg 2005; Veronesi et al. Ann Oncol 2005; Giuliano et al. Ann Surg 2010; Giuliano et al. JAMA 2011).
A high rate of loco-regional control could be achieved with multimodality therapy, even without axillary lymph node dissection (ALND). Despite increasing evidence disfavoring ALND, it remains part of widely recognized guidelines for breast cancer treatment. The modern approach in breast cancer care, which includes improved imaging, more detailed pathological evaluation, improved planning of surgical and radiation therapy, and more effective systemic treatment, emphasizes the need for ongoing re-evaluation of "standard" local therapy. The postsurgical therapy should be considered on the basis of biologic tumor characteristics rather than nodal involvement.

Study design and objectives
INSEMA was a prospective, randomized, surgical trial. Patients were randomized into two treatment arms in a 1:4 allocation for the first randomization and in a 1:1 allocation for the second randomization. The aim of the trial was to compare the invasive disease-free survival after breast-conserving surgery between patients who received no axillary surgery vs. patients who received sentinel lymph node biopsy (SLNB) and between node positive patients who received SLNB alone vs. patients with completion of ALND. Secondary objectives of the study were to compare the invasive disease-free survival after breast-conserving surgery between patients with no axillary surgery vs. node negative patients, between patients with no axillary surgery vs. node positive patients who received

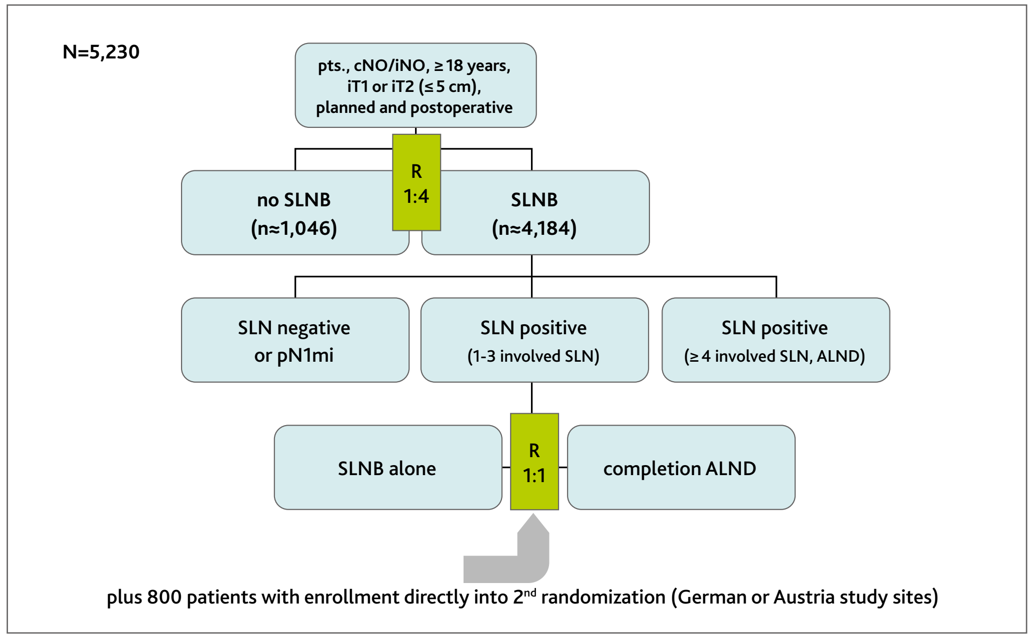

Figure 1: INSEMA study design after amendment 5

SLNB alone, and between patients with no axillary surgery vs. node positive patients with completion of ALND. Furthermore, the study allows comparison of overall survival, locoregional disease-free survival (no tumor in the ipsilateral breast or ipsilateral supraclavicular, subclavicular, internal mammary or axillary nodes), ipsilateral axillary recurrence rate, distant disease-free survival, and quality-of-life between arms as well as the event-free survival in subgroups according to age (< 65 vs. ≥ 65years), grading G1/2 vs. G3), tumor size (≤ 2 vs. > 2cm), and study site (German vs. Austrian sites in randomization 2).

INSEMA also has an attached translational program including biobanking of tumor tissue and serum samples. One translational objective is to determine the value of Memorial Sloan-Kettering Cancer Center nomograms in predicting involved sentinel nodes and positive non-sentinel nodes after positive SLNB.

An amendment of the study protocol (version 15.09.2016) included the following changes: a) within the inclusion criteria: patients with age at diagnosis ≥ 18 years can be enrolled in the study; histological confirmation of the unilateral primary invasive carcinoma of the breast can be also done by open biopsy; multifocal or multicentric tumors are allowed if breast-conserving surgery is planned; patients with SLNB and pN+ (sn) (1-3 macrometastases, stage pN1a) will undergo a second randomization to either SNLB alone or completion ALND; patients with ≥ 4 metastatic SLN should undergo completion ALND; b) within the exclusion criteria: patients with history of malignancy within the last 5 years as well as pregnant or lactating patients are excluded from the study; c) adaptation of the postoperative radiotherapy: patients with ≥ pN2a (≥ 4 involved axillary lymph node metastases) should receive regional nodal irradiation and d) changes in the randomization 2: patients from the German study sites can be also enrolled directly in the randomization 2.

Study report

Between September 2015 and April 2019, a total of 5,501 patients from 151 recruiting centres have been enrolled in the first randomization and 518 patients in the second randomization. The study is now in follow-up phase with patients being followed for 5 years. Final analysis is planned for 2024. The first analysis of patient's characteristics showed that of the 1,001 breast carcinomas included, 96.9 % were hormone receptor positive, 8.5 % were HER2-positive and only 5.4 % of all cases were tumor grade 3 (G3). Pathological analysis of 751 SLNBs showed that 83.0% (n=623) of patients had negative nodal status (pN0), 2.8 % (n=21) micrometastasis (pN1mi), 12.9 % (n=97) 1–2 macrometastases and 1.3 % (n=10) ≥ 3 macrometastases. The case rate of 85.8% without demonstrable axillary lymph node macrometastasis was significantly above the 70% predicted at protocolling. [2].

The second randomization recruited slower than expected due to the following main reasons: 1) as outlined above, the 12.9 % rate of one or two macrometastases after SLNB in the INSEMA study population was lower than expected; 2) around 20 % of patients refused the second randomization; 3) there was a slower than expected accrual at the Austrian centers, which only recruited for the second randomization.

Lack of knowledge of nodal status when SLNB is avoided represents a new challenge for the postoperative tumor board. In particular decisions on chemotherapy for luminal-like tumors and irradiation of the lymphatics (excluding axilla) must be guided by tumor biological parameters [2-4].

Publications:

1. Reimer T, von Minckwitz G, Loibl S et al. Comparison of axillary sentinel lymph node biopsy versus no axillary surgery in patients with early-stage invasive breast cancer and breast-conserving surgery: a randomized prospective surgical trial. The Intergroup-Sentinel-Mamma (INSEMA)-Trial. Cancer Res 2017;77(4 Suppl): OT2-04-02.
2. Reimer T, Stachs A, Nekljudova V, et al. First Results Following Commencement of the Intergroup-Sentinel-Mamma (INSEMA) Trial. Geburtshilfe Frauenheilkd. 2017;77(2):149-157.
3. Reimer T. Update INSEMA-Studie. 38. Jahrestagung Deutsche Gesellschaft für Senologie 2018; oral presentation.
4. Reimer T. Update INSEMA-Studie. 39. Jahrestagung Deutsche Gesellschaft für Senologie 2019; oral presentation.

We are thanking all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the INSEMA study by transferring participants to the General Follow-up and to the self-reported outcome registry in a timely manner.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

WSG

NOGGO

SUCCESS

ABCSG

SPONSOR:
University of Rostock

STUDY CHAIR:
Prof. Dr. Toralf Reimer
Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock

Completed Studies

CONTACT:
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GBG 88: GeparX

Investigating denosumab as an add-on to neoadjuvant chemotherapy in RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-paclitaxel schedules in a 2x2 factorial design

NCT02682693

GeparX is a multicenter, prospective, 2x2 randomized, open-label, phase IIb study that will recruit 778 patients from approximately 50 sites in Germany within 18 months.

Background

RANK ligand (RANKL), a key factor for bone remodeling and metastasis, is crucial for the development of mouse mammary glands during pregnancy. RANKL functions as a major paracrine effector of the mitogenic action of progesterone in mouse and human mammary epithelium via its receptor RANK and has a role in ovarian hormone-dependent expansion and regenerative potential of mammary stem cells. Pharmacologic inhibition of RANKL attenuates the development of mammary carcinoma and inhibits metastatic progression in multiple mouse models (Dougall WC et al. Clin Cancer Res 2012). In a retrospective analysis of 601 patients treated with anthracycline-taxane based chemotherapy from the GeparTrio study, we showed that an elevated immunohistochemical expression of RANK was present in 14.5 % of patients overall (Pfitzner BM et al. Breast Cancer Res Treat 2014). The ABCSG-18 study showed that adjuvant denosumab (a clinically available antibody against RANKL) reduces clinical fractures, improves bone health, and can be administered without added toxicity (Gnant M et al. Lancet 2015). Moreover, denosumab showed a trend in improvement of disease-free survival in postmenopausal woman with hormone receptor positive breast cancer (Gnant M et al. Cancer Res 2016). It appears therefore reasonable to test denosumab in patients with primary breast cancer as an adjunct to neoadjuvant chemotherapy for its ability to increase the pathological complete response (pCR) rate and improve outcome overall and in relation to the expression of RANK/L. Since in the GeparSepto study nab-paclitaxel led to an increased pCR rate compared to standard solvent-based paclitaxel, nab-paclitaxel has been chosen as backbone chemotherapy. Two different nab-Paclitaxel regimens will be compared.

Study design and objectives

GeparX co-primary aims are to compare the pCR (ypT0 ypN0) rates of neoadjuvant treatment with or without denosumab in addition to backbone treatment consisting of nab-paclitaxel (nP) 125 mg/m² weekly (+ carboplatin [Cb]) followed by epirubicin (E) and cyclophosphamide (C) or nP 125 mg/m² day 1,8 q22 (+ Cb) followed by EC plus anti-HER2 treatment (i.e. trastuzumab/pertuzumab in case of HER2-positive status) and to compare the pCR (ypT0, ypN0) rates of nP 125 mg/m² weekly (+ Cb) followed by EC or nP 125 mg/m² day 1,8 q22 (+ Cb) followed by EC plus anti-HER2 treatment. Cb will be administered concomitantly to nP for patients with triple-negative breast cancer (TNBC).

Secondary objectives are to test for interaction of denosumab treatment with RANK expression, to assess the pCR rates per arm in subgroups and according to RANK immunohistochemical expression (high/low), pCR rates according to other definitions, response rates of the breast tumor and axillary nodes, breast conservation rate, toxicity and compliance as well as to determine loco-regional invasive recurrence free survival, distant-disease-free survival, invasive disease-free survival, event-free survival and overall survival for all treatment arms and according to stratified subpopulations. Further secondary objectives are to compare RANK/L expression and Ki-67 from baseline to surgery, to correlate response measured by best appropriate imaging method after the first two cycles of treatment with pCR, to assess mammographic density–changes induced by denosumab and to assess quality of life with a focus on persisting peripheral sensory neuropathy using the FACT-Taxane questionnaire.

In addition, GeparX offers an opportunity to address a range of translational research questions which are summarized below.

An amendment of the study protocol (approved on 27th of July 2017) included the following changes: a) implementation of a HER2-positive substudy in which patients with HER2-positive breast cancer receive trastuzumab in addition to pertuzumab throughout the main trial; after surgery the patients will change to standard Herceptin®; safety and compliance of the patients participating in the substudy will be reported descriptively in treatment arms and b) the GeparPET substudy (designed to investigate whether the presurgical staging with PET-CT in addition to conventional presurgical staging methods can decrease the rate of mastectomy in patients treated with neoadjuvant chemotherapy) has been stopped for futility as recommended by the IDMC based on the interim analysis performed.

Substudies

Pharmacogenetic substudy

The direct involvement of genetic markers in the metabolism and the pharmacokinetic of a drug as well as the influence of the inherited genetic trait on the molecular profile of the tumor could have an influence on an individual's prognosis. Aim of this substudy is therefore to analyze the potential association between the germline genotype of the patient and treatment response, toxicities, long term prognosis, molecular profile of the tumor and breast cancer risk.

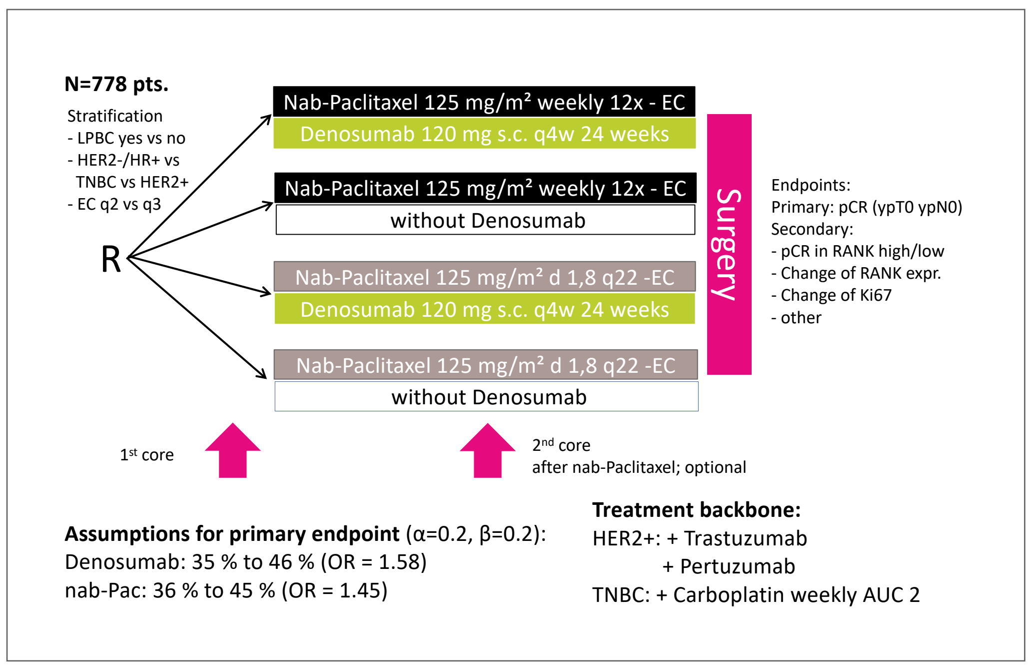

Figure 1: GeparX study design

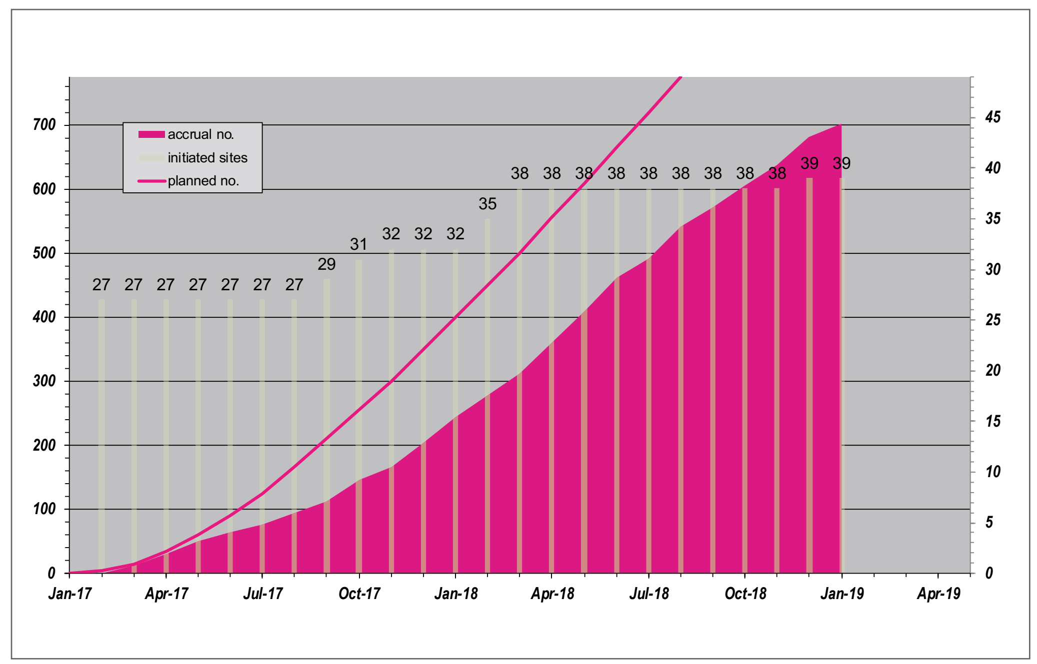

Figure 2: GeparX recruitment as of 31st December 2019

DTC substudy

The persistence of disseminated tumor cells (DTC) in the bone marrow after adjuvant chemotherapy has been ascertained as an independent predictor for poor disease-free survival, cancer-specific and overall survival (Braun et al. N Engl J Med 2005; Janni et al. Clin Cancer Res 2011). Furthermore, denosumab inhibits osteoclastic differentiation by binding to RANK-ligand (RANKL), thereby preventing the interaction between RANKL and its corresponding RANK-receptor (Casas et al. Breast 2013). Aim of this substudy is to investigate whether the application of denosumab in terms of an add-on neoadjuvant treatment eradicates DTCs in the bone marrow of breast cancer patients.

Substudy on urinary miRNA sampling (UMS)

Aberrant expression profiles of microRNAs (miRNAs) with subsequent functional consequences on target gene regulation in physiological and pathological pathways could already be set in clear association with breast cancer. Aim of the substudy is to evaluate a specific microRNA pattern in urine specimen as an innovative tool for subtype-specific diagnosis of breast cancer (HER2-positive vs. TNBC).

Study report

GeparX randomized a total of 780 patients between February 2017 and April 2019 [1-2]. An interim safety analysis included 202 patients randomized to denosumab and nab-paclitaxel treatment (101 patients with weekly and 101 patients with nab-paclitaxel d1,8 q22), of them 196 started treatment, demonstrated that the addition of denosumab to neoadjuvant chemotherapy did not increase toxicity. Moreover, weekly nab-paclitaxel resulted in a higher rate of treatment discontinuations mainly due to non-serious adverse events (AEs), whereas the addition of carboplatin in TNBC resulted in a higher rate of serious AEs (SAEs). First results of the GeparX study were presented at SABCS 2019. The addition of denosumab to neoadjuvant chemotherapy did not increase the pCR rate (41 % with denosumab vs. 43 % without; p=0.582). Nab-paclitaxel 125 mg/m² weekly resulted in a significantly higher pCR rate than given d1,8 q22 (45 % vs 39 %; p=0.062). In contrast, a higher rate of toxicity (SAEs) and a higher rate of treatment discontinuations mainly due to AEs was observed in nab-paclitaxel 125 mg/m² administered weekly compared to nab-paclitaxel d1,8 q22. In TNBC the optimized neoadjuvant chemotherapy with nab-paclitaxel 125 mg/m² weekly plus carboplatin followed by EC demonstrated a pCR rate of at least 60 % [4]. Further translational research (e.g. RANK expression) is ongoing.

Publications

1. Kümmel S, von Minckwitz G, Nekljudova V, Dan Costa S, Denkert C, Hanusch C, Huober J, Jackisch Ch, Paepke S, Blohmer J U, Untch M, Schneeweiss A, Loibl S. Investigating Denosumab as add-on neoadjuvant treatment for hormone receptor-negative, RANK-positive or RANK-negative primary breast cancer and two different nab-Paclitaxel schedules - 2x2 factorial design (GeparX). J Clin Oncol 2016; 34.15_suppl.TPS635.
2. Kümmel S, von Minckwitz G, Vladimirova V et al. Investigating Denosumab as an add-on neoadjuvant treatment for RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-Paclitaxel schedules - 2x2 factorial design (GeparX). 38. Jahrestagung Deutsche Gesellschaft für Senologie 2018; poster.
3. Kümmel S, Wimberger P, von Minckwitz G et al. Investigating denosumab as an add-on neoadjuvant treatment for RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-paclitaxel schedules - 2x2 factorial design (GeparX) – an interim safety analysis. J Clin Oncol 2018; 36.15_suppl.569.
4. Blohmer JU, Link T, Kümmel S, et al. Investigating denosumab as an add-on treatment to neoadjuvant chemotherapy and two different nab-paclitaxel schedules in a 2x2 design in primary breast cancer - First results of the GeparX study. SABCS 2019; GS3-01, oral presentation.

We are thanking all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by providing the remaining biomaterial in a timely manner and by entering participants in the General Follow-up.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

SPONSOR:
GBG Forschungs GmbH

STUDY CHAIRS:
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Prof. Dr. Sibylle Loibl
German Breast Group, Neu-Isenburg

Follow-up Activities

Follow-up Activities 2019

Long-term follow-up of early breast cancer trials is considered highly important as treatment effects might increase, maintain or decrease over time and have to be put into relation with late or chronic toxicities. However, collection of long-term follow-up is very often an near-impossible task due to the logistical and financial burden for study sites and sponsors.

Patient Self-Reported Outcome (PSRO)

To improve follow-up and reduce the workload for the trial sites, we developed a concept to use a Patient Self-Reported Outcome (PSRO) registry for long term follow-up in the GBG early breast cancer trials.

Study participants are invited by the site investigator to join the PSRO registry. They consent that their name, address, and the unique study identifier are being collected and to regularly receive health status questionnaires. German privacy laws and good clinical practice (GCP) regulations forbid the storage of patient-identifying data by the sponsor. Therefore, we developed a registry to collect PSRO with a strict separation of patient-identifying data and pseudonymized medical data via a data trustee. The data trustee is financially and organizationally independent from the GBG. The data trustee is handling names and addresses of the patients with a database strictly not accessible by GBG. Triggered by GBG, the trustee sends a questionnaire asking for current health status, including date and site of relapse, secondary malignancies, and date of death. The questionnaires may also be filled in by a third person in case of death. Forms are to be sent to GBG using only the unique study identifier as pseudonym. For address changes or withdrawal of consent, another form can be returned to the trustee. Thus, GBG links updated data with the original study database and informs the site about their patients.

In 2019 we changed the data trustee to the ZKS (Zentrum für Klinische Studien Köln) at the University of Cologne. This process led to some delay in sending out the questionnaires. In September 2019, we distributed a letter to all participants with information about the changes, the new privacy laws (EU-GDPR) and a new questionnaire including questions about adverse events and quality of life.

Currently over 12,000 participants from 20 trials and 269 sites are included in this registry.

General Follow-Up Database and eCRF

Follow-up documentation over different studies and long timespans is a burden for the sites due to different systems, case report forms (CRFs), schedules and procedures. To mitigate this we developed a unique general follow-up database to document follow-up for all trials with the same electronic Case Report Form (eCRF). This eCRF is simplified as much as possible to collect only the basic information necessary for analysis of the long-term endpoints of our neoadjuvant and adjuvant trials. All these items can be collected during routine aftercare without trial specific examinations.

In November 2019 we established a new set of edit-checks for these eCRF to facilitate date entry and improve data quality.

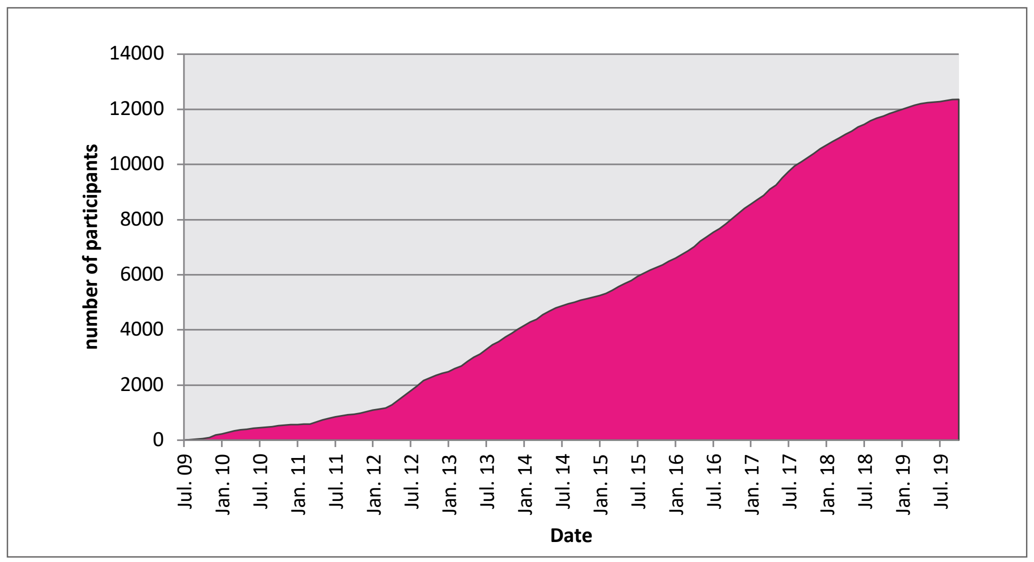

Figure 1: Patient self-reported outcome participants

Current Trials in Follow-up

The follow-up status of the GBG trials is presented in Table 1

Trial		N (patients)	PSRO patients	FU Completeness
GBG: 18	GeparDuo	907	26	40,4%
GBG: 24	GeparTrio	2,357	236	44,3%
GBG: 32	ICE	1,358	197	49,1%
GBG: 33	GAIN	2,995	990	65,1%
GBG: 36	Natan	693	78	50,9%
GBG: 40	GeparQuattro	1,507	286	51,3%
GBG: 44	GeparQuinto	2,572	663	56,2%
GBG: 52	ICE-2	391	150	58,3%
GBG: 53	PANTHER	772	178	26,7%
GBG: 66	GeparSixto	588	338	61,5%
GBG: 68	GAIN-2	2,864	2,246	75,6%
GBG: 69	GeparSepto	1,203	789	68,4%
GBG: 70	Dafne	65	52	51,5%
GBG: 74	Genevieve	333	205	46,0%
GBG: 75	Insema	5,543	2,157	62,2%
GBG: 84	GeparOcto	945	722	72,1%
GBG: 89	GeparNuevo	174	128	44,9%
GBG: 90	GeparOla	107	54	38,6%

Table 1: Status of the GBG trials in follow-up (FU-completeness according to Clark, Lancet 2002;359:1309)

While we desire to increase follow-up completeness for all of our studies, we would like to draw special attention to selected neoadjuvant and adjuvant studies that are planned to be analyzed and/or published in the near future.

Neoadjuvant studies

GeparOcto (GBG 84, NCT 02125344)

is a multicenter, prospective, randomized open-label phase III study that has recruited 961 patients.

The study compared efficacy and safety of two chemotherapy regimens in high-risk early breast cancer: sequential treatment with intense dose-dense epirubicin, paclitaxel, and cyclophosphamide (iddEPC) and weekly treatment with paclitaxel plus non-pegylated liposomal doxorubicin (M) with additional carboplatin (PM(Cb)) in triple-negative breast cancer. Pathological complete response was comparable overall and in subgroups. (Schneeweiss et al. Eur J Cancer, 2019). A substudy on supportive anemia treatment randomized 123 patients to investigate the use of the parenteral iron preparation ferric carboxymaltose compared to treatment of physician`s choice. No difference was found in efficacy between treatments for chemotherapy-induced anemia (Tesch et al. Ann Oncol 2019).

For timely analysis of survival endpoints, planned to be presented at ASCO 2020, we would encourage all participating sites to provide follow-up data for their patients and answer queries.

BRIGHTNESS (GBG 81, NCT 02032277)

is a multicenter, double-blind, placebo-controlled, randomized phase III trial that has globally recruited 634 patients (55 patients in Germany).

The study compared paclitaxel plus carboplatin plus Poly(ADP-ribose) polymerase (PARP) inhibitor veliparib with paclitaxel plus carboplatin and with paclitaxel alone, each followed by standard neoadjuvant chemotherapy with doxorubicin/cyclophosphamide in triple-negative breast cancer (TNBC) patients. Overall, an addition of veliparib to neoadjuvant chemotherapy did not increase the pCR rate in the breast and lymph nodes in TNBC patients. In contrast, the addition of carboplatin to paclitaxel resulted in a significant improvement in pCR rates compared to paclitaxel alone. The increased toxicity of carboplatin with or without veliparib did not impact the delivery of neoadjuvant chemotherapy (Loibl et al. Lancet Oncol. 2018). The assessment of homologous recombination deficiency (HRD) status in 438 BRIGHTNESS patients revealed higher rates of pCR in HRD+ patients across all treatment arms, while patients treated with carboplatin had higher pCR rates in both HRD+ and HRD-subsets. The exploratory HRD threshold of 33 (as compared to 42) appeared to provide greater sensitivity to identify responders with the addition of carboplatin plus veliparib (Telli et al. J Clin Oncol 2018). Another analysis of 519 patients with available baseline and mid-treatment imaging and pathologic response data found that early radiologic response on MRI was strongly associated with pCR or minimal residual disease on final pathology. Complete response on mid-treatment MRI had a positive predictive value of 78 % for pCR (Golshan et al. Eur J Surg Oncol. 2019).

We would encourage all participating sites to provide follow-up data for their patients for the analysis of the secondary endpoints EFS and OS.

GeparNuevo (GBG 89, NCT 02685059)

is a multicenter, prospective, randomized, double-blinded, placebo controlled phase II study that has recruited 174 patients.

The study compared pCR (ypT0 ypN0) rates of neoadjuvant treatment of sequential, nab-paclitaxel followed by epirubicin and cyclophosphamide (EC) +/- the PD-L1 antibody durvalumab in patients with early triple negative breast cancer (TNBC). The addition of durvalumab to anthracycline/taxane based chemotherapy increased the pCR rate especially when patients were treated with durvalumab alone prior to the start of chemotherapy (Loibl et al. Ann Oncol 2019). Within the translational biomarker program, oncogenic pathways and tumor mutational burden (TMB) were investigated using whole genome sequencing on 149 patients with available fresh-frozen core biopsies and blood samples. The main genetic alterations were found in TP53, c-MYC and PTEN and TMB may predict pCR in primary TNBC (Loibl et al. J Clin Oncol 2019). In addition, a correlation of TMB with composition of the immune cell subpopulations in peripheral blood as well as with pCR was evaluated. Patients with higher TMB had better pCR rates. The TMB negatively correlated with the absolute number of CD8+ T-cells, but positively with the percentages of memory cells (Seliger et al. J Clin Oncol 2019).

For timely analysis of survival endpoints we would encourage all participating sites to provide follow-up data for their patients.

GeparOLA (GBG 90, NCT 02789332)

is a multicenter, prospective, randomized, open-label phase II study that has recruited 106 patients.

The study evaluated the efficacy of paclitaxel and olaparib in comparison to paclitaxel and carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and homologous recombination deficiency (HRD) patients with deleterious BRCA1/2 tumor or germline mutation and/or HRD score high. While the addition of olaparib to paclitaxel was well tolerated, a pCR rate of 55.1 % (90 %CI 44.5 %-65.3 %) was not sufficient to exclude the predefined pCR rate of 55% in the olaparib arm. Subgroup analyses revealed higher pCR rates in the olaparib group compared to the carboplatin group with regards to hormone receptor-positive tumors, patients younger than 40 years and patients with HRD score high, BRCA1/2 wildtype (Fasching et al. J Clin Oncol 2019).

Analyses on further exploratory endpoints and translational research are ongoing and we urgently need follow-up to produce long-term results for this important trial.

KATHERINE (GBG 77, NCT 01772472)

is a randomized, multicenter, open-label phase III study that has recruited 1,487 patients.

The trial investigated whether adjuvant T-DM1 was more effective than trastuzumab in patients with HER2-positive primary breast cancer who received neoadjuvant chemotherapy including trastuzumab and had residual invasive disease after surgery.
Interim analyses showed a significantly improved invasive disease-free survival (iDFS) with adjuvant T-DM1 compared to trastuzumab. Safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone (von Minckwitz et al. N Engl J Med 2019). Since patients in the T-DM1 arm initially showed higher rates of peripheral neuropathy, thrombocytopenia and central nervous system (CNS) recurrence as a first iDFS event, an update analysis showed that baseline neuropathy was associated with a longer duration and a lower resolution rate of treatment-associated peripheral neuropathy regardless of treatment arm. Prior platinum therapy was associated with an increased incidence of thrombocytopenia in the T-DM1 arm, but did not affect the duration or resolution of grade 3-4 thrombocytopenia. T-DM1 was not associated with an increased overall risk of CNS recurrence and overall survival was similar in both arms after CNS recurrence (Untch et al. Ann Oncol 2019). Analysis of the patient-

reported outcomes (PROs) demonstrated that more than 80% of randomized patients in both arms had valid baseline and ≥1 post-baseline PRO assessments. Mean scores of the EORTC Quality of Life Questionnaire-Core 30 (QLQ-C30) and QLQ-Breast Cancer (QLQ-BR23) questionnaires showed only small deterioration from baseline in patient-reported treatment-related symptoms in both study arms (Schneeweiss et al. J Clin Oncol 2019).

Further analyses are to follow in 2020 for this important study. Especially in terms of potential licensing of T-DM1, we urgently need a good quality of follow-up and therefore encourage all participating sites to provide follow-up data for their patients.

Adjuvant studies

PANTHER (GBG 53; NCT 00798070)

is an adjuvant, open-label, prospective, randomized phase III trial that has recruited 2,017 patients, including 772 from Germany.

PANTHER investigated efficacy and safety of a tailored dose-dense sequence of epirubicin/cyclophosphamide and docetaxel in the adjuvant setting in a cohort of lymph node positive or high-risk lymph node negative patients compared to a standard anthracycline/taxane containing regimen. An efficacy analysis of the primary endpoint demonstrated that the use of tailored dose-dense chemotherapy compared with standard adjuvant chemotherapy did not result in a statistically significant improvement in breast cancer recurrence-free survival (BCRFS) with non-hematologic toxic effects being more frequent in the tailored dose-dense group (Foukakis et al. JAMA 2016). An exploratory analysis of tailored dosing demonstrated that obese patients (BMI≥30) treated with tailored dose-dense chemotherapy had significantly improved BCRFS compared to non-obese ones (BMI<30) with no differences in terms of toxicity between the BMI groups (Matikas et al. Ann Oncol 2018). A toxicity analysis investigating neutropenic complications reported in the PANTHER study with regards to G-CSF use showed that primary prophylaxis with G-CSF reduces neutropenic events and is both feasible and effective, allowing also for dose-tailoring and increased dose intensity without excess myelotoxicity, which is essential for improved survival outcomes (Papakonstantinou et al. Acta Oncol 2019).

Estimated study completion date is January 2022. We would like to remind participating sites to provide regular follow-up data in order to avoid later delays in the study analysis.

APHINITY (GBG 67, NCT 01358877)

is an adjuvant, prospective, two-arm, randomized, multicenter, international, double-blind, placebo-controlled phase III trial that has recruited 4,805 patients.

The study compared safety and efficacy of a combination therapy with two anti-HER2 agents (trastuzumab and pertuzumab) in addition to chemotherapy in the adjuvant setting, compared to chemotherapy and trastuzumab alone. Addition of pertuzumab significantly improved the rates of invasive disease-free survival (iDFS) when it was added to trastuzumab and chemotherapy (3-year iDFS 94.1 % with pertuzumab, 93.2 % with placebo, HR 0.81 [95 % CI 0.66-1.00]; p=0.045). Diarrhea was more common with pertuzumab than with placebo (von Minckwitz et al. N Engl J Med 2017). A comprehensive biomarker analysis found that higher levels of immune markers and HER2 appeared to be associated with better prognosis and greater trastuzumab and pertuzumab benefit (Krop et al. J Clin Oncol 2019).

APHINITY has a long follow-up period (until 10 years after the randomization of the last patient, which is around September 2023), and we would like to remind participating sites to provide regular follow-up data in order to avoid later delays in the study analysis.

Translational Research

Translational Research & Biobanking

Central Pathology and GBG Tumor Bank - Moving from Berlin to Marburg

At the beginning of the year 2019, the GBG biobank had to tackle a major reorganization. As of 1st January 2019, Prof. Carsten Denkert has taken over the leadership of the Institute of Pathology at the University of Marburg (UKGM). With Prof. Denkert and his group moving from Berlin to Marburg, the GBG tumor bank has also been relocated to Marburg. The move of samples and equipment has been completed at the end of April 2019, so starting from May 1st, central pathology testing and tumor banking has been taking place in Marburg. GBG-specific procedures and SOPs had to be established in the Marburg team, while GBG took over communication with the sites participating in the GBG studies to inform them about the movement. The change of location took few months and was conquered very well. We would like to take the opportunity to thank all participating sites for their cooperation and would be pleased if they would continue to give us their support.

Biobanking 2.0 at GBG

The biomaterial collection in the GBG biobank has been growing constantly over the years. Every year, many translational projects are set up, using tissue or liquid samples for biomarker analysis.
To manage the increasing number of samples according to the ethical requirements for biobanking, we have recently implemented purpose-built software for sample management (CentraXX, KAIROS GmbH). CentraXX is a web-based database system, which allows registration, processing and coordinating samples collected in multicentric trials. Both the GBG tumor bank, represented by Prof. Carsten Denkert, and the GBG liquid bank, run by Dr. Vincent von Walcke-Wulffen at BioKryo GmbH, have access to the CentraXX system and can document sample receipt directly in the database.

Translational Research Activities

ONCOBIOME, a project within EU framework "Horizon 2020"
Horizon 2020 (H2020) is the biggest EU research and innovation program with funding available over 7 years. The proposal "ONCOBIOME" from Prof. Laurence Zitvogel (Institute Gustave Roussy, Paris) has been positively evaluated and GBG is one of the 16 participating partners throughout the EU. The aim of the 5-year project is to determine the relationship between intestinal microbial signatures and the prognosis and treatment resistance in four common cancer entities (breast, colon, lung and melanoma).
The project started early in 2019 with a kick-off meeting of all partners in Paris. The GBG participates with sample collections (tumor tissue and stool sample) as well as expertise in clinical translational research. Starting with amendment 1, the stool sample collection was introduced in the study protocol of GeparDouze. Before start of therapy, stool samples are collected in a special conservation medium and stored frozen at -20°C. The isolation of DNA and RNA for genomic and expression analyses will be conducted by cooperating partners in the ONCOBIOME project.

EPIC GeparOcto (G8), a DKTK (German Cancer Consortium) Project
Methylation profiling of G8 tissue samples is performed in the EPIC-G8 project that is led by Prof. David Capper (Charité, Berlin). The project funded by the Joint Funding Program of the German Cancer Consortium (DKTK) is focused on triple negative (TNBC) breast cancer, the most aggressive breast cancer subtype. There is clear molecular and clinical evidence that TNBC consists of different subtypes, however, existing methods cannot fully capture the diversity of TNBC. Methylation profiling has been extremely successful for classification of brain tumors. By applying this approach to the large and well characterized cohort of TNBC patients from G8 trial, clinically relevant epigenetic subtypes of TNBC may be identified.

INTEGRATE-TN, a Deutsche Krebshilfe Project
Another successful grant supporting breast cancer research is funded by Deutsche Krebshilfe. The collaborative project "INTEGRATE-TN" (coordinator Prof. Carsten Denkert, Marburg) aims to integrate tumor organoid cultures into the GBG clinical trial network to identify tumor-cell biomarkers for adaptive resistance and also to validate the new biomarkers for adaptive resistance in additional clinical trials.
The project has started in October 2019. We are currently setting up a feasibility questionnaire for the GBG study sites for participation in the project. Prerequisite to take part in this project is the ability to provide fresh tissue from surgery, which has to be stabilized in a special media during transport to the TUM in Munich (coordinator Prof. Wilko Weichert).

If your site is interested in taking part in this ambitious project, please contact the Translational Research group at GBG.

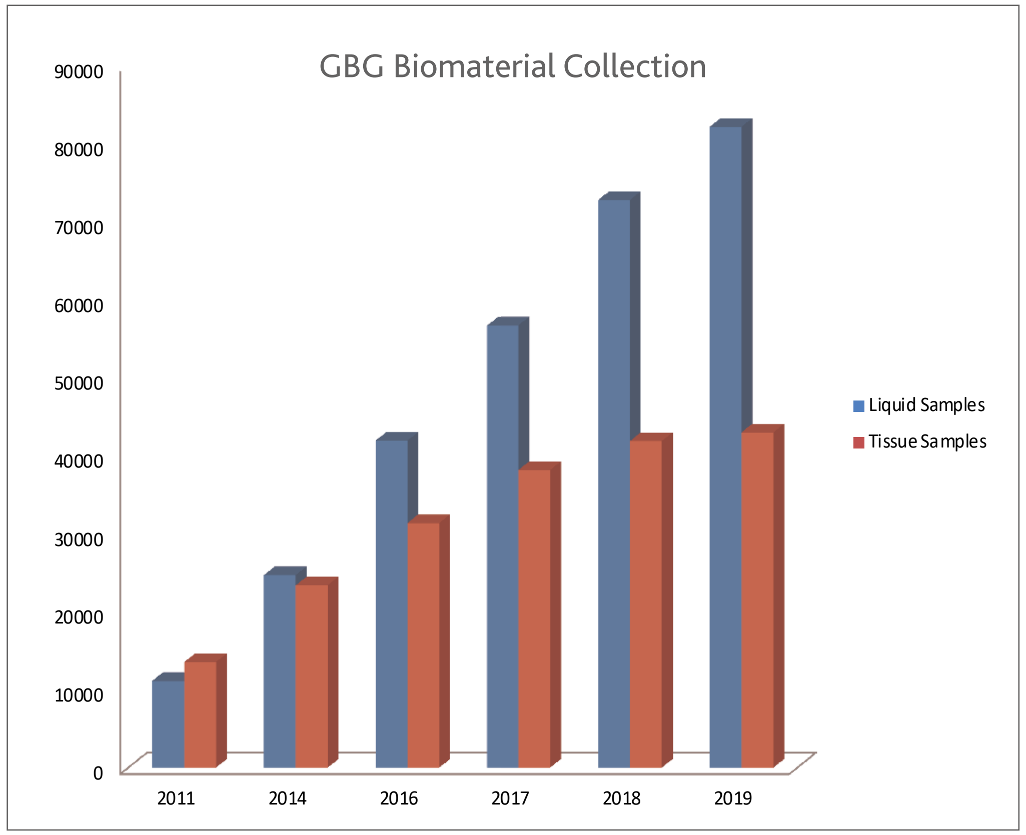

Figure 1: Samples at GBG Biobank

New proposals may also be submitted by groups that are currently not represented in any GBG subboard. https://www.gbg.de/de/forschung/trafo.php

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GBG Study Finder 2020*

Early Breast Cancer

Operative Studies (M0)	
Operable node-positive breast cancer: • Most suspicious lymph node clipped • AJCC/UICC stage II-III • Eligible for primary axillary lymph node dissection or sentinel lymph node biopsy procedure	**TAXIS** Tailored axillary surgery **with or without axillary lymph node dissection** followed by radiotherapy. All patients will receive breast/chest wall and regional nodal irradiation. Patients without axillary lymph node dissection will receive additional irradiation of the axilla
(Neo)adjuvant Studies (M0)	
Untreated triple-negative breast cancer: • cT2-cT3 • cT1c only if N+	**GeparDouze** Neoadjuvant chemotherapy with 12x paclitaxel weekly + carboplatin q3 followed by EC/AC q2 or q3 **+ atezolizumab or placebo q3** followed by **adjuvant therapy with atezolizumab or placebo q3** (total duration of atezolizumab/placebo will be one year)
Operable triple-negative breast cancer: • Stage II-III • pathological tumor size > 2 cm if pN0	**ALEXANDRA** Arm A: Adjuvant chemotherapy with 12x paclitaxel weekly followed by EC/AC q2 **+ atezolizumab q2** followed by **atezolizumab monotherapy q2** (total duration of atezolizumab will be one year) Arm B: Chemotherapy alone
Operable HR+ / HER2- breast cancer: • Age ≥ 70 years • Stage II-III • Adjuvant chemotherapy required and feasible	**APPALACHES** Arm A: **Palbociclib** 2 years + standard adjuvant endocrine treatment ≥ 5 years Arm B: Adjuvant chemotherapy followed by standard adjuvant endocrine treatment ≥ 5 years
HR+ breast cancer: • Ongoing hormone therapy with tamoxifen (20mg)	**TAMENDOX** Genotype and phenotype guided supplementation of a standard therapy with tamoxifen with the active metabolite **endoxifen**
Non-pCR after NACT • HER2-negative breast cancer - HR- (TNBC) or - HR+ with CPS-EG score ≥3 or 2 and ypN+ • At least 16 weeks of taxane-based chemotherapy	**SASCIA** Arm A: **Sacituzumab govitecan** 8 cycles d1,8 q3w Arm B: Treatment of physician`s choice (8 cycles capecitabine or platinum-based chemotherapy or observation) In patients with HR-positive breast cancer, endocrine- based therapy will be administered according to local guidelines
Breast Cancer in Special Situations	
• Patients with **breast cancer in pregnancy** • non-pregnant women with **breast cancer < 40 years** • **M1** possible	**BCP** Prospective and retrospective registry study for the diagnosis and treatment of breast cancer in pregnancy compared to young non-pregnant women

Metastatic Breast Cancer

Metastatic Breast Cancer ER-positive or -negative, HER2-positive or-negative	
• 1st and 2nd line therapy in metastatic setting • Biopsy of a metastatic lesion is feasible, provision of FFPE & Fresh Frozen samples	**AURORA** Tissue collection of the primary tumor and a metastasis and blood collection
Brain metastases of breast cancer	**Brain Metastases in Breast Cancer (BMBC)** Retrospective and prospective registry designed to collect tumor characteristics of the primary and metastatic tumor as well as treatment data and biomaterial from patients diagnosed with brain metastases of breast cancer
HER2+ Breast Cancer	
HER2+ and HR+ metastatic breast cancer: • 1st line chemotherapy (for metastatic breast cancer) with a taxane or vinorelbine in combination with trastuzumab +/- pertuzumab	**PATINA** Maintenance therapy with anti-HER2 and endocrine therapy **+/- palbociclib**
HER2-Breast Cancer	
HER2+ and HR+ metastatic breast cancer: • At least 4 cycles of a 1st line mono- or polychemo-therapy • Pretreatment with CDK 4/6 inhibitors is allowed	**AMICA** Endocrine maintenance therapy after chemotherapy **+/- ribociclib**
HER2- and HR+ metastatic breast cancer: • 1st systemic therapy for the treatment of metas-tatic breast cancer • No asymptomatic oligometastases of the bone as the only site of meatstatic disease	**PADMA** Endocrine therapy **+ palbociclib versus mono-chemotherapy +/-** endocrine maintenance therapy Possible mono-chemotherapies (Physician's choice): • Capecitabine p.o. • Epirubicine i.v. • Paclitaxel i.v. • Vinorelbine i.v.
HER2- and HR+ metastatic breast cancer: • Postmenopausal women • Recurrence or progression after therapy with a non-steroidale aromatase inhibitor	**DESIREE** Exemestane in combination with **induction dose escalation of everolimus** versus exemestane in combination with **standard therapy with everolimus**

*Further studies are currently in planning. Please refer to www.gbg.de

Notes

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GROUP

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