GBG

GERMAN
BREAST
GROUP

Heilung durch Innovation, Kompetenz und Partnerschaft

Annual Scientific Report

2020

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Index

Introduction

Introduction

Headquarters:

GBG Forschungs GmbH
Martin-Behaim-Strasse 12
63263 Neu-Isenburg
GERMANY
Phone: +49 6102 7480-0
Fax: +49 6102 7480-440
www.GBG.de

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.

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

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 2020 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
Dr. M. Reinisch, Essen
PD Dr. K. Rhiem, Köln
Prof. Dr. A. Schneeweiss, Heidelberg
Prof. C. Solbach, Frankfurt am Main
Prof. Dr. M. Untch, Berlin

Adjuvant
Prof. Dr. W. Janni, Ulm
Prof. Dr. S. Loibl, Neu-Isenburg
Prof. Dr. F. Marmé, Mannheim
Dr. L. Michel, Heidelberg
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

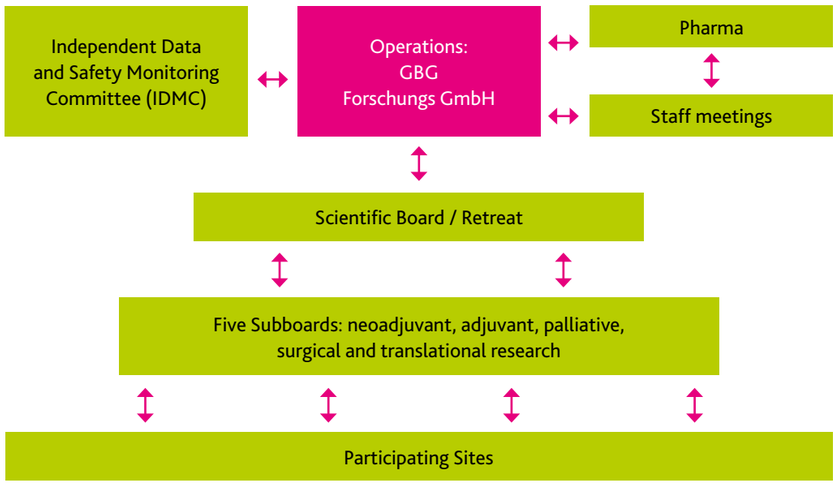


Figure 1: Structure of the German Breast Group

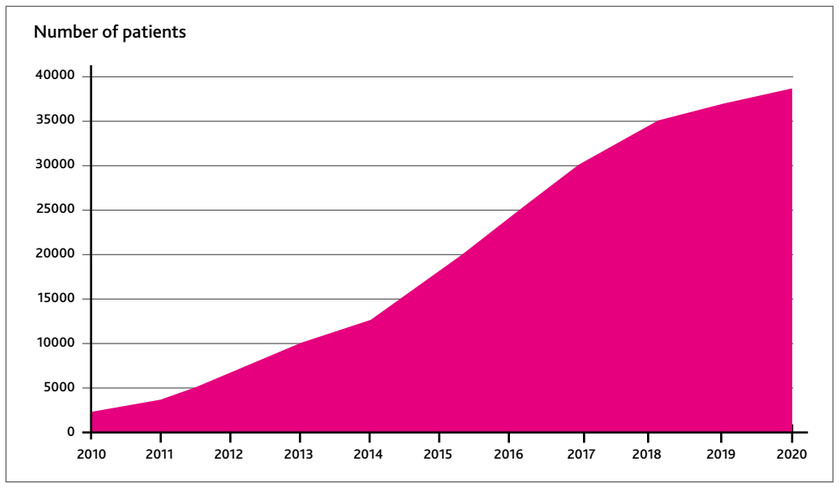


Figure 2: Annual recruitment of patients 2020

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
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. Marmé, 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

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

EBCTCG:
Early Breast Cancer Trialists' Collaborative Group

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

KCSG:
Korean Cancer Study Group

LACOG:
Latin American Cooperative Oncology Group

NOGGO:
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie

NRG:
Oncology

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 UNICANCER

UNICANCER:
UNICANCER Group, France

Universitätsklinikum Hamburg-Eppendorf

Uniklinik Köln

Universität Rostock

UZL:
University Hospital of Leuven

WSG:
Westdeutsche Studiengruppe

4. Publications in 2020

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 AACR, ASCO, ESMO Breast Cancer, ESMO and SABCS.

Peer-review articles, reviews and congress contributions in 2020 are listed in 4.1., 4.2. and 4.3.

4.1. Peer-reviewed articles in 2020

1. Furlanetto J, Möbus V, Schneeweiss A, Rhiem K, Tesch H, Blohmer JU, Lübbe K, Untch M et al. Germline BRCA1/2 mutations and severe hematological toxicities in patients with breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer. 2021; 145:44-52 (accepted for publication 2020).

2. Reimer T, Glass A, Botteri E, Loibl S, D Gentilini O. Avoiding Axillary Sentinel Lymph Node Biopsy after Neoadjuvant Systemic Therapy in Breast Cancer: Rationale for the Prospective, Multicentric EUBREAST-01 Trial. Cancers (Basel). 2020;12:3698.

3. Kolberg HC, Kühn T, Krajewska M, Bauerfeind I, Fehm TN, Fleige B, et al. Residual Axillary Burden After Neoadjuvant Chemotherapy (NACT) in Early Breast Cancer in Patients with a priori Clinically Occult Nodal Metastases - a transSENTINA Analysis. Geburtshilfe Frauenheilkd. 2020;80:1229-1236.

4. André F, Ciruelos EM, Juric D, Loibl S, Campone M, Mayer IA, et al. Alpelisib Plus Fulvestrant for PIK3CA-Mutated, Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor-2-Negative Advanced Breast Cancer: Final Overall Survival Results From SOLAR-1. Ann Oncol. 2020; doi: 10.1016/j.annonc.2020.11.011.

5. Massa C, Karn T, Denkert C, Schneeweiss A, Hanusch C, Blohmer JU, Zahm DM, Jackisch C, van Mackelenbergh M, Thomalla J, Marme F, Huober J, Müller V, Schem C, Mueller A, Stickeler E, Biehl K, Fasching PA, Untch M, Loibl S, Weber K, Seliger B. Differential effect on different immune subsets of neoadjuvant chemotherapy in patients with TNBC. J Immunother Cancer. 2020; 8:e001261.

6. Rüger AM, Schneeweiss A, Seiler S, Tesch H, van Mackelenbergh M, Marmé F, et al. Cardiotoxicity and Cardiovascular Biomarkers in Patients With Breast Cancer: Data From the GeparOcto-GBG 84 Trial. J Am Heart Assoc. 2020;9:e018143.

7. Chan A, Moy B, Mansi J, Ejlertsen B, Holmes FA, Chia S, et al. Final Efficacy Results of Neratinib in HER2-positive Hormone Receptor-positive Early-stage Breast Cancer From the Phase III ExteNET Trial. Clin Breast Cancer. 2020; doi: 10.1016/j.clbc.2020.09.014.

8. Fasching PA, Link T, Hauke J, Seither F, Jackisch C, Klare P, et al. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). Ann Oncol. 2020; doi: 10.1016/j.annonc.2020.10.471.

9. Guerini-Rocco E, Gray KP, Fumagalli C, Reforgiato MR, Leone I, Rafaniello Raviele P, et al. Genomic aberrations and late recurrence in postmenopausal women with hormone receptor-positive early breast cancer: Results from the SOLE Trial. Clin Cancer Res. 2020; doi: 10.1158/1078-0432.CCR-20-0126.

10. Laakmann E, Witzel I, Neunhöffer T, Weide R, Schmidt M, Park-Simon TW, et al. Characteristics and Clinical Outcome of Breast Cancer Patients with Asymptomatic Brain Metastases. Cancers (Basel). 2020; 12:2787.

11. O'Leary B, Cutts RJ, Huang X, Hrebien S, Liu Y, André F, Loibl S, Loi S, Garcia-Murillas I, Cristofanilli M, Bartlett CH, Turner NC. Circulating Tumor DNA Markers for Early Progression on Fulvestrant With or Without Palbociclib in ER+ Advanced Breast Cancer. J Natl Cancer Inst. 2020; djaa087.

12. Jank P, Gehlhaar C, Lederer B, Fontanella C, Schneeweiss A, Karn T, et al. MGMT promoter methylation in triple negative breast cancer of the GeparSixto trial. PLoS One. 2020;15:e0238021.

13. Lin NU, Borges V, Anders C, Murthy RK, Paplomata E, Hamilton E, et al. Intracranial Efficacy and Survival With Tucatinib Plus Trastuzumab and Capecitabine for Previously Treated HER2-Positive Breast Cancer With Brain Metastases in the HER2CLIMB Trial. J Clin Oncol. 2020;38:2610-2619.

14. Karn T, Denkert C, Weber KE, Holtrich U, Hanusch C, Sinn BV, et al. Tumor mutational burden and immune infiltration as independent predictors of response to neoadjuvant immune checkpoint inhibition in early TNBC in GeparNuevo. Ann Oncol. 2020;31:1216-1222.

15. Hildebrandt G, Stachs A, Gerber B, Potenberg J, Krug D, Wolter K, et al. Central Review of Radiation Therapy Planning Among Patients with Breast-Conserving Surgery: Results from a Quality Assurance Process Integrated into the INSEMA Trial. Int J Radiat Oncol Biol Phys. 2020;107:683-693.

16. Rugo HS, André F, Yamashita T, Cerda H, Toledano I, Stemmer SM, et al. Time Course and Management of Key Adverse Events During the Randomized Phase 3 SOLAR-1 Study of PI3K Inhibitor Alpelisib Plus Fulvestrant in Patients With HR-Positive Advanced Breast Cancer. Ann Oncol. 2020;31:1001-1010.

17. Conte P, Schneeweiss A, Loibl S, Mamounas EP, von Minckwitz G, Mano MS, et al. Patient-reported outcomes from KATHERINE: A phase 3 study of adjuvant trastuzumab emtansine versus trastuzumab in patients with residual invasive disease after neoadjuvant therapy for human epidermal growth factor receptor 2-positive breast cancer. Cancer. 2020;126:3132-3139.

18. Werutsky G, Untch M, Hanusch C, Fasching PA, Blohmer JU, Seiler S, et al. Locoregional recurrence risk after neoadjuvant chemotherapy: A pooled analysis of nine prospective neoadjuvant breast cancer trials. Eur J Cancer. 2020;130:92-101.

19. Pohl-Rescigno E, Hauke J, Loibl S, Möbus V, Denkert C, Fasching PA, et al. Association of Germline Variant Status With Therapy Response in High-risk Early-Stage Breast Cancer: A Secondary Analysis of the GeparOcto Randomized Clinical Trial. JAMA Oncol. 2020;6:744-748.

20. Karn T, Meissner T, Weber K, Solbach C, Denkert C, Engels K, et al. A small hypoxia signature predicted pCR response to bevacizumab in the neoadjuvant GeparQuinto breast cancer trial. Clin Cancer Res. 2020; 26:1896-1904.

21. Guo S, Loibl S, Minckwitz GV, Darb-Esfahani S, Lederer B, Denkert C. PIK3CA H1047R Mutation Associated with a Lower Pathological Complete Response Rate in Triple-Negative Breast Cancer Patients Treated with Anthracycline-Taxane-Based Neoadjuvant Chemotherapy. Cancer Res Treat. 2020;52:689-696.

22. Sonnenblick A, Salmon-Divon M, Salgado R, Dvash E, Pondé N, Zahavi T, et al. Reactive stroma and trastuzumab resistance in HER2-positive early breast cancer. Int J Cancer. 2020;147:266-276.

23. Murthy RK, Loi S, Okines A, Paplomata E, Hamilton E, Hurvitz SA, et al. Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer. N Engl J Med. 2020;382:597-609.

4.2. Peer-reviewed reviews in 2020

1. Kos Z, Roblin E, Kim RS, Michiels S, Gallas BD, Chen W, et al. Pitfalls in assessing stromal tumor infiltrating lymphocytes (sTILs) in breast cancer. NPJ Breast Cancer. 2020;6:17.

2. Furlanetto J, Loibl S. Optimal Systemic Treatment for Early Triple-Negative Breast Cancer. Breast Care (Basel). 2020;15:217-226.

3. Saini KS, Lanza C, Romano M, de Azambuja E, Cortes J, de Las Heras B, et al. Repurposing anticancer drugs for COVID-19-induced inflammation, immune dysfunction, and coagulopathy. Br J Cancer. 2020; 123:694-697.

4. de Azambuja E, Trapani D, Loibl S, Delaloge S, Senkus E, Criscitiello C, et al. ESMO Management and treatment adapted recommendations in the COVID-19 era: Breast Cancer. ESMO Open. 2020;5(Suppl 3):e000793.

5. Hudeček J, Voorwerk L, van Seijen M, Nederlof I, de Maaker M, van den Berg J, et al. Application of a risk-management framework for integration of stromal tumor-infiltrating lymphocytes in clinical trials. NPJ Breast Cancer. 2020;6:15. Published 2020; 6:15.

6. Amgad M, Stovgaard ES, Balslev E, Thagaard J, Chen W, Dudgeon S, et al. Report on computational assessment of Tumor Infiltrating Lymphocytes from the International Immuno-Oncology Biomarker Working Group. NPJ Breast Cancer. 2020;6:16.

7. Gonzalez-Ericsson PI, Stovgaard ES, Sua LF, Reisenbichler E, Kos Z, Carter JM, et al. The path to a better biomarker: application of a risk management framework for the implementation of PD-L1 and TILs as immuno-oncology biomarkers in breast cancer clinical trials and daily practice. J Pathol. 2020;250:667-684.

4.3. Congress contributions in 2020

SABCS:
San Antonio Breast Cancer Symposium, December 8-11, 2020, Virtual Meeting

Loibl S, Marmé F, Martin M, et al. Phase III study of palbociclib combined with endocrine therapy (ET) in patients with hormone-receptor-positive (HR+), HER2-negative primary breast cancerand with high relapse risk after neoadjuvant chemotherapy (NACT): First results from PENELOPE-B. SABCS 2020, oral presentation.

Sestak I, Cuzick J, Bonanni B, et al. 12 year results of anastrozole versus tamoxifen for the prevention of breast cancer in postmenopausal women with locally excised ductal carcinoma in-situ. SABCS 2020, oral presentation.

Krop I, Mittempergher L, Paulson J, et al. BluePrint performance in predicting pertuzumab benefit in genomically HER2-positive patients: a biomarker analysis of the APHINITY trial. SABCS 2020, poster discussion.

Ciruelos EM, Loibl S, Mayer IA, et al. Clinical Outcomes of Alpelisib Plus Fulvestrant in Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer With PIK3CA Alterations Detected in Plasma ctDNA by Next-Generation Sequencing: Biomarker Analysis From the SOLAR-1 Study. SABCS 2020, poster discussion.

Mayer EL, Fesl C, Dueck A et al. Treatment exposure and discontinuation in the PALLAS trial: PALbociclib CoLlaborative Adjuvant Study of palbociclib with adjuvant endocrine therapy for HR+/HER2- early breast cancer. SABCS 2020, poster discussion.

Franzoi MA, Procter M, Emond O, et al. Timelines to initiate an adjuvant phase III trial across the globe: a sub-analysis of the APHINITY trial. SABCS 2020, poster.

Gelber RD, Wang XV, Cole BF, et al. 6-year absolute invasive disease-free survival (IDFS) benefit of adding adjuvant pertuzumab to trastuzumab and chemotherapy for patients with early HER2-positive breast cancer: a STEPP analysis of the APHINITY (BIG 4-11) trial. SABCS 2020, poster.

Núria N, Luen SJ, Nuciforo P, et al. CelTIL score and long-term survival outcome in early stage HER2-positive (HER2+) breast cancer treated with anti-HER2-based chemotherapy: A correlative analysis of neoALTTO trial. SABCS 2020, poster.

Mayer I, Farooki A, Rugo HS, et al. Early intervention for and management of alpelisib (ALP)-induced hyperglycemia: case studies from the Phase III SOLAR-1 trial. SABCS 2020, poster.
Rugo HS, Tolaney SM, Loirat D, et al. Impact of UGT1A1 status on the safety profile of sacituzumab govitecan in the phase 3 ASCENT study in patients (pts) with metastatic triple-negative breast cancer (mTNBC). SABCS 2020, poster.

Geyer, Jr CE, Untch M, Prat A, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) vs trastuzumab emtansine (T-DM1) in high-risk patients with HER2-positive, residual invasive early breast cancer after neoadjuvant therapy: a randomized, phase 3 trial (DESTINY-Breast05). SABCS 2020, TIP.

DGGG:
63. Kongress der Deutschen Gesellschaft für Gynäkologie und Geburtshilfe 2020, October 7-9, 2020, Virtual Meeting

Riecke K, Müller V, Neunhöffer T, et al. Predicting prognosis of breast cancer patients with brain metastases in the BMBC registry – comparison of three different prognostic scores. oral presentation.

EBCC:
European Breast Cancer Conference 2020, October 2-3, 2020, Virtual Meeting

Nuciforo P, Townend J, Saura C et al. Nine-year survival outcome of neoadjuvant lapatinib with trastuzumab for HER2-positive breast cancer (NeoALTTO, BIG 1-06): final analysis of a multicentre, open-label, phase 3 randomised clinical trial. Eur J Cancer 2020; Vol 138, S15-S16, oral presentation.

Rugo H, Cristofanilli M, Loibl S, et al. Predictors of efficacy in patients (pts) with hormone receptor–positive/human epidermal growth factor receptor 2–negative advanced breast cancer (HR+/HER2– ABC): Subgroup analyses of PALOMA-3. Eur J Cancer 2020; Vol 138, S7-S8, oral presentation.

Laakmann E, Witzel I, Neunhöffer T, et al. Characteristics and clinical outcome of breast cancer patients with asymptomatic brain metastases. Eur J Cancer 2020; Vol 138, S19, poster.

ESMO:
European Society for Medical Oncology, September 19-21, 2020, Virtual Meeting

Schneeweiss A, Möbus V, Tesch H, et al. Survival analysis of the randomized phase III GeparOcto trial comparing neoadjuvant chemotherapy (NACT) of iddEPC versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer, TNBC) (PM(Cb)) for patients (pts) with high-risk early breast cancer (BC). Ann Oncol 2020; Vol. 31, Suppl.4, S303-S304, oral presentation.

Mayer EL, Gnant MI, DeMichele A, et al. PALLAS: A randomized phase III trial of adjuvant palbociclib with endocrine therapy versus endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol 2020; Vol. 31, Suppl.4, S1145, oral presentation (proffered paper).

André F, Ciruelos EM, Juric D, et al. Overall Survival (OS) Results From SOLAR-1, a Phase 3 Study of Alpelisib (ALP) + Fulvestrant (FUL) for Hormone Receptor-Positive (HR+), Human Epidermal Growth Factor Receptor 2-Negative (HER2–) Advanced Breast Cancer (ABC). Ann Oncol 2020; Vol. 31, Suppl.4, S1142-S1215, oral presentation.

Link T, Blohmer J-U, Just M, et al. GeparX: Denosumab (Dmab) as add-on to different regimen of nab-paclitaxel (nP)-anthracycline based neoadjuvant chemotherapy (NACT) in early breast cancer (BC): Subgroup analyses by RANK expression and HR status. Ann Oncol 2020; Vol. 31, Suppl.4, S308-S309, minioral presentation.

Hauke J, Ernst C, Fasching PA, et al. Germline mutation status and therapy response in patients with homologous recombination deficient, HER2-negative early breast cancer: Results of the GeparOLA study (NCT02789332). Ann Oncol 2020; Vol. 31, Suppl.4, S313, poster.

Rugo HS, Cristofanilli M, Loibl S, et al. Prognostic Factors for Overall Survival in Patients With Hormone Receptor–Positive/Human Epidermal Growth Factor Receptor 2–Negative Advanced Breast Cancer: Analyses From PALOMA-3. Ann Oncol 2020; Vol. 31, Suppl.4, S372-S373, poster.

Loibl S, Rastogi P, Seiler S, et al. A randomized, double-blind, phase III trial of neoadjuvant chemotherapy (NACT) with atezolizumab/placebo in patients (pts) with triple-negative breast cancer (TNBC) followed by adjuvant continuation of atezolizumab/placebo (GeparDouze). Ann Oncol 2020; Vol. 31, Suppl.4, S339, TIP.

AACR:
American Association for Cancer Research, Annual Meeting June 22-24, 2020, Virtual Meeting
Benelli M, Biagioni C, Fimereli D, et al. Characterization of gene fusions in paired primary and metastatic samples of breast cancer in the AURORA molecular screening program. Cancer Res 2020;80(16 Suppl):Abstract nr 2488, poster.

ASCO:
American Society of Clinical Oncology, Annual Meeting May 29-30, 2020, Virtual Meeting
Denkert C, Lambertini C, Fasching PA, et al. Biomarker data from KATHERINE: A phase III study of adjuvant trastuzumab emtansine (T-DM1) versus trastuzumab (H) in patients with residual invasive disease after neoadjuvant therapy for HER2-positive breast cancer. J Clin Oncol.2020; 38.15_suppl.502, oral presentation.

Möbus V, Lueck HJ, Ladda E, et al. GAIN-2: Neo-/adjuvant phase III trial to compare intense dose-dense chemotherapy (CT) to tailored dose-dense CT in patients (pts) with high risk early breast cancer (EBC): Results on safety and interim invasive disease-free survival (iDFS). J Clin Oncol.2020; 38.15_suppl.516, poster discussion.

Rediti M, Venet D, Rothe F, et al. Association of T- and B-cell receptor repertoires with molecular subtypes and outcome in HER2+ breast cancer: An analysis of the NeoALTTO clinical trial. J Clin Oncol. 2020; 38.15_suppl.511, poster discussion.

Cui W, Francis PA, Loi S, et al. Assessment of ovarian function as an endpoint in breast cancer clinical trials: A systematic review. J Clin Oncol.2020; 38. 15_suppl. e14098, session publication only.

Wimberger P, Blohmer J-U, Krabisch P, et al. Influence of denosumab on disseminated tumor cells (DTC) in the bone marrow of breast cancer (BC) patients with neoadjuvant treatment: A GeparX translational substudy. J Clin Oncol.2020; 38.15_suppl.580, poster.

Kolberg HC, Kühn T, Krajewska M, et al. Factors associated with axillary conversion after neoadjuvant chemotherapy in initially node positive breast cancer patients: A transSENTINA analysis. J Clin Oncol.2020; 38.15_suppl.557, poster.

ESMO-Breast Cancer
May 23-24, 2020, Virtual Meeting
Loibl S, Huang CS, Mano MS, et al. Adjuvant trastuzumab emtansine (T-DM1) vs trastuzumab (T) in patients (pts) with residual invasive disease after neoadjuvant therapy for HER2+ breast cancer: Subgroup analysis from KATHERINE. Ann Oncol. 2020; Vol 31, S48, oral presentation.

Karn T, Denkert C, Weber K, et al. Tumour mutational burden and immune infiltration as independent predictors of response to neoadjuvant immune checkpoint inhibition in early TNBC in GeparNuevo. Ann Oncol 2020, Vol. 31, S58, oral presentation.

Curigliano G, Murthy R, Loi R, et al. Tucatinib vs placebo added to trastuzumab and capecitabine in previously treated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB). Ann Oncol 2020; Vol. 31, Suppl.4, S62-S63, oral presentation.

Reinisch M, Untch M, Reimer T, et al. Patients (pts) preference for different administration methods of trastuzumab (T) in pts with HER2+ early breast cancer (BC) treated within the GAIN-2 trial. Ann Oncol 2020, Vol. 31, S44, poster.

Riecke K, Mueller V, Neunhöffer T, et al. Predicting prognosis of breast cancer patients with brain metastases in the BMBC registry: Comparison of three different prognostic scores. Ann Oncol 2020, Vol. 31, S70, poster.

DKK:
34. Deutsche Krebskongress 2020, February 19-22, 2020, Berlin Germany
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). DKK 2020, oral presentation.

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). DKK 2020, poster.

Pohl-Rescigno E, Hauke J, Rhiem K, et al. Germline mutation status and therapy response in high-risk early-stage breast cancer: A secondary analysis of the GeparOcto randomized clinical trial (NCT02125344). DKK 2020, 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. DKK 2020, poster.

Seiler S, Schmatloch S, Reinisch M, et al. Cancer Management and Outcome of young patients (pts) with breast cancer (BC) diagnosed at 40 years (yrs) or younger. DKK 2020, poster.

Loibl S, Jackisch C, Seiler S, et al. Randomized, Double-Blind, Phase III Trial of Neoadjuvant Chemotherapy (NACT) with Atezolizumab/Placebo in Patients with Triple-Negative Breast Cancer (TNBC) Followed by Adjuvant Continuation of Atezolizumab/Placebo (GeparDouze). DKK 2020, TIP.

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.

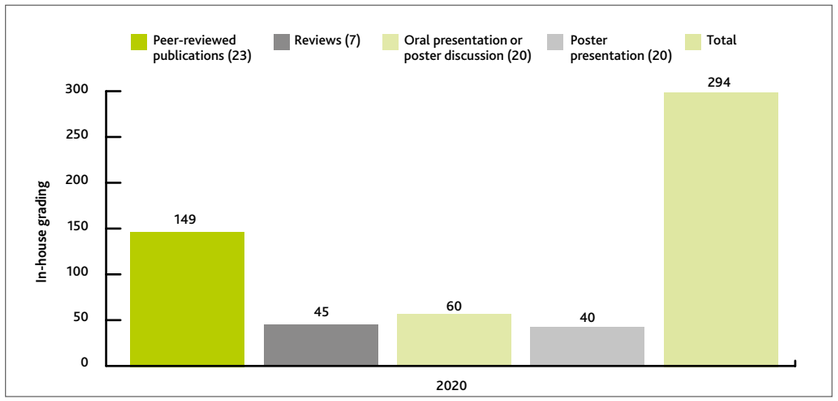


Figure 3: Overview of GBG's in-house grading for publications in 2020

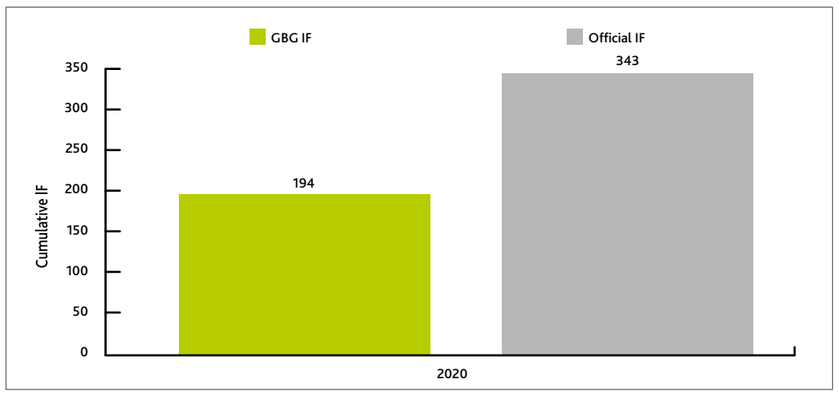


Figure 4: GBG and official Impact Factor (IF) in 2020

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

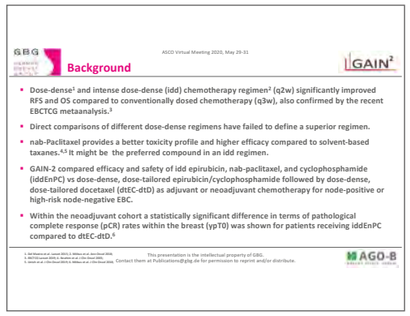
Publications on translational research project

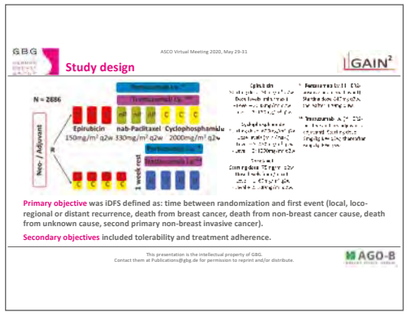
- Project leader (should prepare manuscript)
- Involved team member of this TRAFO project
- TRAFO board / protocol board members*
- Biomaterial provider
- 1-2 local pathologists providing most tumor tissue
- Biomarician
- PI (if involved in TRAFO project)

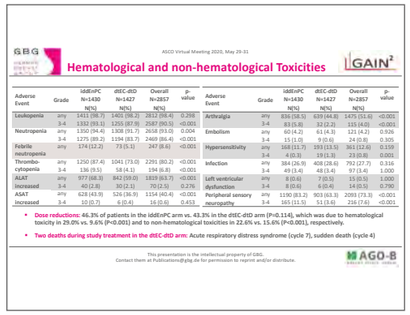
* Subboard and protocol board members will share in general authorships with best biomaterial providers on a 2:1 basis

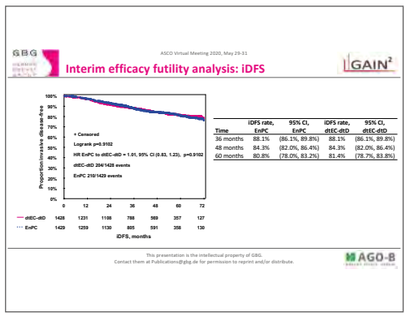
4.6. Oral and poster presentations

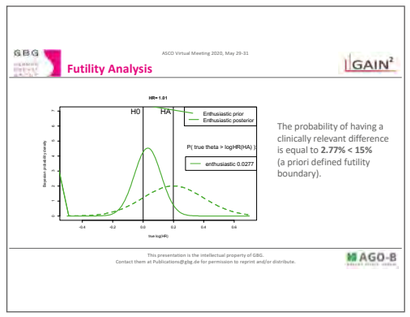
GAIN-2 study
(ASCO 2020)

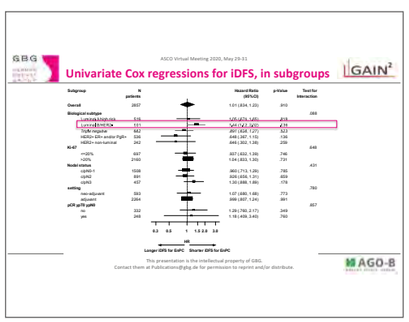












Chemotherapy-induced ovarian failure (DKK 2020)

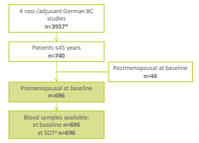
DKK 2020

Impact of Chemotherapy-Induced Ovarian Failure on Disease-Free Survival and Overall Survival in Young Women with Early Breast Cancer

Jenny Furlanetto, Valentina Nekljudova, Andreas Schneeweiss, Christian Thode, Carsten Denkert, Michael Untch, Martina Bassy, Thomas Karn, Peter A. Fasching, Elmar Stickeler, Christian Schem, Frederik Marmé, Eva-Maria Grischke, Marion van Mackelenbergh, Dominika Strik, Sabine Schmatloch, Volkmar Müller, Sibylle Loibl

DKK 2020

Flow of Patients



*patients started treatment as of 31st January 2016 (GeparSixto, GeparSepto, Geparnuevo, GAIN2); †EOT, end of treatment, samples collected 4 weeks after last therapy infusion

DKK 2020

Baseline Characteristics

CHARACTERISTICS (n=696)		OVERALL N	OVERALL %
Age (median [range])		39	[21-45]
Hormone Receptor Status	Positive	395	56.8
	Negative	301	43.2
T status	T1-2	621	89.6
	T3-4	72	10.4
N status	N0	404	59.2
	N+	278	40.8
Chemotherapy Regimen	PM	97	13.9
	PMCb	98	14.1
	P-EC	179	25.7
	Nab-P-EC	153	22.0
	Cabazitaxel	28	4.0
	Paclitaxel	28	4.0
	ddEcPC	50	7.2
	Dose tailored EC-D	63	9.1
CT Duration	12 weeks*	56	8.0
	16-18 weeks	308	44.3
	24 weeks	332	47.7

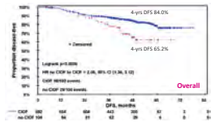
*paclitaxel, cabazitaxel

Abbreviations:
C, cyclophosphamide
Cb, carboplatin
D, docetaxel
E, epirubicin
ddi, intense dose-dense
M, doxorubicin
P, paclitaxel

DKK 2020

DFS by CIOF at End of Treatment

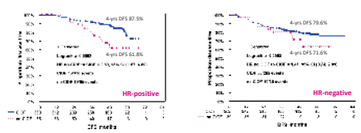
Median Follow-up 49.6 months



Chemotherapy-induced ovarian failure (CIOF) was defined as: estradiol <52.2 ng/L and FSH >12.4 IU/L after chemotherapy for those patients with premenopausal hormone levels at baseline.

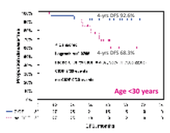
DKK 2020

DFS by CIOF according to Hormone Receptor Status



DKK 2020

DFS by CIOF according to Age

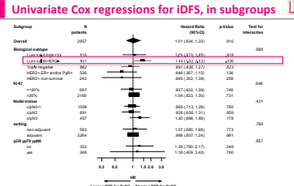


Age groups	N	4-year rate (%)		p-value*	HR [95% CI]
		No CIOF	CIOF		NO CIOF vs CIOF
<30 years	60	68.3	92.6	0.026	4.87 [1.05-22.63]
30-34 years	99	59.9	80.1	0.108	1.99 [0.85-4.68]
35-39 years	200	63.5	81.9	0.116	1.85 [0.85-4.04]
≥40 years	337	69.3	85.2	0.565	1.41 [0.44-4.51]

*log rank p-value

ASCO Virtual Meeting 2020, May 29-31

Univariate Cox regressions for iDFS, in subgroups



DKK 2020

Summary and Conclusion

- Patients with CIOF after anthracyclines/taxane-based chemotherapy for early breast cancer show a better DFS, especially in women with hormone-receptor positive breast cancer or <30 years.
- The improvement in DFS seems to translate in an OS advantage in patients with hormone-receptor positive early breast cancer.
- Patients with the highest levels of FSH after treatment derived a great benefit in DFS compared to patients with lower FSH levels.
- Not only the achievement of postmenopausal level of FSH is fundamental in order to obtain a better prognosis, but also the degree of ovarian suppression plays an important role.

Tumor mutational burden in early TNBC (ESMO Breast Cancer 2020)

ESMO Breast Cancer Virtual Meeting 2020 Congress, 23-24 May

Tumor mutational burden and immune infiltration as independent predictors of response to neoadjuvant immune checkpoint inhibition in early TNBC in GeparNuevo

T. Karn, C. Denkert, K. Weber, U. Holtrich, C. Hanusch, B. Sinn, B. Higgs, P. Jank, J. Huober, J.-U. Blohmer, W. Schmitt, S. Wu, M. van Mackelenbergh, C. Schem, E. Stickeler, C. Jackisch, M. Untch, A. Schneeweiss, S. Loibl

ESMO BREAST CANCER VIRTUAL MEETING

ESMO Breast Cancer Virtual Meeting 2020 Congress, 23-24 May

Objectives

- To assess the predictive value of TMB for pCR to neoadjuvant ICB and chemotherapy in TNBC from the GeparNuevo trial
- To assess the predictive value of a combination of TMB and an immune GEP for pCR in GeparNuevo

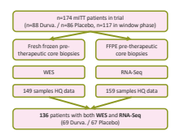
ESMO BREAST CANCER VIRTUAL MEETING

ESMO Breast Cancer Virtual Meeting 2020 Congress, 23-24 May

Methods

- 174 patients in GeparNuevo
- Pre-treatment core biopsies:
  - 149 patients with Whole Exome Seq (WES)
  - 159 patients with RNA-Seq (HTG-EdgeSeq Oncology Biomarker Panel, 2549 genes)
  - 136 patients with both data
- Pre-defined immune gene expression signature (GEP)
  "GeparSixto signature": CXCL9, CCL5, CD8A, CD80, CXCL13, IDO1, POCO1, CD274, CTLA4, FOXP3

CONSORT :



ESMO BREAST CANCER VIRTUAL MEETING

ESMO Breast Cancer Virtual Meeting 2020 Congress, 23-24 May

Results

Differences in TMB according to clinical parameters of GeparNuevo samples:

- Median TMB 1.52 mut/Mb (0.02-7.65)
- Higher TMB in patients ≥40 yr (P<0.001)
- Higher TMB in patients with pCR (P=0.005)

Parameter	Category	Median TMB	P-value (Wilcoxon test)
Age	< 40yr	1.11	**<0.001**
	≥ 40yr	1.74	
Stage	II-I	1.43	0.086
	IIA or higher	1.62	
Histol. Grade	G2	1.56	0.826
	G3	1.52	
Treatment arm	Placebo	1.59	0.672
	Durvalumab	1.47	
Window treatment	No	1.70	0.303
	Yes	1.46	
TILs	< 60%	1.61	0.190
	≥ 60%	1.35	
PD-L1	negative	1.43	0.989
	positive	1.59	
Response	RD	1.39	**0.005**
	pCR (ypT0ypN0)	1.87	

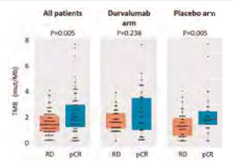
ESMO BREAST CANCER VIRTUAL MEETING

ESMO Breast Cancer Virtual Meeting 2020 Congress, 23-24 May

Results

Association of pCR and TMB:

- Median TMB significantly higher in patients with pCR (1.87 vs. 1.39; P=0.005)
- Significant association in placebo (chemo) arm (P=0.005)



ESMO BREAST CANCER VIRTUAL MEETING

ESMO Breast Cancer Virtual Meeting 2020 Congress, 23-24 May

Results

Predictive Value of TMB for pCR in GeparNuevo in Logistic Regression Analysis:

			All patients	Durvalumab	Placebo	Test for interaction
Continuous TMB (mut/Mb)	Univariate	N	149	74	75	
		OR (95% CI)	1.62 (1.20-2.20)	1.45 (0.99-2.14)	1.87 (1.13-3.08)	
		P-value	**0.002**	0.060	**0.014**	0.439
	Multivariate *	N	133	64	69	
		OR (95% CI)	2.06 (1.33-3.20)	1.77 (1.00-3.13)	2.82 (1.21-6.54)	
		P-value	**0.001**	**0.049**	**0.016**	0.436
Dichotomized TMB (upper tertile)	Univariate	N	149	74	75	
		OR (95% CI)	2.22 (1.11-4.43)	2.51 (0.95-6.64)	1.89 (0.70-5.12)	
		P-value	**0.024**	0.065	0.208	0.694
	Multivariate *	N	133	64	69	
		OR (95% CI)	3.45 (1.43-8.45)	4.66 (1.18-18.48)	2.21 (0.60-8.12)	
		P-value	**0.007**	**0.028**	0.232	0.438

* including age, stage, grading, stromal TILs, PD-L1 status, and window treatment

ESMO BREAST CANCER VIRTUAL MEETING

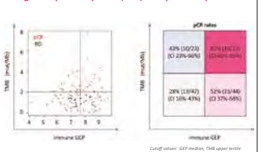
ESMO Breast Cancer Virtual Meeting 2020 Congress, 23-24 May

Results

Joint relationship of TMB and immune gene expression profile (GEP) with pCR in GeparNuevo:

- Independent predictive value of both TMB and GEP in multivariate LogReg
- High pCR rate (82%) in patients with both high TMB and high GEP

	Multivariate Log Reg *
TMB (mut/Mb)	OR 2.06 (1.34-3.16) P<0.001
Immune GEP	OR 1.58 (1.03-2.41) P=0.036



* including TMB, GEP, age, stage, grading, treatment window

Cutoff values: GEP-median, TMB upper tertile

ESMO BREAST CANCER VIRTUAL MEETING

ESMO Breast Cancer Virtual Meeting 2020 Congress, 23-24 May

Conclusions

- Tumor mutational burden predicted pCR after neoadjuvant treatment in GeparNuevo
- This result was obtained for both arms of the trial, i.e. for ICB in combination with chemotherapy and for chemotherapy alone.
- Both TMB and an immune gene expression profile (GEP) add independent value for pCR prediction in multivariate analysis.
- Our results suggest a combination of TMB and immune GEP can increase the precision of response prediction, and recommend both validation and further analysis of TMB in combination with immune parameters.

ESMO BREAST CANCER VIRTUAL MEETING

GeparX study (ESMO 2020)

GeparOcto (ESMO 2020)

- GBG 88

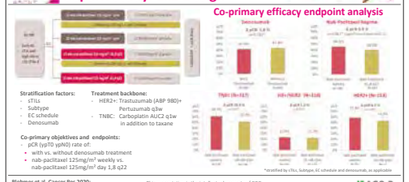
Denosumab as add-on to different regimen of nab-paclitaxel-anthracycline based neoadjuvant chemotherapy in early breast cancer: Subgroup analyses by RANK expression and HR status

Theresa Link, Jens-Uwe Blohmer, Marianne Just, Michael Untch, Oliver Stötzer, Peter A. Fasching, Andreas Schneeweiss, Pauline Wimberger, Sabine Seiler, Jens Huober, Wolfgang D. Schmitt, Christian Jackisch, Kerstin Rhiem, Claus Hanusch, Carsten Denkert, Bruno Sinn, Knut Engels, Valentina Nekljudova, Sibylle Loibl

-This is a joint study by GBG and AGO-B-

GeparX Study: 2x2 Design

Co-primary efficacy endpoint analysis



Stratification factors:
- sTILs
- Subtype
- EC schedule
- Denosumab

Treatment backbone:
- HER2+: Trastuzumab (ABP 980)+ Pertuzumab q3w
- TNBC: Carboplatin AUC2 q3w in addition to taxane

Co-primary objektives and endpoints:
- pCR (ypT0 ypN0) rate of:
- with vs. without denosumab treatment
- nab-paclitaxel 125mg/m² weekly vs. nab-paclitaxel 125mg/m² day 1,8 q22

*stratified by sTILs, Subtype, EC schedule and denosumab, as applicable

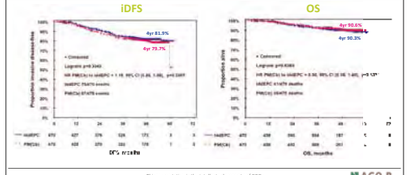
Blohmer et al. Cancer Res 2020; 80(4 Suppl): Abstract # GS3-01

Survival analysis of the randomized phase III GeparOcto trial comparing neoadjuvant chemotherapy (NACT) of iddEPC versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer, TNBC) (PM(Cb)) for patients (pts) with high-risk early breast cancer (BC)

Andreas Schneeweiss, Volker Möbus, Hans Tesch, Peter Klare, Carsten Denkert, Karin Kast, Claus Hanusch, Theresa Link, Michael Untch, Christian Jackisch, Jens-Uwe Blohmer, Peter A. Fasching, Christine Solbach, Jens Huober, Kerstin Rhiem, Valentina Nekljudova, Kristine Lübbe, Sibylle Loibl

- A joint study of the AGO Breast and German Breast Group

iDFS and OS overall



Predefined Subgroups: pCR Rates

Subgroup	pCR rates Denosumab (%) with	without	p-value*	pCR rates nab-Paclitaxel (%) nP q1w	nP d1, 8 q22	p-value*
HR+/HER2-	21.6	22.3	0.961	22.6	21.3	0.913
TNBC	52.5	58.0	0.313	60.4	50.0	0.056
HER2+	55.8	53.9	0.821	57.9	51.9	0.289
EC q2w	40.3	43.3	0.609	46.9	36.7	0.038
EC q3w	41.8	42.3	0.794	42.6	41.5	0.597
>50% sTILs	71.0	61.3	0.528	71.0	61.3	0.135
≤50% sTILs	38.4	41.2	0.453	42.6	37.0	0.126
With Dmab	X	X	X	48.2	33.8	0.027
Without Dmab	X	X	X	41.5	44.1	0.665

* stratified by sTILs, Subtype, EC schedule and denosumab, as applicable

Subgroup Analysis by RANK

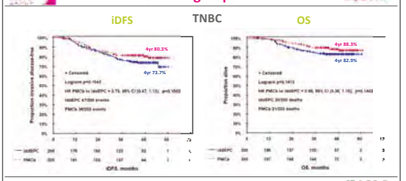
Association of RANK expression with baseline patient and tumor characteristics

Parameter	Category	RANK low (≤5%), N (%)	RANK high (>5%), N (%)	p-value
Age (years)	<40	82 (15.5)	45 (32.4)	<0.001
BC subtype	HR+/HER2-	233 (44.1)	33 (23.7)	<0.001
	TNBC	182 (34.5)	87 (62.6)	
	HER2+	113 (21.4)	19 (13.7)	
Tumor grade	G3	336 (63.6)	104 (74.8)	0.033
Ki-67	>20%	426 (80.7)	127 (91.4)	0.002
sTILs	median (range)	10.0 (0.0-90.0)	20.0 (2.0-90.0)	0.002

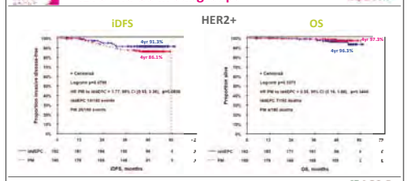
- Of the 780 patients included in GeparX study, 667 had evaluable RANK protein values.
- RANK expression was categorized at 75th percentile (Q3) into low (≤5%) or high (>5%).
- A high RANK expression was detected in 139/667 (20.8%) of the patients.

Pfitzner B et al. Breast Cancer Res Treat. 2014.

iDFS and OS in Subgroups



iDFS and OS in Subgroups

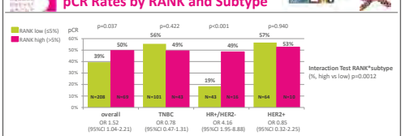


pCR Rates by RANK and Treatment

*stratified by sTILs, subtype, EC schedule and denosumab; nP, nab-paclitaxel

Parameter	Denosumab: OR (with vs. without) [95% CI]	p-value	interaction p-value	Nab-paclitaxel (nP) regime: OR (nP weekly vs. nP d1,8 q22) [95% CI]	p-value	interaction p-value
RANK low	1.10 [0.78-1.56]	0.589	0.528	1.19 [0.84-1.69]	0.318	0.833
RANK high	0.86 [0.44-1.68]	0.667		1.30 [0.67-2.52]	0.447	

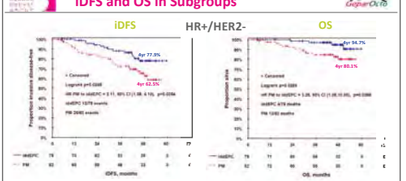
pCR Rates by RANK and Subtype



OR 1.52 (95%CI 1.04-2.21)
OR 0.78 (95%CI 0.47-1.31)
OR 4.16 (95%CI 1.95-8.88)
OR 0.85 (95%CI 0.32-2.25)

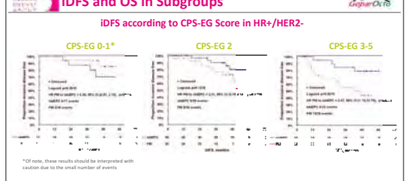
- Overall, RANK expression did not add additional predictive value (OR=1.05 [95%CI 0.69-1.60], p=0.823) when adjusted for BC subtype and the continuous variables age, Ki-67 and sTILs in multivariate model.
- In HR+/HER2- RANK expression was an independent significant predictor of pCR (OR=2.98 [95%CI 1.30-6.79], p=0.010) when adjusted for the continuous variables age, Ki-67 and sTILs.

iDFS and OS in Subgroups



iDFS and OS in Subgroups

iDFS according to CPS-EG Score in HR+/HER2-

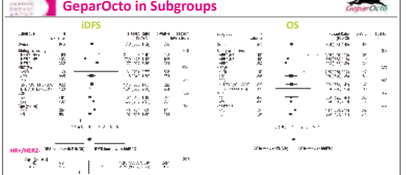


*Of note, these results should be interpreted with caution due to the small number of events

Summary and Conclusion

- **A high RANK expression was detected in 20.8% of the patients.**
- **A high RANK expression was associated with significantly higher pCR rates (49.6% vs. 39.4%; p=0.037).**
- **This effect was driven by patients with HR+/HER2- BC.**
- **However, a clinical benefit of denosumab in relation to RANK expression could not be shown. Further explorative analyses are still ongoing.**

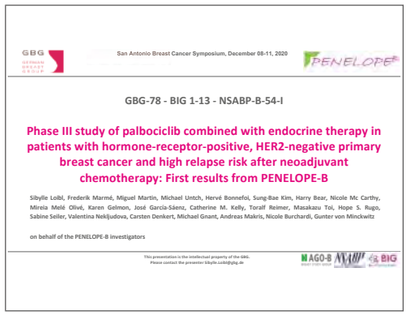
GeparOcto in Subgroups

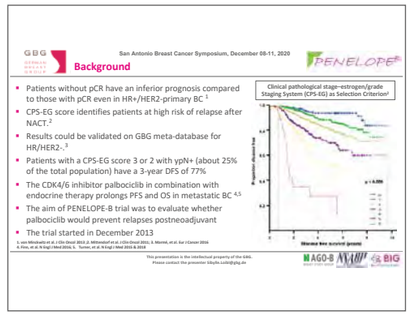


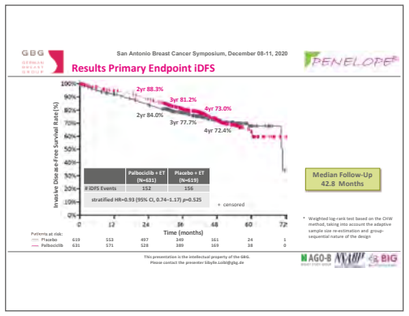
Summary and Conclusions

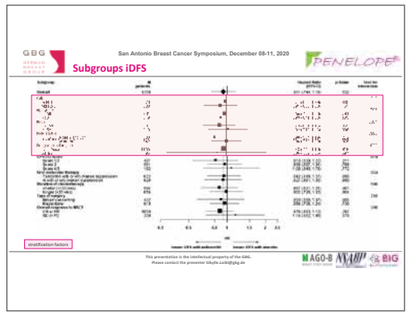
- With a median follow-up of 47 months there was no significant difference in iDFS and OS following NACT with iddEPC or PM(Cb) for the entire cohort
- No significant difference in iDFS and OS was observed in the subgroup of patients with HER2+ and TNBC
- Patients with HR+/HER2- BC, however, had better iDFS and OS following iddEPC supporting the concept of an additional effect of NACT in patients with luminal-like HER2- BC which is not indicated by intermediate prognostic marker like pCR and CPS-EG score
- Cyclophosphamide might play an important role in adjuvant treatment of patients with high-risk HR+/HER2- BC

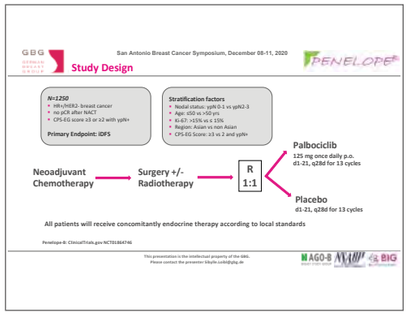
Penelope[B] (SABCS 2020)

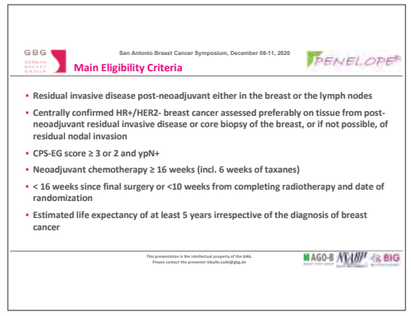


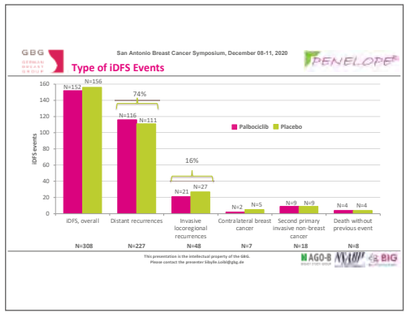


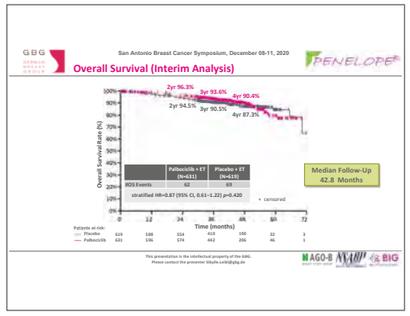


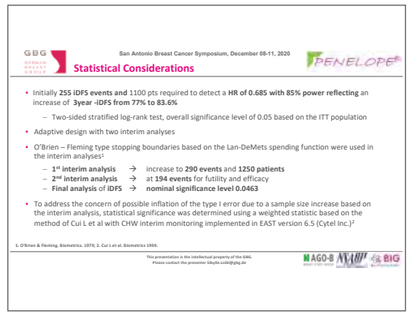


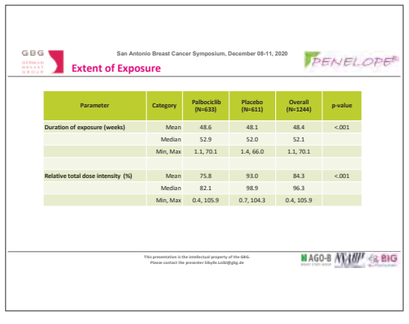




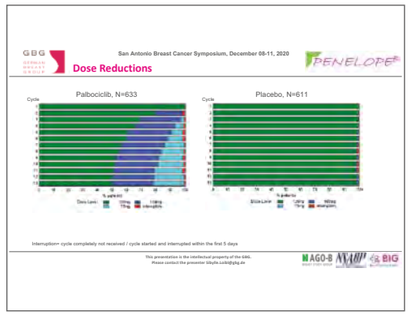


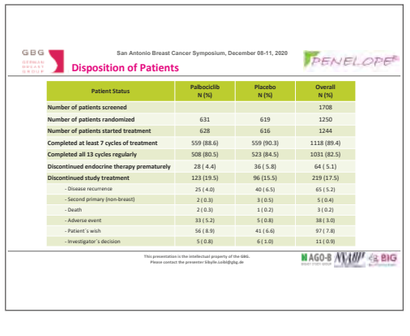




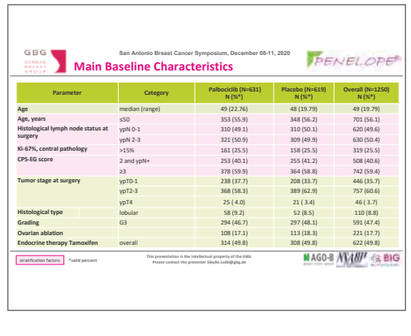


Parameter	Category	Palbociclib (N=633)	Placebo (N=611)	Overall (N=1244)	p-value
Duration of exposure (weeks)	Mean	48.6	48.1	48.4	<.001
	Median	52.9	52.0	52.1	
	Min, Max	1.1, 70.1	1.4, 66.0	1.1, 70.1	
Relative total dose intensity (%)	Mean	75.8	93.0	84.3	<.001
	Median	82.1	98.9	96.3	
	Min, Max	0.4, 105.9	0.7, 104.3	0.4, 105.9	



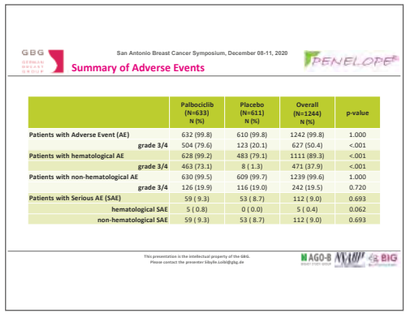


Patient Status	Palbociclib N (%)	Placebo N (%)	Overall N (%)
Number of patients screened			1708
Number of patients randomized	631	619	1250
Number of patients started treatment	628	616	1244
Completed at least 7 cycles of treatment	559 (88.6)	559 (90.3)	1118 (89.4)
Completed all 13 cycles regularly	508 (80.5)	523 (84.5)	1031 (82.5)
Discontinued endocrine therapy prematurely	28 (4.4)	36 (5.8)	64 (5.1)
Discontinued study treatment	123 (19.5)	96 (15.5)	219 (17.5)
- Disease recurrence	25 (4.0)	40 (6.5)	65 (5.2)
- Second primary (non-breast)	2 (0.3)	3 (0.5)	5 (0.4)
- Death	2 (0.3)	1 (0.2)	3 (0.2)
- Adverse event	33 (5.2)	5 (0.8)	38 (3.0)
- Patient´s wish	56 (8.9)	41 (6.6)	97 (7.8)
- Investigator´s decision	5 (0.8)	6 (1.0)	11 (0.9)

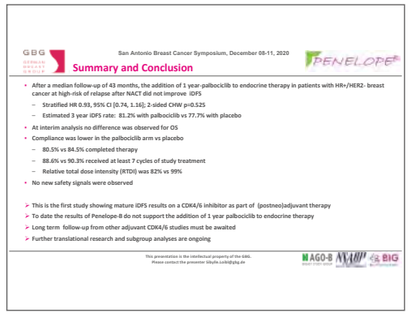


Parameter	Category	Palbociclib (N=631) N (%*)	Placebo (N=619) N (%*)	Overall (N=1250) N (%*)
Age	median (range)	49 (22.76)	48 (19.79)	49 (19.79)
Age, years	≤50	353 (55.9)	348 (56.2)	701 (56.1)
Histological lymph node status at surgery	ypN 0-1	310 (49.1)	310 (50.1)	620 (49.6)
	ypN 2-3	321 (50.9)	309 (49.9)	630 (50.4)
Ki-67%, central pathology	>15%	161 (25.5)	158 (25.5)	319 (25.5)
CPS-EG score	2 and ypN+	253 (40.1)	255 (41.2)	508 (40.6)
	≥3	378 (59.9)	364 (58.8)	742 (59.4)
Tumor stage at surgery	ypTO-1	238 (37.7)	208 (33.7)	446 (35.7)
	ypT2-3	368 (58.3)	389 (62.9)	757 (60.6)
	ypT4	25 (4.0)	21 (3.4)	46 (3.7)
Histological type	lobular	58 (9.2)	52 (8.5)	110 (8.8)
Grading	G3	294 (46.7)	297 (48.1)	591 (47.4)
Ovarian ablation		108 (17.1)	113 (18.3)	221 (17.7)
Endocrine therapy Tamoxifen	overall	314 (49.8)	308 (49.8)	622 (49.8)

stratification factors *valid percent



	Palbociclib (N=633) N (%)	Placebo (N=611) N (%)	Overall (N=1244) N (%)	p-value
Patients with Adverse Event (AE)	632 (99.8)	610 (99.8)	1242 (99.8)	1.000
grade 3/4	504 (79.6)	123 (20.1)	627 (50.4)	<.001
Patients with hematological AE	628 (99.2)	483 (79.1)	1111 (89.3)	<.001
grade 3/4	463 (73.1)	8 (1.3)	471 (37.9)	<.001
Patients with non-hematological AE	630 (99.5)	609 (99.7)	1239 (99.6)	1.000
grade 3/4	126 (19.9)	116 (19.0)	242 (19.5)	0.720
Patients with Serious AE (SAE)	59 (9.3)	53 (8.7)	112 (9.0)	0.693
hematological SAE	5 (0.8)	0 (0.0)	5 (0.4)	0.062
non-hematological SAE	59 (9.3)	53 (8.7)	112 (9.0)	0.693



Influence of denosumab on disseminated tumor cells (DTC) in the bone marrow of breast cancer patients with neoadjuvant treatment – a GeparX translational substudy

Pauline Wimberger[1,2,3], Jens-Uwe Blohmer[4], Petra Krabisch[5], Theresa Link[1,2,3], Marianne Just[6], Bruno Sinn[7], Eike Simon[8], Christine Solbach[9], Tanja Fehm[10], Carsten Denkert[11], Cristin Kühn[12], Kerstin Rhiem[13], Hans Tesch[14], Sherko Kümmel[15], Andrea Petzold[1,2,3], Oliver Stötzer[16], Cornelia Meisel[1,2,3], Jan Dominik Kuhlmann[1,2,3], Valentina Nekljudova[17], Sibylle Loibl[17]

[1]Department of Gynecology and Obstetrics, Medical Faculty and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; [2]National Center for Tumor Diseases (NCT), Dresden, Germany: German Cancer Research Center (DKFZ), Heidelberg, Germany; Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany; Helmholtz-Zentrum Dresden-Rossendorf (HZDR), Dresden, Germany; [3]German Cancer Consortium (DKTK), Dresden and German Cancer Research Center (DKFZ), Heidelberg, Germany; [4]Charité Universitätsmedizin Berlin, Germany; [5]Klinikum Chemnitz, Germany; [6]Onkologische Schwerpunktpraxis Bielefeld , Germany; [7]Charité Berlin, Germany; [8]Kreiskrankenhaus Torgau , Germany

Background

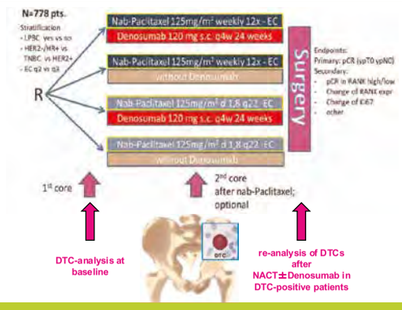
Disseminated tumor cells (DTCs) in the bone marrow (BM) are observed in up to 30% at primary diagnosis of breast cancer and their presence is an independent prognostic factor for reduced survival. It has been shown that antiresorptive therapy eradicates DTCs and improves prognosis in DTC-positive breast cancer patients. In the GeparX phase III prospective randomized trial, denosumab (a monoclonal IgG2-anti-RANKL-antibody) was investigated as the add-on treatment to neoadjuvant chemotherapy (NACT) with two different nab-paclitaxel schedules in early high-risk primary breast cancer.

Objectives

1. Does the application of **short-term denosumab** (24 weeks) as add-on neoadjuvant treatment **eradicate DTCs** in the bone marrow of patients with breast cancer?
2. Does a potential **eradication of DTCs** by denosumab treatment influence the rate of **pathological complete response** (pCR)?

Patients and Study Design

A total of 167 patients from the GeparX trial were available for **DTC-analysis at baseline** by immunocytochemistry using the pan-cytokeratin antibody A45-B/B3. Patients who are DTC-positive at baseline were **re-analyzed for DTCs after NACT±Denosumab**.



Results

- A total of **60/167 patients (35.9%)** treated with NACT±Denosumab **had a pathological complete response (pCR).** The highest pCR rate was observed in triple-negative breast cancer (TNBC), followed by HER2+ and hormone receptor -positive (HR+)/HER2- patients (**Figure 1**).
- At baseline, **43/167 patients (25.7%)** were **DTC-positive** and **41 of those** were available for **re-analysis of DTCs** after NACT±Denosumab.
- **DTC-eradication** was observed in **77.8%** after NACT+Denosumab and in **69.6%** after NACT alone (p=0.726; **Figure 2**).
- Due to the limited number of patients eligible for DTC re-analysis after NACT, a **subtype specific analysis** for the effect of denosumab was **not possible**.
- There was **no significant association** between pCR and i) the **presence of DTCs** at baseline (37.1% DTC-negative vs 32.6% positive; p=0.71) or ii) the **eradication of DTCs** after NACT±Denosumab (36.7% vs 27.3% in DTC-persistence; p=0.72) (**Figure 1 and 3**).
- In **TNBC patients**, we observed a numerical trend that **DTC-positivity at baseline** (41.2% pCR-rate in DTC-positive vs. 60.4% pCR-rate in DTC-negative; p=0.256) **or DTC-persistence** (25% pCR-rate in DTC-persistent vs. 50% pCR-rate in DTC-eradicated; p=0.585) after NACT could be associated with **reduced pCR-rate** (**Figure 1+3**).
- In **TNBC patients** that achieved a pCR in the denosumab arm, **0/3 (0%) patients were DTC-positive after NACT**, whereas **1/4 patients (25%)** with a pCR without denosumab treatment were DTC-positive after NACT.

Figure 1: pCR-rate and DTC-status in BM at baseline

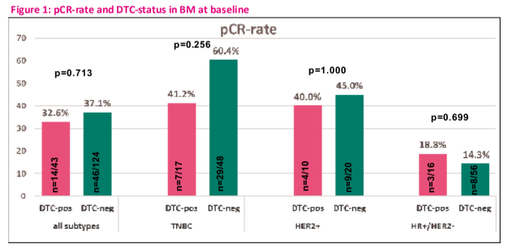


Figure 2: Rate of DTC-eradication

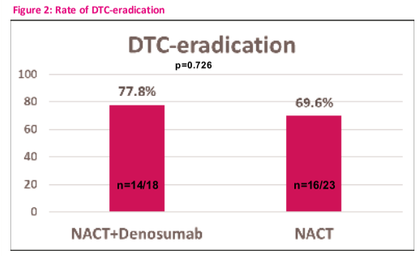
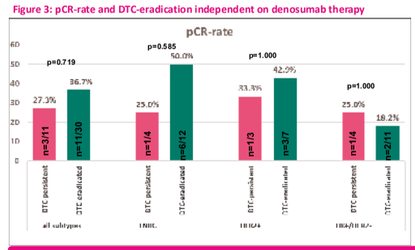


Figure 3: pCR-rate and DTC-eradication independent on denosumab therapy



Conclusions

Denosumab in addition to NACT does not improve pCR, but a potential effect of denosumab on DTC-eradication should be further analyzed in TNBC patients.

Presented at ASCO Annual Meeting 2020, Virtual Meeting, May 29-June 2

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PB-004

Characteristics and clinical outcome of breast cancer patients with asymptomatic brain metastases

Elena Laakmann[1], Isabell Witzel[1], Tanja Neunhöffer[2], Rudolf Weide[3], Marcus Schmidt[4], Tjoung-Won Park-Simon[5], Volker Möbus[6], Christoph Mundhenke[7], Arkadius Polasik[8], Kristina Lübbe[9], Tobias Hesse[10], Kerstin Riecke[1] , Marc Thill[11], Peter A. Fasching[12], Carsten Denkert[13], Tanja Fehm[14], Valentina Nekljudova[15], Julia Rey[15], Sibylle Loibl[15], Volkmar Müller[1]

1 Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, 2 Frauenärzte am Dom, Mainz, Germany, 3 Institut für Versorgungsforschung in der Onkologie Koblenz, Germany, 4 Universitätsmedizin Mainz, 5 Medizinische Hochschule Hannover, Germany, 6 Medizinische Klinik II, Abtlg. Hämatologie/Onkologie, Universitätsklinikum Frankfurt, Germany, 7 Universität Kiel, Germany, 8 Universitätsklinikum Ulm, Germany, 9 Diakovere Henriettenstift, Breast Center, Hannover, Germany, 10 Agaplesion Diakonieklinikum Rotenburg, Germany, 11 Agaplesion Markus Krankenhaus, Frankfurt, Germany, 12 Frauenklinik des Universitätsklinikums Erlangen, Germany, 13 Institut für Pathologie UKGM - Universitätsklinikum Marburg, Germany, 14 Universitätsklinikum Düsseldorf, 15 German Breast Group, Neu-Isenburg, Germany

Background

- The incidence of brain metastases (BM) in breast cancer (BC) patients is increasing in the last decades and has become one of the major clinical challenges in the management of patients with advanced BC.
- A median overall survival (OS) of 7.4 months after diagnosis of BM was observed in our previous analysis of the Brain Metastases in Breast Cancer (BMBC) registry [1].
- Until now it is unclear if an early detection of BMs for patients with asymptomatic BM of BC has a clinical benefit. BM screening is not part of the management of patients with BC today, while brain MRI screening is part of the clinical routine for the management of patients with lung cancer [2] which has also a high propensity to metastasize in the brain.
- The aim of this retrospective analysis was to characterize the cohort of BC patients with asymptomatic BM at diagnosis as well as to compare the OS data of patients with and without neurological symptoms of BM.

Patients and Methods

Clinical data for this analysis was derived from the BMBC registry.
A total of 2589 patients were included: 580 without neurological symptoms of BM and 2009 with neurological symptoms.

Objectives:

- To characterize the patient cohort with BM of BC with vs. without documented neurological symptoms (seizure, nausea/vomiting, motoric deficits/ failure, headache, impaired vision, mental disorder/psychologic disorder).
- To characterize the cohort of the patients with neurological symptoms according to the biological subtype of the initial BC. Biological subtype was defined as HER2-positive, TNBC (ER-, PR-negative and HER2-negative), luminal A-like (ER and/or PR positive, HER2-negative, grade 1-2) and luminal B-like (ER and/or PR positive, HER2-negative, grade 3).
- Furthermore, we performed an analysis of OS for patients with and without neurological symptoms of BM. OS was defined as the time interval from the first diagnosis of BM to death due to any reason.

All reported p-values were two-sided, the significance level was set to 0.05. Data was analyzed using SAS® (Statistical Analysis Software) version 9.4.

Results

Characteristics of patients with or without neurological symptoms at diagnosis of BM

The statistical **univariate analysis** (Tables 1 and 2) showed that patients with asymptomatic BM

- were significantly younger than symptomatic patients at diagnosis of BM (median age 55.5 vs. 57.0 years, p=0.01) and at diagnosis of primary BC (median age 51.00 vs. 52.0, p=0.042)
- had a better performance status at BM diagnosis (Karnofsky Index 80-100% 68.4% vs. 57%, p<0.001)
- lower tumor grading of the primary tumor (G1 3.1% vs. 1.4%, p=0.015)
- lower number of BM (one BM 34.1% vs. 30.1%, p=0.027, <=4 BMs: 37.7% vs. 44.4%)
- had a smaller diameter of BM (median: 1.5 vs. 2.2 cm, p<0.001)
- showed less commonly a meningeosis carcinomatosa (6.3% vs. 10.9%, p<0.001)
- had less intensive BM therapy (combined surgery and radiotherapy: 21% vs. 26.9%, p=0.001).
- had significantly more often extracranial metastases (ECM) at time of BM diagnosis (86.7% vs. 81.5%, p=0.003). The most common localisations of ECM were bone (54.0%), lung (39.0%) and liver (37.2%).
- The BC subtype did not differ significantly between the two groups (p=0.312).

In a **multivariate logistic** regression analysis (n=705) asymptomatic patients showed a significantly higher performance status than symptomatic patients (odds ratio 1.1, 95% CI: 1.06-1.13; p<0.001).

Further, patients with more than 4 BM in comparison to 1 BM were more frequent among symptomatic than asymptomatic patients (odds ratio 1.98, 95% CI: 1.11-3.52; p=0.02).

Table 1. Baseline characteristics (continuous parameters)

Parameter	Category	Asymptomatic patients	Symptomatic patients	Overall	p-value
Age at first diagnosis of BC, years	Mean	51.8	53.0	52.7	0.042
	StD	12.6	12.5	12.5	
	Median (min, max)	51.0 (22.0, 87.0)	52.0 (20.0, 98.0)	52.0 (20.0, 98.0)	
Age at diagnosis of BM, years	Mean	56.0	57.5	57.2	0.010
	StD	12.4	12.4	12.4	
	Median (min, max)	55.5 (26.0, 87.0)	57.0 (22.0, 99.0)	57.0 (22.0, 99.0)	
max diameter of BM	Mean	2.0	2.6	2.5	<0.001
	StD	2.1	3.3	3.1	
	Median (min, max)	1.5 (0.0, 22.0)	2.2 (0.0, 85.0)	2.0 (0.0, 85.0)	
	Missing	200	529	729	

Table 2. Baseline characteristics (categorical parameters)

Parameter	Category	Asymptomatic patients N (valid %)	Symptomatic patients N (valid %)	Overall N (valid %)	p-value
Histological tumor type	ductal or ductal-lobular-invasive	415 (72.3)	1461 (73.5)	1876 (73.3)	0.774
	lobular-invasive	43 (7.5)	151 (7.6)	194 (7.6)	
	other	116 (20.2)	375 (18.9)	491 (19.2)	
	missing	6	22	28	
Tumor grading	G1	16 (3.1)	26 (1.4)	42 (1.8)	0.015
	G2	214 (42.1)	713 (39.4)	927 (40.0)	
	G3	278 (54.7)	1069 (59.1)	1347 (58.2)	
	missing	72	201	273	
Biological subtype	TNBC	103 (20.0)	419 (23.6)	522 (22.8)	0.312
	Luminal A	96 (18.6)	296 (16.7)	392 (17.1)	
	Luminal B	69 (13.4)	244 (13.8)	313 (13.7)	
	HER2+	247 (48.0)	815 (45.9)	1062 (46.4)	
	missing	65	235	300	
Karnofsky-Index at diagnosis of BM	100%	60 (31.6)	94 (10.2)	154 (13.9)	<.001
	80-90%	70 (36.8)	431 (46.8)	501 (45.1)	
	60-70%	46 (24.2)	276 (30.0)	322 (29.0)	
	40-50%	13 (6.8)	90 (9.8)	103 (9.3)	
	10-30%	1 (0.5)	30 (3.3)	31 (2.8)	
	missing	390	1088	1478	
Number of BM	1	170 (34.1)	548 (30.1)	718 (30.9)	0.027
	2-3	141 (28.3)	466 (25.6)	607 (26.1)	
	≥4	188 (37.7)	809 (44.4)	997 (42.9)	
	missing	81	186	267	
Local treatment of BM	Surgery only	21 (4.4)	119 (7.1)	140 (6.5)	0.001
	Radiotherapy only	360 (74.7)	1112 (66.1)	1472 (68.0)	
	both	101 (21.0)	452 (26.9)	553 (25.5)	
	missing	98	326	424	
ECM at time of BM diagnosis	yes	502 (86.7)	1637 (81.5)	2139 (82.7)	0.003
	no	77 (13.3)	371 (18.5)	448 (17.3)	
	missing	1	1	2	
Existence of Meningiosis Carcinomatosa	no	523 (93.7)	1769 (89.1)	2292 (90.1)	<.001
	yes	35 (6.3)	217 (10.9)	252 (9.9)	
	missing	22	23	45	

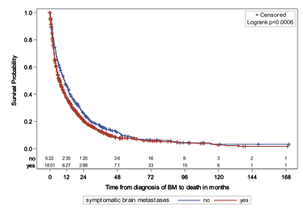
Distribution of neurological symptoms according to biological subtypes

The statistical evaluation of the neurological complaints of BM showed similar results in all BC subtypes (TNBC, HER2-positive, luminal A-like and luminal B-like).

Survival analysis of patients with asymptomatic vs. symptomatic BMs

- Median time from the diagnosis of BC to the diagnosis of BM: 36.4 months for the patients with asymptomatic BM and 36.0 months for symptomatic patients (p=0.248).
- Median time from diagnosis of BC to the diagnosis of ECM (with diagnosis of BM after the diagnosis of ECM) 26.0 months and 24.9 months respectively, (p=0.812).
- OS of patients with asymptomatic BM: median 10.4 vs. 6.90 months for patients with symptomatic BMs (p<0.001, Figure 1).
- Additional OS analysis without patients with meningeosis carcinomatosa: median OS of asymptomatic patients was longer (10.4 vs.7.82 months, p=0.012).

Figure 1. Kaplan-Meier curve for the time from first diagnosis of BM to death due to any reason.



Conclusions

- Our analyses indicate that asymptomatic patients have a minor severity of the metastatic disease in the brain and have a better outcome despite a less intense local BM therapy compared to symptomatic patients.
- This analysis is of clinical relevance in the context of prospective trials examining the benefit of BM early detection.
- Of course, a lead time bias of the earlier diagnosis cannot be ruled out.

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Patients preference for different administration methods of trastuzumab in patients with HER2+ early breast cancer treated within the GAIN-2 trial (GBG 68)

Reinisch M[1], Untch M[2], Reimer T[3], Mahlberg R[4], Aydogdu M[5], Hitschold T[6], Jackisch C[7], Marmé F[8], Lück HJ[9], Ladda E[10], Schmatloch S[11], Schmidt M[12], Klare P[13], Sinn B[14], Stickeler E[15], Seiler S[16], Rey J[16], Klutinus N[17], Möbus V[18], Loibl S[16]

[1] Kliniken Essen-Mitte, Brustzentrum, Essen, Germany, [2] HELIOS Klinikum Berlin Buch, Germany, [3] Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock, Germany, [4] Klinikum Mutterhaus der Borromäerinnen , Trier, Germany, [5] Klinikum Bremen-Mitte, Frauenklinik, Germany, [6] Klinikum Worms, Frauenklinik, Germany, [7] Sana Klinikum Offenbach, Germany, [8] Universitätsklinikum Mannheim, Universität Heidelberg, Germany, [9] Gynäkologisch-onkologische Praxis Hannover, Germany, [10] Onkologische Praxis Neumarkt, Germany, [11] Elisabeth Krankenhaus Kassel, Brustzentrum, Germany, [12] Universitätsmedizin Mainz, Germany, [13] Praxisklinik Krebsheilkunde für Frauen Berlin, Germany, [14] Charité, Universitätsmedizin Berlin, Institut für Pathologie, Germany, [15] Unklinik RWTH Aachen, Germany, [16] German Breast Group, Neu-Isenburg, Germany, [17] HELIOS Klinikum Pforzheim GmbH, Brustzentrum, Pforzheim, Germany, [18] Universität Frankfurt, Medizinische Klinik II,Hämatologie/Onkologie, Germany

P86

Background

Trastuzumab given intravenously (i.v.) every three weeks (q3w) is standard of care for patients (pts) with early HER2+ breast cancer (BC). The Hannah trial proofed a comparable efficacy and safety profile of the subcutaneous (s.c.) formulation of trastuzumab (600mg) q3w administered into the thigh vs. i.v. formulation in early BC with a median follow up of 6 years.[1,2] Other trials support these findings.[3,4] Advantages of s.c. administration were reported to be a shorter treatment time, a reduction in the use of health care resources, increased convenience for pts, and greater patient preference.[3,4] None of the studies investigated other sites of injection besides the thigh. Nevertheless, injections into the abdominal wall might be more convenient for pts.

The aim of this analysis was therefore to evaluate patient preference for s.c. administration of trastuzumab either into the thigh or into the abdominal wall .

Patients and Methods

This study is a prospective, multi-center, controlled, non-blinded, randomized phase II substudy to determine the patient preference for s.c. trastuzumab either into the thigh or the abdominal wall compared to previous i.v. trastuzumab within the GAIN-2 trial (EudraCT No.: 2011-005214-11).[5] Pts with HER2+ BC who have received trastuzumab i.v. simultaneously to (neo)adjuvant chemotherapy (CT) within the GAIN-2 study were randomized (1:1) to receive postoperatively trastuzumab 600mg s.c. either into the thigh or the abdominal wall (**Figure 1**).

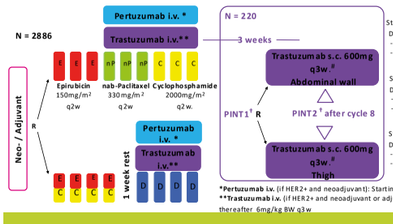
Patient preferences were evaluated by two patient interviews (PINTs):

- PINT1: -20 to -1 days prior to randomization, pts were assessed regarding the factors influencing preference after having received 8-12 weeks of i.v. trastuzumab infusions.
- PINT2: At the end of the 8th cycle of s.c. trastuzumab, concluding with a single binary assessment of preference.

The **primary efficacy endpoint** was the proportion of pts preferring s.c. trastuzumab (thigh vs abdominal wall) compared to previous i.v. trastuzumab, assessed by the question on PINT2: "All things considered, which method of administration do you prefer?" (answer options: "i.v.", "s.c.", "no preference").

Secondary objectives were to validate factors potentially influencing patient preference of trastuzumab s.c. as detected in the PrefHer study.[3] A modified intention-to-treat (mITT) analysis was conducted for randomized pts with at least one dose of s.c. trastuzumab.

Figure 1. Study design



***Pertuzumab i.v.** (if HER2+ and neoadjuvant): Starting dose 840mg q3w, thereafter 420mg q3w.
****Trastuzumab i.v.** (if HER2+ and neoadjuvant or adjuvant): Starting dose 8mg/kg BW q3w, thereafter 6mg/kg BW q3w

Results

A total of 226 pts were randomized (113 in each arm), 219 pts represented the mITT set. 7 pts did not start therapy and were excluded from the mITT set (6 due to pts decision, 1 due to progress). Baseline characteristics were well balanced between arms (**Table 1**). The LVEF did not significantly change along the study according to administration site. Randomization was stratified according to CT study arm and age (50 vs >50 years; 102 (46.6%) pts were >50 years). 123 pts completed treatment, 60 pts (54.5%) in the thigh and 63 (57.8%) in the abdominal wall group. Reasons for early discontinuation are summarized in **Table 2**.

Primary Efficacy: Overall, 83.5% of 182 pts preferred s.c. over i.v. injection/no preference (thigh 93 pts (80.6%); abdominal wall 89 pts (86.5), p=0.322) (**Table 3**). 23 of pts (thigh 15; abdominal wall 8) had no preference regarding s.c. or i.v. treatment.

Secondary Efficacy: The expected preferences given in PINT1 (i.v./no preference vs s.c.) showed a significant influence on the preference of the application site given in PINT2 (univariate analysis; OR 3.04 [95% CI 1.36-6.78]; p=0.007, **Figure 2**). Shorter administration time is the main reason for preferring s.c. over i.v. administration.

PINT1/PINT2: PINT1 showed no significant differences between thigh and abdominal wall. **Table 4** summarizes relevant details of PINT2. Pts did not report a preferred setting of administration (hospital/breast centre/oncological practice; p=0.374).

No increased **toxicity** was observed and the study **compliance** was comparable between injection sites.

Table 1. Baseline characteristics

Parameter	Category	Thigh N= 110 N (%)	Abdominal wall N=109 N (%)	Overall N=219 N (%)
Age, years	Median	50.0	50.0	50.0
	Min, Max	25.0, 69.0	30.0, 67.0	25.0, 69.0
BMI, kg/m²	Median	24.00	24.60	24.20
	Min, Max	17.4, 50.7	18.4, 43.2	17.4, 50.7
pre-study trastuzumab therapy (i.v.) cycles	Median	12.40	12.20	12.30
	Min, Max	7.0, 26.9	6.0, 23.9	6.0, 26.9
	missing	0	1	1
Tumor stage (all)	c/pT1	53 (48.2)	42 (38.5)	95 (43.4)
	c/pT2	43 (39.1)	57 (52.3)	100 (45.7)
	c/pT3	11 (10.0)	7 (6.4)	18 (8.2)
	c/pT4	3 (2.7)	3 (2.8)	6 (2.7)
Nodal status (all)	c/pN0-1	73 (66.4)	75 (68.8)	148 (67.6)
	c/pN2	26 (23.6)	14 (12.8)	40 (18.3)
	c/pN3	11 (10.0)	20 (18.3)	31 (14.2)
Estrogen/ Progesterone Receptor (ER/PgR) central testing	both ER and PgR negative	35 (79.5)	30 (81.1)	65 (80.2)
	ER and/or PgR positive	9 (20.5)	7 (18.9)	16 (19.8)
	missing	66	72	138
Ki67, central testing	≤20%	17 (15.5)	18 (16.5)	35 (16.0)
	>20%	93 (84.5)	91 (83.5)	184 (84.0)
Setting	neoadjuvant	30 (27.3)	27 (24.8)	57 (26.0)
	adjuvant	80 (72.7)	82 (75.2)	162 (74.0)

Table 2. Reason for early discontinuation

Early discontinuation of treatment	Thigh N=50 N (%)	Abdominal wall N=46 N (%)	Overall N=96 N (%)
Relapse	1 (0.9)	1 (0.9)	2 (0.9)
Death	0 (0.0)	0 (0.0)	0 (0.0)
Adverse Event	4 (3.6)	4 (3.7)	8 (3.7)
Patient´s decision	9 (8.2)	6 (5.5)	15 (6.8)
Investigator´s decision*	36 (32.7)	35 (32.1)	71 (32.4)

*Reason was typically that the number of usually given 18 cycles of trastuzumab was already achieved together with the trastuzumab i.v. treatment in the main study

Table 3. Proportion of pts preferring s.c. over i.v. trastuzumab injection/no preference

	Proportion %	95% CI	p-value
Thigh (N=93)	80.6	(72.6, 88.7)	0.322
Abdominal wall (N=89)	86.5	(79.4, 93.6)	.
Difference of the two proportions	-5.9	(-17, 4.84)	
Overall (N=182)	83.5	(78.1, 88.9)	.

Figure 2. Univariate logistic regression for patient preference to s.c. vs. i.v./no preference trastuzumab

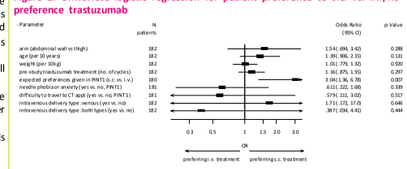


Table 4. Summary of analysis on PINT2 (patient preference of s.c. vs i.v. trastuzumab)

Parameter	Category	Thigh N=110 N (%)	Abdominal wall N=109 N (%)	Overall N=219 N (%)	p-value
In how far were irritations around the s.c. injection site a problem for you?	very	2 (2.2)	0 (0.0)	2 (1.1)	0.033
	a bit	23 (24.7)	11 (12.4)	34 (18.7)	
	never	68 (73.1)	78 (87.6)	146 (80.2)	
	missing	17	20	37	
How often were the reactions a problem for you?	only at the 1st and/or 2nd administration	12 (54.5)	3 (20.0)	15 (40.5)	0.036
	in most of the administrations	10 (45.5)	12 (80.0)	22 (59.5)	
	missing	88	94	182	
How would you generally describe the s.c. administrations?	very uncomfortable	1 (1.1)	7 (8.0)	8 (4.4)	0.014
	a bit uncomfortable	17 (18.3)	7 (8.0)	24 (13.3)	
	acceptable	75 (80.6)	74 (84.1)	149 (82.3)	
	missing	17	21	38	
Which method of administration caused the least pain?	i.v.	20 (21.5)	11 (12.4)	31 (17.0)	0.010
	s.c.	19 (20.4)	36 (40.4)	55 (30.2)	
	no difference	54 (58.1)	42 (47.2)	96 (52.7)	
	missing	17	20	37	

Conclusions

- This analysis confirmed the results previously demonstrated by others[1-4] regarding the preference of the s.c. administration.
- The s.c. injection was well tolerated and preferred over i.v. administration. Main reason for preferring s.c. was the shorter administration time.
- There were no safety signals or differences in compliance regarding the different areas of s.c. injection (thigh vs abdominal wall).
- Pharmakokinetic parameters of the s.c. trastuzumab administered into the thigh were in line with those from the HannaH study.[1,2]
- As reported earlier[6], thigh injections led to higher systemic bioavailability than abdominal wall injections and remain the preferred site of injection.
- Trastuzumab s.c. 600 mg into the thigh should remain the standard of care when giving trastuzumab s.c.

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Predicting prognosis of breast cancer patients with brain metastases in the BMBC registry – comparison of three different prognostic scores

Kerstin Riecke[1], Volkmar Müller[1], Tanja Neunhöffer[2], Rudolf Weide[3], Marcus Schmidt[4], Tjoung-Won Park-Simon[5], Christoph Mundhenke[6], Arkadius Polasik[7], Tobias Hesse[8], Kristina Lübbe[9], Elena Laakmann[1], Marc Thill[10], Peter A. Fasching[11], Carsten Denkert[12], Tanja Fehm[13], Valentina Nekljudova[14], Julia Rey[14], Sibylle Loibl[14], Isabell Witzel[1]

1 Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany, 2 Frauenärzte am Dom, Mainz, Germany, 3 Institut für Versorgungsforschung in der Onkologie Koblenz, Germany, 4 Universitätsmedizin Mainz, Germany, 5 Medizinische Hochschule Hannover, Germany, , 6 Klinikum Bayreuth GmbH, Bayreuth, Germany, 7 Universitätsklinikum Ulm, Germany, 8 Agaplesion Diakonieklinikum Rotenburg, Germany, 9 Diakovere Henriettenstift, Breast Center, Hannover, Germany, 10 Agaplesion Markus Krankenhaus, Frankfurt, Germany, 11 Frauenklinik des Universitätsklinikums Erlangen, Germany, 12 Institut für Pathologie UKGM - Universitätsklinikum Marburg, Germany, 13 Universitätsklinikum Düsseldorf, 14 German Breast Group, Neu-Isenburg, Germany

P 4-21-06

Background

- The incidence of brain metastases (BM) from breast cancer (BC) is increasing and the treatment is still a major challenge.
- In our previous analysis of the Brain Metastases in Breast Cancer (BMBC) registry[1,3] we observed a median overall survival (OS) of 7.4 months after diagnosis of BM.
- Several scores have been developed in order to estimate the prognosis of patients with BM by objective criteria.
- The aim of this retrospective analysis from the BMBC registry was to validate the diagnostic accuracy on the overall survival (OS) of three Graded Prognostic Assessment (GPA) scores in a large cohort of BC patients with BM.[1,2,4]

Patients and Methods

- All clinical data for this analysis derived from the BMBC registry. For 882 out of 2589 patients included in the registry all GPA scores could be determined.
- The original-GPA score [2] includes age, Karnofsky performance status (KPS), number of BM and extracranial metastases (ECM), the breast-GPA score age, KPS and tumor subtype, and the updated breast-GPA adds subtype to the original GPA score.

Objectives:

- To assess the prognostic impact of age at first diagnosis of BM, number of BM, biological subtype (according to [2]), ECOG, appearance of ECM)on OS.
- To investigate the association of the OS in the BMBC registry with the survival times estimated by the original GPA, breast-GPA and the updated breast-GPA
- To determine the diagnostic accuracy by time dependent sensitivities, specificities, positive and negative predictive values (PPV, NPV) to identify a long life expectancy (>12 months) as well as the area under the Receiver-Operating-Characteristic (ROC)-curve (AUC).

All reported p-values were two-sided, the significance level was set to 0.05. The data was analyzed using SAS® version 9.4 and R from the R Foundation for Statistical Computing (version 3.6.0).

Table 1. Baseline characteristics (continuous and categorical parameters)

Parameter	Category	GPA-subgroup (N=882)	Overall (N=2589)
Age at diagnosis of BM, years	Median (min, max)	57.0 (25.0, 90.0)	57.0 (22.0, 99.0)
Histological tumor type	ductal or ductal-lobular-invasive	691 (78.8)	1876 (73.3)
	lobular-invasive	60 (6.8)	194 (7.6)
	other	126 (14.4)	491 (19.2)
	missing	5	28
Tumor grading	G1	16 (1.9)	42 (1.8)
	G2	324 (38.6)	927 (40.0)
	G3	500 (59.5)	1347 (58.2)
	missing	42	273
Biological subtype (according to [2])	TNBC	197 (22.3)	522 (23.2)
	Luminal A	295 (33.4)	750 (33.3)
	HR+/HER2+ (luminal B)	221 (25.1)	556 (24.7)
	HR-/HER2+	169 (19.2)	421 (18.7)
	missing	0	340
Karnofsky-Index at diagnosis of BM	100%	119 (13.5)	154 (13.9)
	80-90%	393 (44.6)	501 (45.1)
	60-70%	267 (30.3)	322 (29.0)
	40-50%	80 (90.1)	103 (9.3)
	10-30%	23 (2.6)	31 (2.8)
	missing	0	1478
Number of BM	1	234 (26.5)	718 (30.9)
	2-3	245 (27.8)	607 (26.1)
	≥4	403 (45.7)	997 (42.9)
	missing	0	267
ECM at time of BM diagnosis	yes	744 (84.4)	2139 (82.7)
	no	138 (15.6)	448 (17.3)
	missing	0	2

Table 2. Median Survival after the diagnosis of BM with the corresponding 95%-confidence intervals for the three GPA scores

Parameter	Category	Median Survival	95% CI
Original GPA	0-1	3.71	(3.19-4.67)
	1.5-2.5	10.1	(8.87, 12.3)
	3.0	22.4	(10.8, 28.2)
	3.5-4.0	38.2	(21.2-65.4)
Breast GPA	0-1	2.23	(1.61,2.96)
	1.5-2	5.39	(4.4, 7.10)
	2.5-3.0	8.57	(6.44,10.4)
	3.5-4.0	21.7	(18.4,24.9)
Updated Breast GPA	0-1	2.69	(2.04-3.35)
	1.5-2.0	5.22	(4.40,6.34)
	2.5-3.0	15.2	(12.3-18,5)
	3.5-4.0	32.2	(23.7,43.5)

Results

Patient characteristics within the prognostic indices (for all results see **Table 1**):

- Median age at the diagnosis of BM was 57 years.
- 22.3% of patients (n=197) had a triple-negative (HR-/HER2-), 33.4% (n=295) Luminal A (HR+/HER2-), 25.1% (n=221) Luminal B (HR+/HER2+), 19.2% (n=169) HR-/HER2+ BC (according to Sperduto et al.2012).
- 15.6% of patients (n=138) had no ECM and 45.7% had ≥4 BM.
- More than half of the patients had a good KPS at diagnosis of BM (KPS ≥80%: 58.1%).

Prognostic factors for worse OS:

- Age >60 years, evidence of ECM, higher number of BM, triple-negative subtype and low KPS were all associated with worse OS in univariate analysis (p<0.0001 each).

Median survival within the prognostic indices (for all results see **Table 2** and **Figures 1-3**):

- For the original GPA score median survival between the subgroups were 3.71 for subgroup 0-1 points, 10.1 for 1.5-2.5, 22.4 months for 3 points and 38.2 months for patients in the group with 3.5-4 points.
- The median survival between the four subgroups of the breast GPA score 0-1, 1.5-2.0, 2.5-3,3.5-4 differed between 2.23, 5.39, 8.57 and 21.7 months.
- Median survival in the updated breast GPA variated between 2.69, 5.22, 15.2 and 32.2 months for the subgroups 0-1, 1.5-2, 2.5-3 and 3.5-4.

Diagnostic accuracy of the GPA-Scores (for all results see **Table 3**):

- The original GPA had a high time dependent sensitivity of 92.2%, but a low time dependent specificity of 21.8% to identify patients with a short time life expectancy (>12 months, score value < vs. ≥ 3) with PPV of 62.6 and a NPV of 66.3%.
- The breast-GPA scores showed lower sensitivities, but higher specificities (breast-GPA: 68.7%; updated breast-GPA: 48.1%), higher PPV (breast-GPA: 75.6%; updated breast-GPA: 69.9%) and lower NPV.
- There were no significant differences between the AUC of the scores after 12 months (breast-GPA (73%) vs. updated breast-GPA (74.2%), p=0.09; breast-GPA vs. original GPA (69.5%): p=0.18).

Table 3. Diagnostic accuracy of the original, breast-GPA and updated breast-GPA score at 3 and 12 months

GPA score	Time months	sensitivity (%) (95% CI)	specificity(%) (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
Original GPA	3	96.2 (93.7, 98.6)	17.2 (14.2, 20.1)	29.7 (26.4, 33.0)	92.5 (87.7, 97.2)
	12	92.2 (89.9, 94.6)	21.8 (17.4, 26.2)	62.6 (59.1, 66.1)	66.3 (57.7, 75.0)
Breast GPA	3	72.2 (66.5, 77.9)	53.5 (49.6, 57.4)	36.1 (31.8, 40.5)	84.1 (80.5, 87.6)
	12	68.1 (64.0, 72.2)	68.7 (63.8, 73.7)	75.6 (71.6, 79.6)	60.2 (55.4, 65.0)
Updated Breast GPA	3	91.9 (88.4, 95.4)	35.7 (32.0, 39.4)	34.2 (30.5, 37.9)	92.4 (89.0, 95.7)
	12	84.8 (81.7, 88.0)	48.1 (42.8, 53.4)	69.9 (66.2, 73.6)	69.1 (63.2, 74.9)

Figure 1. Kaplan-Meier curves for the time from diagnosis of BM to death (original GPA score)

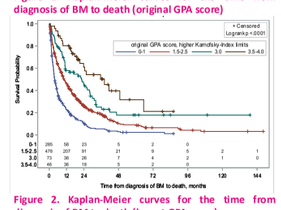


Figure 2. Kaplan-Meier curves for the time from diagnosis of BM to death (breast GPA score)

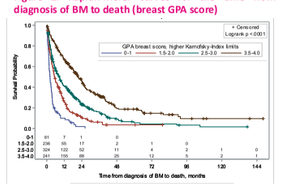
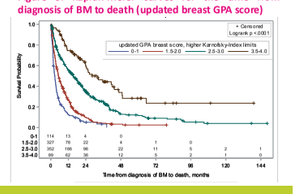


Figure 3. Kaplan-Meier curves for the time from diagnosis of BM to death (updated breast GPA score)



Conclusions

In this analysis, several clinical parameters as well as the GPA-scores were significantly associated with OS. However, in our cohort all GPA-scores show only a moderate diagnostic accuracy in predicting the OS. Even the updated breast-GPA with most of the statistically significant parameters included did not result in a better performance.

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Presented at: ESMO Breast 2020, Virtual Meeting, 23-24 May 2020

Germline mutation status and therapy response in patients with homologous recombination deficient, HER2-negative early breast cancer: Results of the GeparOLA study (NCT02789332)

Jan Hauke[1], Corinna Ernst[1], Peter A. Fasching[2], Christian Jackisch[3], Fenja Seither[4], Peter Klare[5], Kerstin Rhiem[1], Sabine Schmatloch[6], Jens Huober[7], Andrea Stefek[8], Sabine Seiler[4], Christoph Uleer[9], Gabriele Doering[10], Andreas Schneeweiß[11], Carsten Denkert[12], Michael Untch[13], Jens-Uwe Blohmer[14], Rita K. Schmutzler[1], Sibylle Loibl[8], Eric Hahnen[1]

[1] Center for Familial Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Cologne, Faculty of Medicine and University Hospital Cologne, Cologne, Germany; [2] University Hospital Erlangen, Erlangen, Germany; [3] Sana Klinikum Offenbach GmbH, Offenbach, Germany; [4] German Breast Group (GBG), Neu-Isenburg, Germany; [5] MediOnko-Institut GbR Berlin, Berlin, Germany; [6] Elisabeth Krankenhaus Kassel, Kassel, Germany; [7] Ulm University Medical Center, Ulm, Germany; [8] Johanniter-Krankenhaus Genthin-Stendal, Stendal, Germany; [9] Gemeinschaftspraxis Hildesheim, Hildesheim, Germany; [10] Hämato-Onkologie im Medicum Bremen, Bremen, Germany; [11] National Center for Tumor Diseases,University of Heidelberg, Heidelberg, Germany; [12] Institut für Pathologie, Philipps-Universität Marburg und Universitätsklinikum Marburg; [13] Department of Gynecology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin, Germany; [14] Charité, Department of Gynecology, Berlin, Germany.

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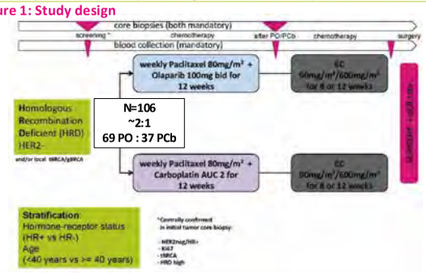
Background

The phase II GeparOla study randomized patients with homologous recombination deficient (HRD), HER2-negative early breast cancer to receive neoadjuvant treatment with paclitaxel plus either olaparib (PO) or carboplatin (PCb) prior to epirubicin /cyclophosphamide (EC). We determined pathological complete response (pCR, ypT0/is ypN0) according to treatment arm and germline mutation status

Patients and Methods

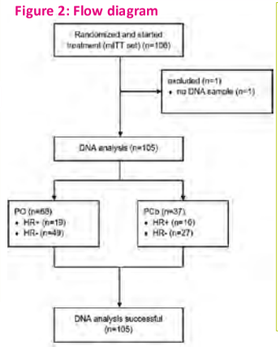
Overall 105 patients (68 in PO and 37 in PCb arm) were analyzed by next generation sequencing (NGS)-based germline mutation analysis for mutations in *BRCA1/2* and 16 other cancer predisposition genes [1] (*ATM, BARD1, BRIP1, CDH1, CHEK2, FANCM, MRE11A, NBN, PALB2, PTEN, RAD50, RAD51C, RAD51D, STK11, TP53, XRCC2*) (Fig. 2). Bioinformatic analyses were carried out using VARBANK 2.0 as previously described [2] Deleterious (International Agency for Research on Cancer (IARC) class 4/5) variants were validated by Sanger sequencing. Detection of copy number variations (CNV) was carried out using an in-house CNV detection tool and established open access tools [3]. Validation of CNVs was performed by either Multiplex Ligation-dependent Probe Amplification (MLPA) or real-time polymerase chain reaction. The definition of mutation status contains pathogenic mutations on the genes *BRCA1/2* regardless of mutations in 16 non *BRCA1/2* genes. The pCR rates were compared using a two-sided continuity corrected χ2-test.

Figure 1: Study design



Results

Figure 2: Flow diagram



- The *gBRCA1/2* mutation prevalence was 56.2% (59/105) overall, 72.4% (21/29) in HR+ and 50.0% (38/76) in HR- breast cancer.
- Nine of the 46 *BRCA1/2* wild type patients carried mutations in additional genes analyzed.
- Overall pCR rates were significantly higher in patients with *gBRCA1/2* mutations than in patients without. This could also be observed in subgroup of HR+ BC (Fig. 3).
- A trend towards a significant difference between gBRCA1/2 carriers vs non-carriers could be seen in the PCb but not in the PO arm (Fig. 4)
- Differences in pCR rates between PO and PCb arm were not significant for patients with *gBRCA1/2* mutations (61.0% vs 66.7%, p=0.901) or patients without mutation (48.1% vs 31.6%, p=0.412).
- Regardless of the treatment arm, pCR rates were higher in patients with HR- than in patients with HR+ breast cancer .

Figure 3: *gBRCA1/2* mutation status and pCR rates overall and in subgroups by hormone receptor status

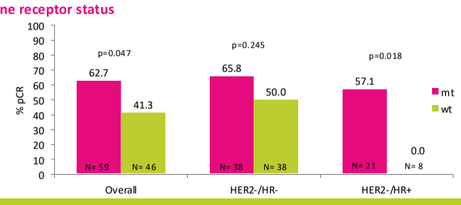
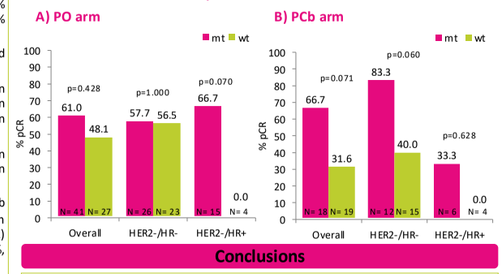


Figure 4: *gBRCA1/2* mutation status and pCR rates overall and in subgroups of HR- and HR+ breast cancer per treatment arm



Conclusions

Even in patients with HRD tumors, germline *BRCA1/2* mutation status predicts therapy outcome. For patients without *gBRCA1/2* mutations, numerically higher pCR rates were observed in the PO arm vs the PCb arm. Overall results should be interpreted with caution due to limited sample size but may guide future clinical trials.

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Conflicts of interest

The first author has no conflicts of interest to declare.

Presented at: ESMO Virtual Congress, 19-21 September 2020.

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New Study Concepts

Interview with Prof. Dr. Toralf Reimer, coordinating investigator of the EUBREAST-01 trial in Germany

A surgical trial on the omission of sentinel lymph node biopsy in triple-negative and HER2-positive breast cancer patients with radiologic and pathologic complete response in the breast after neoadjuvant systemic therapy (EUBREAST-01)

Prof. Dr. Toralf Reimer
University of Rostock

EUBREAST-01 is a single-arm, multi-center, prospective trial to investigate the omission of sentinel lymph node biopsy (SLNB) in triple-negative and HER2-positive breast cancer patients with radiologic and pathologic complete response in the breast after neoadjuvant systemic therapy (NAST).

Primary objective: 3-year rate of axillary recurrence-free survival (ARFS) after breast-conserving surgery (BCS) in patients without SLNB.

1. How would the study potentially change the axilla management of breast cancer patients?

Three scenarios of final results can be envisaged which will lead to the following conclusions:

- *The experimental arm (no axillary SLNB) shows a high 3-year ARFS (≥ 98.5 %). Omitting the axillary SLNB according to the inclusion criteria would then be considered as a new standard option for BCS of patients with neoadjuvant treated, primary breast cancer.*
- *The experimental arm (no axillary SLNB) shows an unacceptable 3-year ARFS rate of ≤ 96 %. In this case the current guidelines for SLNB are confirmed.*
- *The experimental arm (no axillary SLNB) shows an intermediate 3-year ARFS rate (96.1–98.4 %). No final conclusion for routine clinical practice can be given; the conduction of a randomized clinical trial must be discussed.*

2. Why are you going to select triple-negative breast cancer (TNBC) and HER2-positive patients?

The population of the EUBREAST-01 trial will include patients (≥ 18 years) of two intrinsic subtypes described for breast carcinoma. The decision to recruit only patients with HER2-positive disease or TNBC is supported by the following reasons:

- *NAST is the standard approach for these two subtypes, at least for stage II and III.*
- *The highest rates of breast pathologic complete response (pCR) rates were seen in these two subtypes.*
- *The highest rates of axillary nodal pCR (ypN0) rates were described for these two subtypes. Accordingly, the lowest rates for ypN positivity after NAST were observed in these two subtypes.*

3. What is the major challenge for recruitment in this study?

The recruitment for EUBREAST-01 must be seen as competition to ongoing neoadjuvant trials for systemic therapy. The majority of these trials will require a mandatory axillary staging after NAST, so that these trial patients are not eligible for EUBREAST-01.
Furthermore, potential EUBREAST-01 patients with a non-pCR in the breast after lumpectomy, will have the routine SLNB as two-stage procedure which is not common clinical practice today.

4. Which timepoint is the best to approach the patients for the study?

All initially clinical node-negative patients with a radiologic complete response (rCR) after standard NAST for HER2-positive disease or TNBC are candidates for the screening population of EUBREAST-01 trial. The rCR will be determined by mammography and ultrasound of the breast plus axilla at the end of NAST. Magnetic resonance imaging (MRI) is an option, but not mandatory for evaluation of rCR. Taken together, patients should be selected at the timepoint of preoperative radiologic evaluation (imaging) after NAST.

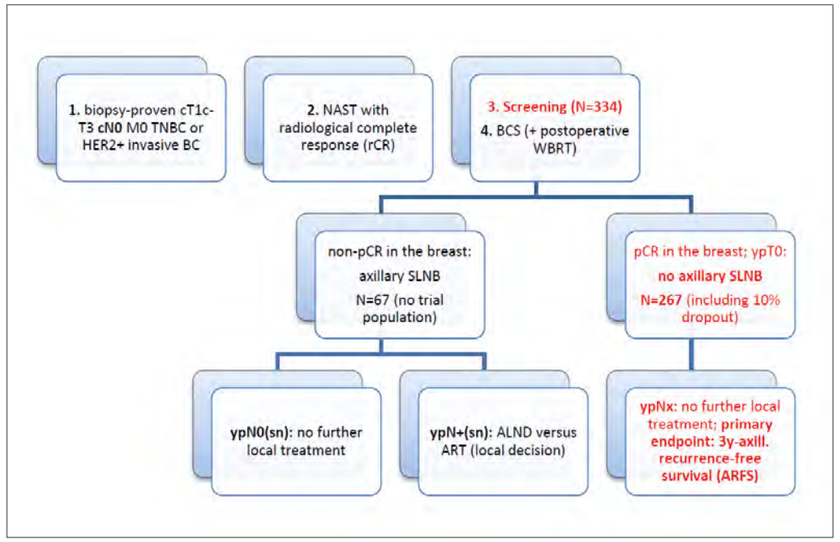

Figure 1: Flow chart of the EUBREAST-01 study

Interview with Prof. Dr. Peter A. Fasching, coordinating investigator of the TruDy trial in Germany

A phase III study of Trastuzumab-Deruxtecan versus Trastuzumab-DM1 in high-risk HER2-positive patients with residual invasive breast cancer (TruDy)

Prof. Dr. Peter A. Fasching
Department of Gynecology and Obstetrics,
University Hospital Erlangen,
Comprehensive Cancer Center Erlangen-Nuremberg,
National Center for Tumor Diseases, Erlangen

TruDy (DESTINY-Breast05; AGO-B-050; NSABP B-60; SOLTI-2001) is a phase III, multicenter, randomized, open-label, active-controlled study of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients with high-risk HER2-positive primary breast cancer who have residual invasive disease in breast or regional lymph nodes following neoadjuvant therapy.

Primary objective: to evaluate invasive disease-free survival (iDFS) with T-DXd treatment as compared to T-DM1.

1. Trastuzumab Deruxtecan (T-DXd) shows promise in HER2-targeted therapy. Can you elaborate on the mechanism of action of this drug?

T-DXd is a HER2-targeted antibody-drug conjugate (ADC) designed to deliver optimal anti-tumor effect. It has several key attributes to overcome the efficacy and toxicity limitations that earlier ADCs faced:

1) *high potency of payload (DXd; topoisomerase I inhibitor);*
2) *high drug-to-antibody ratio ≈ 8;*
3) *payload with short systemic half-life;*
4) *specific linker properties;*
5) *tumor-selective cleavable linker;*
6) *membrane-permeable payload.*

With these ADC properties we believe that there is a good chance that T-DXd can outperform existing therapies in this setting.

2. Can you explain the background to evaluate T-DXd vs. T-DM1 in high-risk HER2-positive patients with residual invasive breast cancer following neoadjuvant therapy?

The KATHERINE study (T-DM1 vs. trastuzumab) showed that the post-neoadjuvant treatment of the ADC T-DM1 was superior with regard to the prognosis than post-neoadjuvant trastuzumab in patients without a pathological complete response (pCR) after a neoadjuvant treatment with chemotherapy and an anti-HER2 treatment. However, despite the fact that the KATHERINE study was a positive trial, with novel very effective anti-HER2 treatments like T-DXd, there is a high chance that the treatment in the post-neoadjuvant therapy situation can be improved further.

3. Which aspects of the patient population need special attention in the TruDy study?

The TruDy is a straightforward randomized trial for a HER2-positive patient population. With the KATHERINE trial approximately 55 % of patients that were either inoperable at presentation or node-positive after neoadjuvant therapy had an estimated 3-year iDFS rate of approximately 81 %, representing a patient population which could benefit from another treatment option that could further improve their outcome.
The expected 3-year iDFS rate after a neoadjuvant anti-HER2 treatment is approximately 83 %, assuming there will be an increased use of dual HER2-tagetedtherapy (e.g. pertuzumab and trastuzumab). It is recognized that patients with absence of pCR after appropriate neoadjuvant therapy are identified as a patient population with higher risk of disease recurrence. This is a clinical setting where the application of more effective therapies would have a potentially large absolute impact on patient outcomes and can be considered an area of unmet medical need.
The TruDy trial will include patients with pathologic residual disease after neoadjuvant chemotherapy and one additional high-risk factor: inoperable breast cancer at primary diagnosis (before neoadjuvant therapy) or pathologically positive axillary lymph nodes following neoadjuvant therapy. The proposed exclusion criteria are aligned with the safety profiles of each study drug (i.e. T-DM1 and T-DXd).

4. Within the TruDy trial patients will undergo several imaging procedures. What is the rationale for these safety assessments?

T-DXd and other anti-HER2 treatments have been described to have side effects which are important to diagnose and which could, if not treated properly, result in unfavorable outcomes. Interstitial lung disease (ILD)/pneumonitis is an important identified risk for both T-DXd and T-DM1 and it is unclear if there may be an increased risk in the adjuvant setting where concomitant radiotherapy may also be given. In order to mitigate this risk, we have introduced scheduled chest CTs not exceeding 1.5 to 2 mSv or as per institutional guidelines to 1) determine if there is any underlying ILD/pneumonitis at baseline; 2) carefully monitor for signs of ILD/pneumonitis during the treatment period starting at approximately 6 weeks after first dose and then approximately every 12 weeks during the treatment and for up to one year after the treatment has been completed.
For subjects that will receive sequential radiotherapy after randomization but prior to first dose, an additional CT scan following completion of radiotherapy but prior to first dose will also be collected.

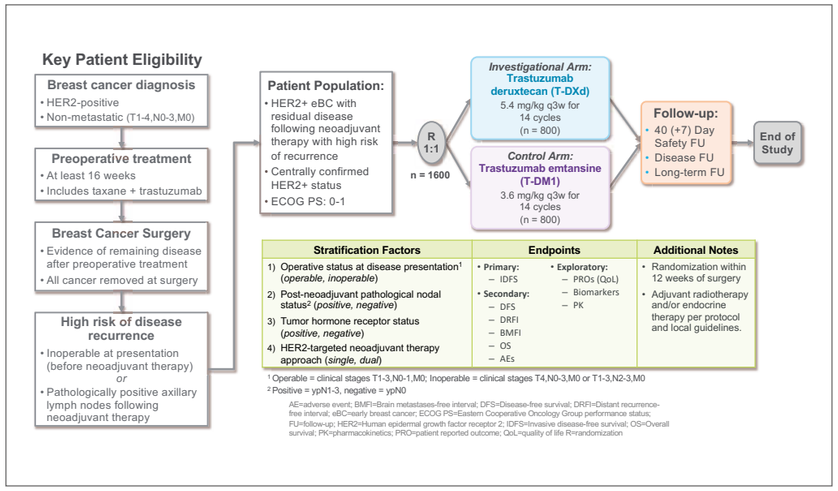

Figure 1: Study design of the TruDy (DESTINY-Breast05) study

Recruiting Studies

GBG 102: SASCIA

CONTACT:
Dr. Stefan Dröse /
Dr. Laura Schöllhorn
Clinical Project Management
sascia@GBG.de

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

NCT04595565

SASCIA is a prospective, multi-center, randomized, open-label, parallel group, phase III study to evaluate the efficacy and safety of post-neoadjuvant 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 residual disease after standard neoadjuvant treatment.

Background

Neoadjuvant chemotherapy (NACT) allows monitoring of tumor response to treatment and a pathological complete response (pCR) is associated with superior survival. This association is strongest in the most aggressive subtype, i.e. in patients with triple-negative breast cancer (TNBC). Patients with TNBC not achieving a pCR have a 5-year event-free survival rate of about 50 % (Hahnen et al. JAMA Oncol, 2017; Sikov et al. J Clin Oncol. 2015; Petrelli et al. Breast Cancer Res Treat. 2014). The association between pCR and prognosis is less pronounced in hormone receptor (HR)-positive/HER2-negative patients. However, the CPS+EG scoring system for prognosis after NACT, taking into account clinical stage, post treatment pathological stage, estrogen receptor status and grade allows to select patients at high risk of relapse for post-neoadjuvant therapy (Marme et al. Eur J cancer. 2016). Patients with TNBC not achieving a pCR as well as those with HR-positive/HER2-negative tumors and a CPS+EG score of ≥ 3 or 2 with nodal involvement after NACT (ypN+) are at high risk of relapse, warranting additional experimental therapies after NACT.

There is proof of concept, that post-neoadjuvant therapy can significantly improve survival. Several randomized trials in patients with residual tumor after NACT reported on disease-free survival (DFS) and overall survival (OS). The CREATE X study demonstrated a significant improvement in DFS and OS in the overall population, which was confined to the TNBC subgroup (Masuda et al. N Engl J Med. 2017). The phase III KATHERINE study showed an improved invasive (i)DFS in HER2-positive patients without pCR after trastuzumab +/- pertuzumab treated postoperatively with T-DM1, an antibody-drug conjugate compared to trastuzumab (von Minckwitz et al. N Engl J Med. 2019).

The post-neoadjuvant approach, in contrast to the adjuvant setting (Piccart-Gebhart et al. J Clin Oncol. 2016; von Minckwitz et al. N Engl J Med. 2017), avoids overtreatment, limits sample size and risk of trial failure from lack of events by selecting a high-risk population. In contrast to neoadjuvant trials, which so far have mainly been powered for pCR rates, post-neoadjuvant trials result in a survival endpoint that is relevant for patients. Thus, post-neoadjuvant trials are probably a more appropriate setting to introduce new therapies into clinical routine for early breast cancer.

Sacituzumab govitecan is an antibody-drug conjugate composed of a humanized monoclonal antibody which binds to Trop-2 (trophoblast cell-surface antigen-2). The attached small molecule SN-38 is an active metabolite of irinotecan, a topoisomerase I inhibitor and is covalently bound to the antibody by a linker. Sacituzumab govitecan has demonstrated unprecedented activity in heavily pretreated patients with metastatic triple-negative and HR-positive/HER2-negative breast cancer, even after prior immune-checkpoint inhibitors or CDK4/6 and mTOR inhibitors (Bardia et al. J Clin Oncol. 2018, Bardia et al. N Engl J Med. 2019). Sacituzumab govitecan constitutes a compound with strong activity against highly resistant clones of metastatic breast cancer and may represent a new option against the resistant residual disease after standard NACT regardless of HR status. Therefore, the SASCIA study will evaluate the activity of sacituzumab govitecan in HER2-negative patients at high risk of relapse after NACT.

Study design and objectives

Eligible patients (aged ≥ 18 years) must have received taxane-based NACT for 16 weeks, including at least 6 weeks of a taxane. Patients should be at high risk of recurrence after treatment, defined as having centrally confirmed HER2-negative BC (IHC score 0-1 or FISH negative according to ASCO/CAP guideline) assessed preferably on tissue from post-neoadjuvant residual invasive disease of the breast and either HR-negative (< 1% positive stained cells), with any residual invasive disease > ypT1mi after NACT or HR-positive (≥ 1% positive stained cells), with a CPS+EG score ≥ 3 or CPS+EG score 2 and ypN+ using local ER and grade assessed on core biopsies taken before NACT. Radiotherapy should be delivered before the start of study treatment.

Patients will be allocated (1:1) to receive either sacituzumab govitecan (days 1, 8 q3w for eight cycles; experimental arm) or treatment of physician's choice (TPC, defined as capecitabine or platinum-based chemotherapy for eight

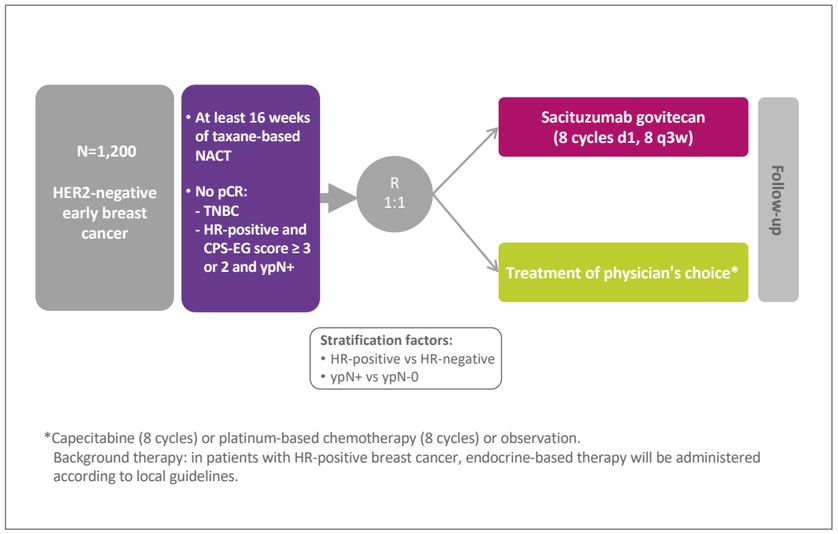

Figure 1: Study design of the SASCIA study

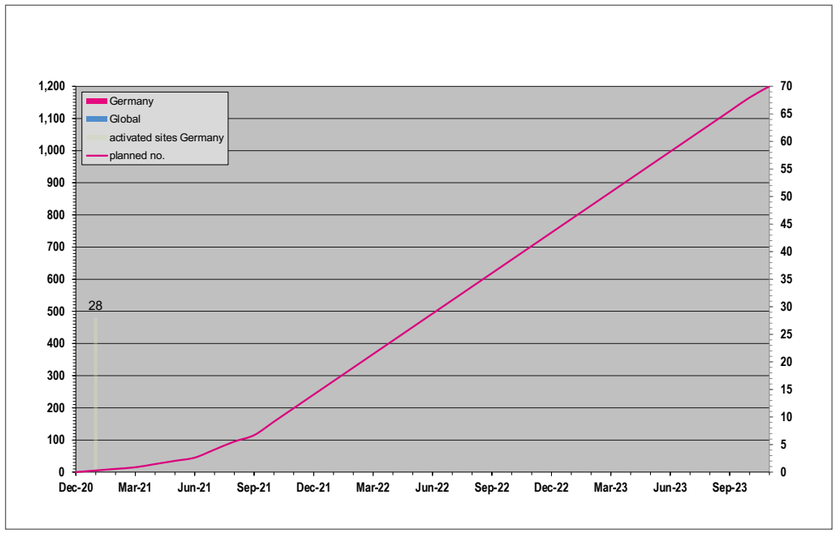

Figure 2: SASCIA recruitment as of 31st December 2020

cycles or observation; control arm). Randomization will be stratified by HR status (HR-negative vs HR-positive) and ypN (ypN+ vs ypN0). Treatment in either arm will be given for eight cycles. In patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines. The start of endocrine therapy will be at the discretion of the investigator; however, it will be encouraged to start after surgery/radiotherapy in patients without additional cytotoxic agents.
Primary objective of the SASCIA trial is to compare iDFS between patients treated with sacituzumab govitecan versus treatment of physician's choice; primary endpoint is iDFS. Secondary objectives and endpoints include comparison of OS, distant DFS and locoregional recurrences-free interval between both treatment groups, iDFS and OS in predefined stratified subgroups, iDFS and OS in exploratory subgroups, safety and compliance, patient reported outcome and quality of life. The SASCIA study will also address translational research questions such as to explore circulating tumor DNA (ctDNA) dynamics as early predictors of ctDNA clearance in ctDNA-positive patients; to explore the predictive value of markers (including genetic and immune markers) for sacituzumab govitecan.
One interim analysis for overwhelming efficacy will be performed when 256 events (2/3 of the total events) have occurred.

Study report
SASCIA recruitment started on November 10, 2020 in Germany. As of 31st December 2020, there are 4 patients enrolled in the study. Planned recruitment start in other European countries is Q1 2021. The expected study duration is approximately 36 months.

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:

GBG GERMAN BREAST GROUP
AGO-B BREAST STUDY GROUP
GEICAM spanish breast cancer group
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cancer trials ireland
ABCSG AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

SPONSOR:
GBG Forschungs GmbH

COORDINATING INVESTIGATOR:
Prof. Dr. Frederik Marmé
University Hospital Mannheim

GBG 101: TAXIS

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

NCT03513614

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.

Background
The removal of all lymph nodes in the armpit through conventional axillary dissection has been standard care for all patients with breast cancer for almost a century. In the nineties, the sentinel lymph node (SLN) procedure, which involves the selective removal of the first few lymph nodes in the lymphatic drainage system, was introduced in clinical practice. Today, conventional axillary dissection is still performed on many women with breast cancer that has spread to the nodes. It is the cause for relevant morbidity in the form of lymphedema, impairment of shoulder mobility, sensation disorders and chronic pain in as much as one third of all women undergoing the procedure. The TAXIS trial will 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 TAS, a new technique that aims at selectively removing the positive lymph nodes. TAS is a promising procedure that may significantly decrease morbidity in breast cancer patients by avoiding surgical overtreatment. This trial has the potential to establish a new worldwide treatment standard with hopefully less side effects and a better quality of life, while keeping the same efficacy as provided by radical surgery.

Study design and objectives
Women aged ≥ 18 years with node positive breast cancer (histologically or cytologically proven both in primary tumor and in lymph node) AJCC/UICC stage II-III (all molecular subtypes) fulfilling all inclusion criteria at randomization are eligible. Patients will be assigned to either TAS followed by ALND and regional nodal irradiation excluding the dissected axilla as a target volume (arm A) or to TAS followed by regional nodal irradiation including the full axilla (arm B). It is planned to enroll a

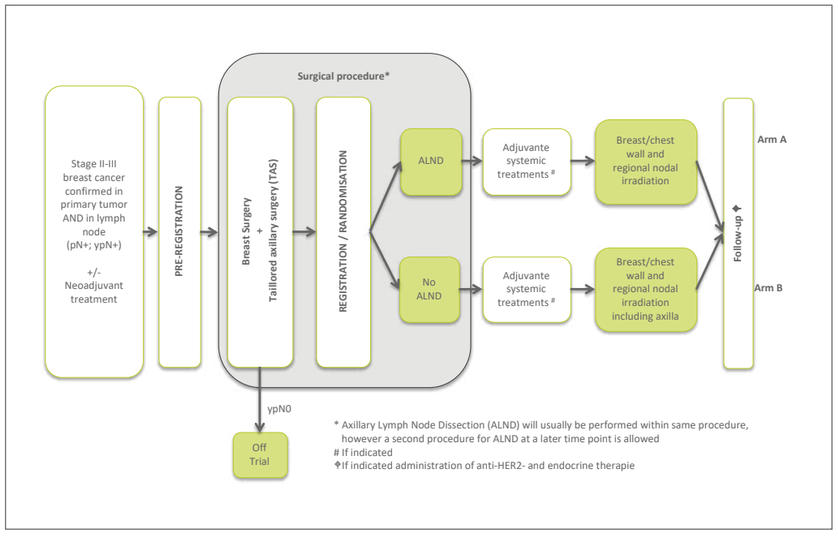


Figure 1: TAXIS study design

SAKK WE BRING PROGRESS TO CANCER CARE

CONTACT:
Dr. Laura Schöllhorn
Clinical Project Management
taxis@GBG.de

total of 1,500 patients (750 per treatment arm) in the trial. All patients will undergo adjuvant whole-breast irradiation after breast conserving surgery and chest wall irradiation after mastectomy. Radiation therapy (RT) should start preferably within 8 weeks from the last breast surgical procedure and not later than 12 weeks. In case chemotherapy was applied, RT should start within 6 weeks after the end of the last cycle of chemotherapy and not later than 8 weeks. Dose to the breast/thoracic wall as well as the regional nodal pathways is: 50 Gy in 25 fractions of 2 Gy or 50.4 Gy in 28 fractions of 1.8 Gy; daily, five days a week. Hypofractionated schedule is allowed: 40 Gy in 15 fractions of 2.67 Gy to the same volume. Patients will be followed up to 20 years after randomization of the last patient.

Primary objective of TAXIS trial is to show that TAS and axillary RT is non-inferior to axillary lymph node dissection (ALND) in terms of disease-free survival (DFS) of breast cancer patients with positive nodes at first presentation. The primary endpoint is DFS. Secondary endpoints include Quality of Life (QoL), overall survival (OS), breast cancer-specific survival (BCSS), time to local recurrence (TTLR), time to regional recurrence (TTRR), time to distant recurrence (TTDR), reported morbidity outcomes: lymphedema and decreased, and range of shoulder motion, adverse events, late radiotherapy-related adverse events, surgical site infections (SSI).

Study report

TAXIS recruitment started in August 2019 in Germany. As of 31st December 2020, there are 32 patients enrolled in the study. The expected study duration (from randomization to the end of radiation therapy) is approximately 7 months. Follow-up is planned for up to 20 years. The end of the study (i.e. last visit of the last patient randomized) is planned for QIV/2043 819 [1].

Publications

1. Henke G, Knauer M, Ribi K, et al. Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. Trials. 2018;19:667.

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.

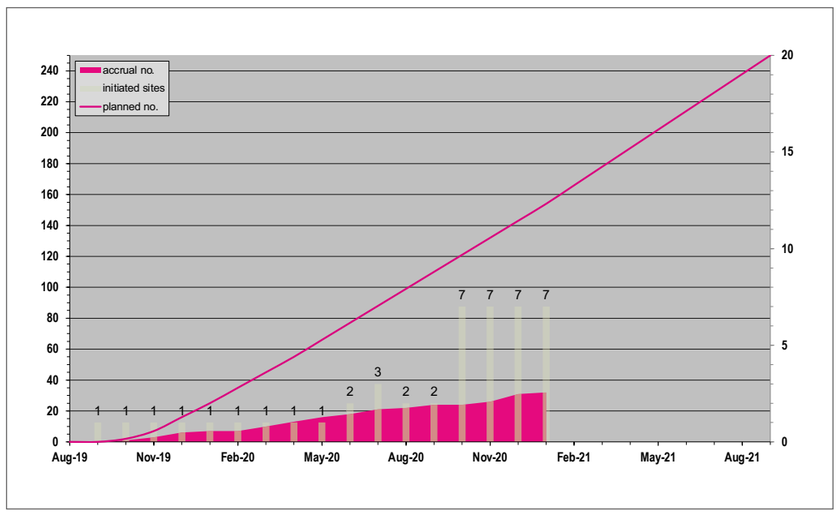


Figure 2: TAXIS recruitment as of 31st December 2020

COLLABORATING STUDY GROUPS:

SPONSOR:
SAKK

COORDINATING INVESTIGATOR:
Prof. Dr. Jörg Heil
Universitätsklinikum Heidelberg

GBG 100: APPALACHES

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

NCT03609047

APPALACHES (EORTC 1745 ETF BCG) is a two-arm open-label multi-center randomized non-comparative 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.

Background

Cancer in older patients is a major public health issue since the incidence of cancer increases with age, and life expectancy of the Western population is increasing. Advanced age at diagnosis of breast cancer is associated with more favorable tumor biology as indicated by increased hormone sensitivity, attenuated HER2 overexpression, and lower grades and proliferative indices (Pierga, et al. 2004). However, older patients are more likely to present with larger and more advanced tumors (Singh, et al. 2004). Age alone should not be a barrier to decide treatment of patients with cancer, and ageing is a continuous process making it difficult to set a unique threshold to define older patients. However many recent studies used 70 years to define older patients, recognizing that patient vulnerability or frailty should also be taken into account (Wildiers, et al. 2007). In older patients with estrogen receptor (ER)+/HER2- early breast cancer, historical data about recurrence rate and the benefit of adjuvant chemotherapy is sparse. In general, the chemotherapy-induced benefit is lower and toxicity is higher than in younger women, and there are competing risks for morbidity and mortality. Several randomized studies in older patients have reported on disease free survival (DFS, including local recurrence as well) and 3-year overall survival (OS, including death from other causes). The 3-year DFS and OS were 85 % and 95 % in ICE-2 study (unpublished data), 78 % and 90 % in ELDA study (Perrone, et al. 2015), and 86 % and 93 % in CALGB49907 study (Muss, et al. 2009). Less toxic adjuvant treatment with comparable efficacy might improve the benefit-toxicity balance of the overall treatment strategy.

Study design and objectives

Women or men aged ≥ 70 years with stage II or stage III, early invasive breast cancer fulfilling all inclusion criteria will be centrally registered at EORTC after written informed consent has been obtained. Randomization will be stratified by country, pathological TNM stage (stage II versus stage III) and potential clinical frailty as defined by the G8 geriatric assessment score (> 14 versus ≤ 14). Patients will be randomized with a 2:1 allocation rate to receive either an standard adjuvant endocrine therapy for a duration of at least 5 years + palbociclib for a total duration of up to 2 years (experimental palbociclib arm) or an adjuvant chemotherapy, followed by standard adjuvant endocrine therapy for a duration of at least 5 years (control chemotherapy arm).

In the experimental arm palbociclib 125 mg will be administered once a day, orally, for 21 days followed by 7 days off treatment in the 28-day cycle with an objective of 2-years total duration of study medication, in combination with standard adjuvant endocrine therapy for a duration of at least 5 years. Longer duration can be proposed to patients according to investigators and patients. In patients for whom adjuvant radiation therapy is indicated, radiation therapy will be administered before the start of palbociclib. Patients in the control treatment arm will be treated with adjuvant chemotherapy as initial adjuvant systemic treatment. The investigator has to select for each patient one out of the 4 following schemes: 1) 4 cycles docetaxel 75 mg/m2 / cyclophosphamide 600 mg/m^2 q3w; 2) 4 cycles doxorubicin 60 mg/m^2 / cyclophosphamide 600 mg/m2 q3w; 3) 4 cycles epirubicin 90 mg/m2 / cyclophosphamide 600 mg/m2 q3w; 4) 4 cycles weekly paclitaxel 80 mg/m2 D1, D8, and D15 q3w. The chemotherapy can start after sufficient wound healing is achieved according to the investigator, but in any case ≤ 13 weeks after last surgery. Prophylactic use of G-CSF is recommended after each cycle of the 3-weekly regimens), with type and length decided per local institutional guidelines. In patients for whom radiation therapy is indicated, radiation therapy will be administered after the last dose of chemotherapy.

Primary objective of APPALACHES trial is to assess the efficacy of the combination of at least 5 year-endocrine therapy and 2 year-palbociclib as adjuvant systemic treatment instead of adjuvant chemotherapy followed by endocrine

CONTACT:
Konstantin Reißmüller
Clinical Project Management
appalaches@GBG.de

therapy in older patients with stage II-III ER+/HER2- early breast cancer. Secondary objectives include evaluation of the efficacy with respect to different time-to-event endpoints (distant recurrence-free interval (DRFI), breast cancer specific survival (BCSS), OS) at 3, 6 and 10 years in both arms; evaluation of toxicity, treatment discontinuation and dose reduction rates in both arms as well as reasons for treatment discontinuation; assessment of completion of oral therapy in the experimental arm, Health-Related Quality of Life (HRQoL) in both arms; prognostic and predictive effects of geriatric assessment in both arms.

APPALACHES study will also address translational research questions such as to evaluate biomarkers of aging during treatment and their correlation with treatment-related toxicity. Thus, blood samples will be collected at baseline, 6 months and 3 years after treatment start. All samples will be stored centrally at the Integrated BioBank of Luxembourg (IBBL), Luxembourg.

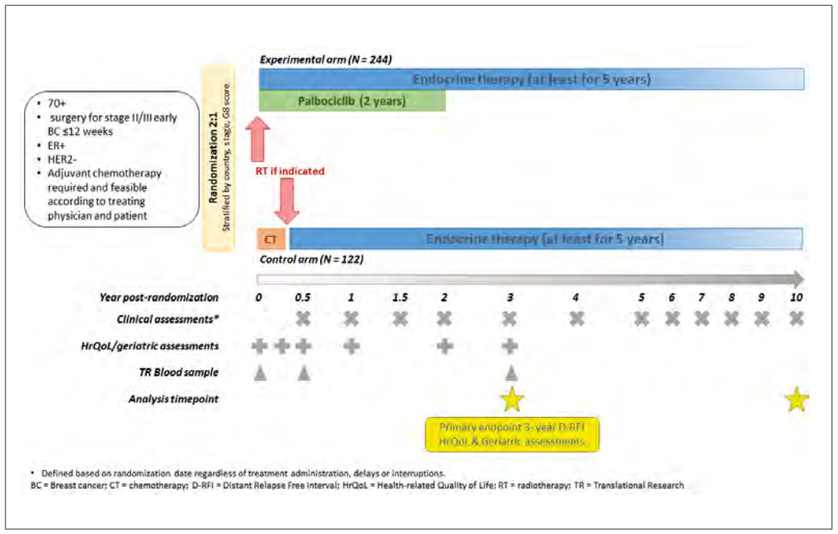


Figure 1: APPALACHES study design

Study report

APPALACHES recruitment started in March 2020. As of 31st December 2020, there are 10 patients enrolled in the study. The expected study duration is approximately 42 months.

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.

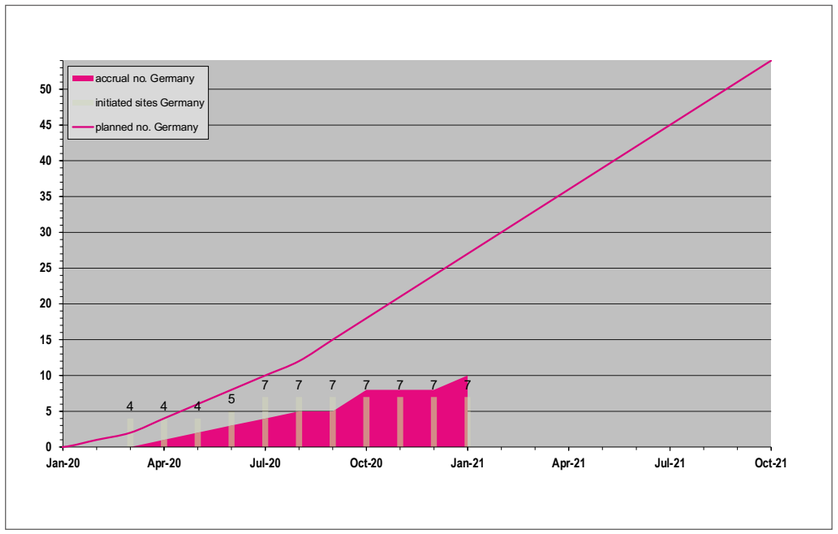


Figure 2: APPALACHES recruitment as of 31st December 2020

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

EORTC The future of cancer therapy

SPONSOR:
EORTC

STUDY CHAIR:
Dr. Mattea Reinisch
Kliniken Essen-Mitte

GBG 98: ALEXANDRA/Impassion030

CONTACT:
Dr. Ioannis Gkantiragas
Clinical Project Management
impassion030@GBG.de

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.

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 2020, there are 30 patients enrolled in the study. Enrollment is targeted to be completed at QIV 2021.

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.

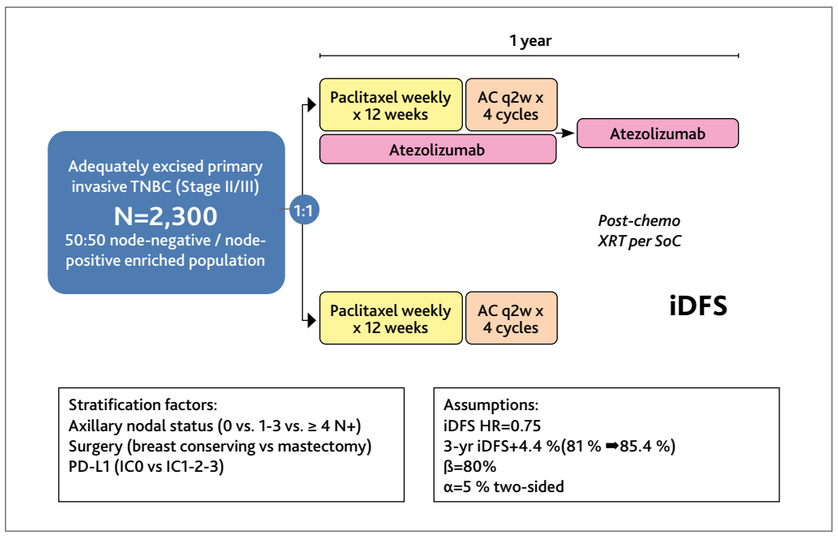


Figure 1: Study design of the ALEXANDRA/Impassion030 study

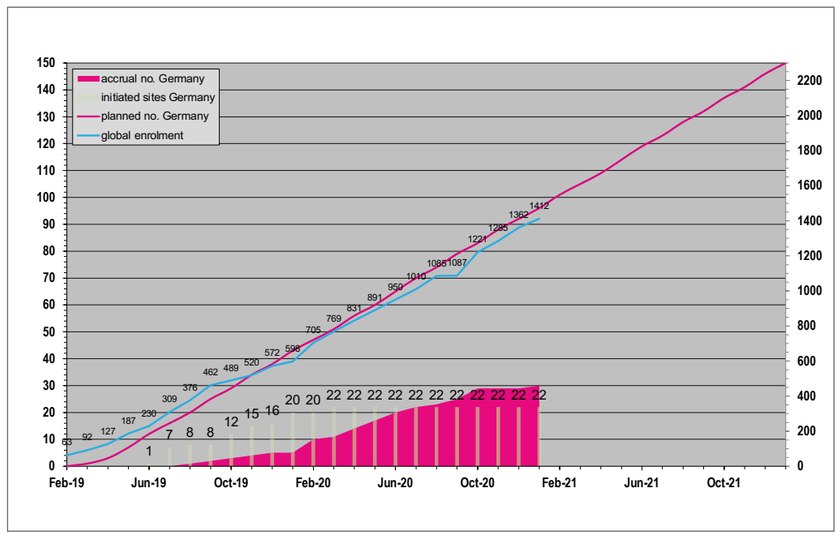


Figure 2: ALEXANDRA/Impassion030 recruitment as of 31st December 2020

COLLABORATING STUDY GROUPS:
GBG German Breast Group
BIG Breast International Group
frontier science
ALLIANCE for Clinical Trials in Oncology
Institut Jules Bordet Instituut

SPONSOR:
Hoffmann-La Roche

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

GBG 97: AMICA

CONTACT:
Konstantin Reißmüller
Clinical Project Management
amica@GBG.de

Anti-hormonal maintenance treatment with 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, open-label, controlled phase II study that will recruit 95 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 improved progression-free survival (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

With amendment 3 of the study protocol (approved on 2nd September 2020) the study design of AMICA was changed from a randomized into a single-arm trial and thereby reducing the sample size to 95. In addition, a molecular screening is offered to the patients included in the study to identify molecular changes of therapeutic relevance within the context of precision medicine (for more details see section Translational Research). After at least 4 cycles of chemotherapy of physician´s choice, patients with at least stable disease will be registered to receive endocrine maintenance therapy together with the CDK4/6 inhibitor ribociclib. Endocrine therapy, at the discretion of the investigator, could have already been started up to 4 weeks before registration but not later than with first dose of ribociclib. Treatment will be given until disease progression, unacceptable toxicity, or withdrawal of consent of the patient
AMICA primarily aims to estimate the median PFS with 95 % confidence interval (CI) of an anti-hormonal maintenance therapy with ribociclib after 1st line chemotherapy at the discretion of the investigator (e.g. taxanes, capecitabine, vinorelbine, anthracycline). Secondary objectives are to determine the median overall survival with 95 %CI; to describe safety, treatment compliance and clinical benefit rate 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).
With the first amendment of the study protocol patients who had been previously treated with a CDK4/6 inhibitor were allowed to enter into the study. The use of herbal medication during study therapy, and surgery for primary tumor at the discretion of the investigator were accepted. The use of tamoxifen as one of the possible endocrine therapies was prohibited due to new safety data reported from the MONALEESA-7 trial, showing an increased risk of heart problem known as QTcF prolongation.

Study report

AMICA recruitment started in March 2018. As of 31st December 2020, there were 40 patients enrolled in the study. The expected study duration initially was 21 months, first increased to 40 months via amendment 1 and then to 52 months via amendment 2 of the study protocol.

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.

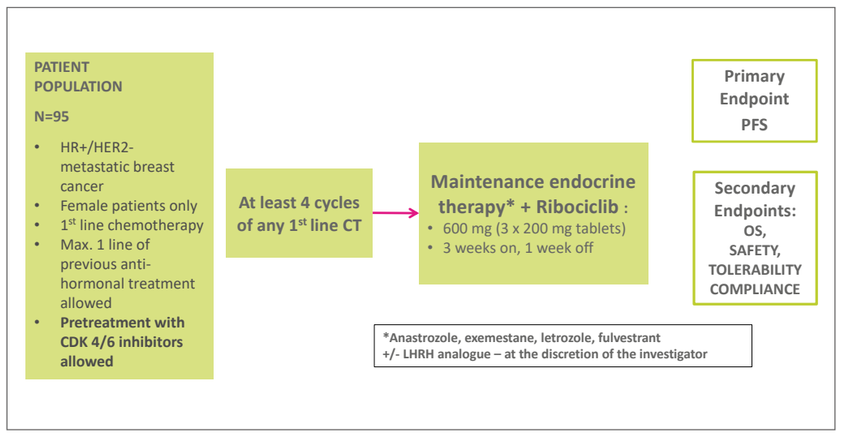


Figure 1: AMICA study design

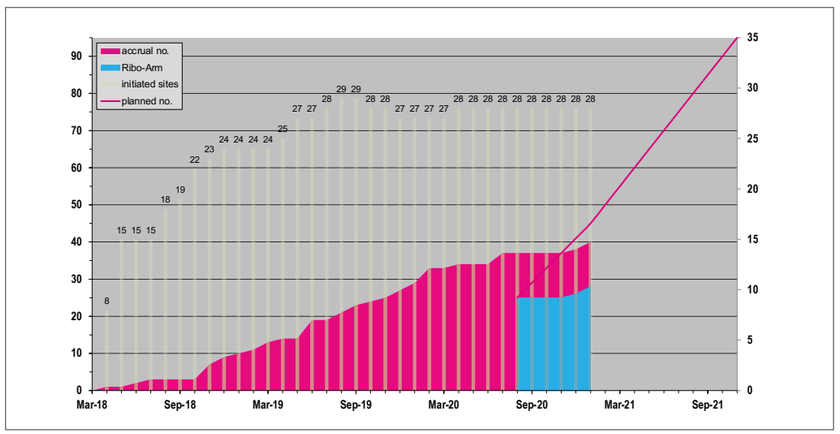


Figure 2: AMICA recruitment as of 31st December 2020

COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

COORDINATING INVESTIGATOR:
Prof. Dr. Thomas Decker
Gemeinschaftspraxis
Onkologie Ravensburg

GBG 96: GeparDouze

CONTACT:
Dr. Karin Hesse
Clinical Project Management
gepardouze@GBG.de

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 260 sites in approximately 4 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).

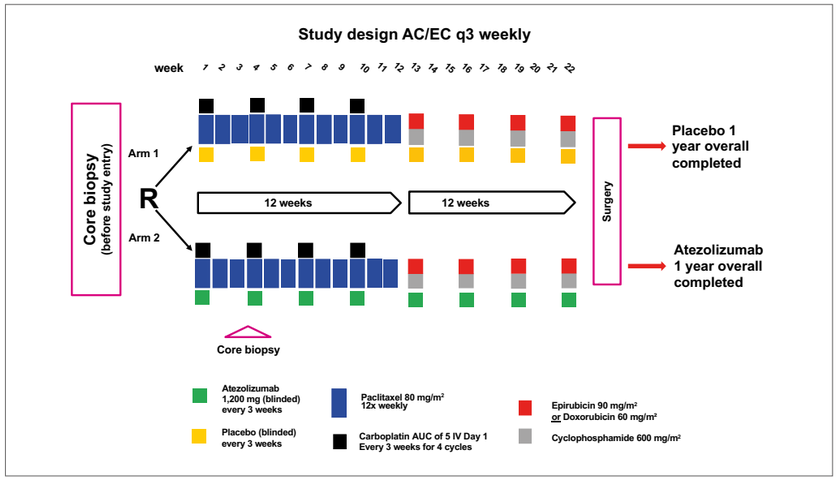
Given these results, the GeparDouze trial aims to explore the efficacy and safety of neoadjuvant and adjuvant administration of atezolizumab/placebo in patients with high-risk TNBC. It is hypothesied that the cohort receiving atezolizumab will have a higher pCR rate, and this increased activity will 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. 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 with residual invasive cancer at the time of surgery may receive capecitabine concurrently with atezolizumab/placebo in the adjuvant setting per investigator discretion and local guidelines.

Patients are randomized in a 1:1 ratio to receive either neoadjuvant chemotherapy + atezolizumab 1,200 mg or placebo IV every 3 weeks followed by surgery and continuation of atezolizumab 1,200 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 fol-



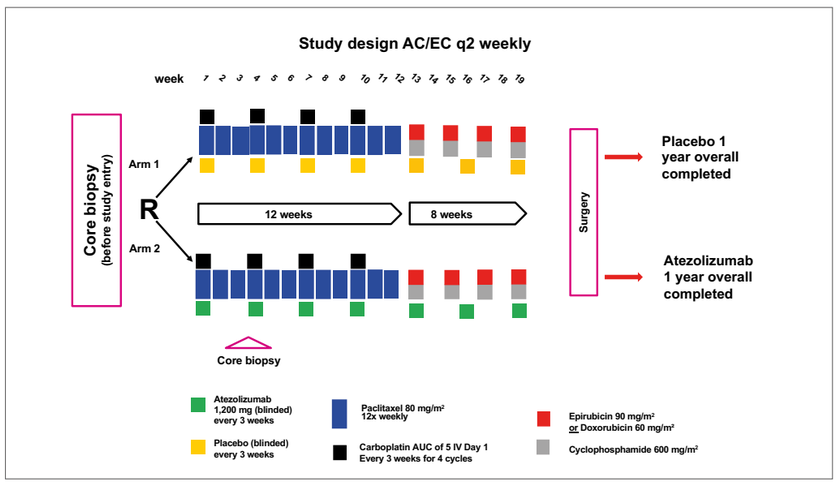


Figure 1: GeparDouze study design

lowed 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; disease-free 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 evaluate the rate of chemotherapy-induced ovarian failure.

Study report

GeparDouze recruitment started in December 2017. As of 31st December 2020, there are 685 patients enrolled in the study. Follow-up of an additional 30 months after completion of accrual is planed to obtain 269 EFS events. The expected study duration is approximately 72 months [1-2].

Publications

1. Loibl S, Jackisch C, Seiler S, et al. Randomized, Double-Blind, Phase III Trial of Neoadjuvant Chemotherapy (NACT) with Atezolizumab/Placebo in Patients with Triple-Negative Breast Cancer (TNBC) Followed by Adjuvant Continuation of Atezolizumab/Placebo (GeparDouze). 34. Deutsche Krebskongress 2020, TIP.

2. Loibl S, Rastogi P, Seiler S, et al. A randomized, double-blind, phase III trial of neoadjuvant chemotherapy (NACT) with atezolizumab/placebo in patients (pts) with triple-negative breast cancer (TNBC) followed by adjuvant continuation of atezolizumab/placebo (GeparDouze). Ann Oncol 2020; Vol. 31, Suppl.4, S339, Abstract nr. 248, TIP.

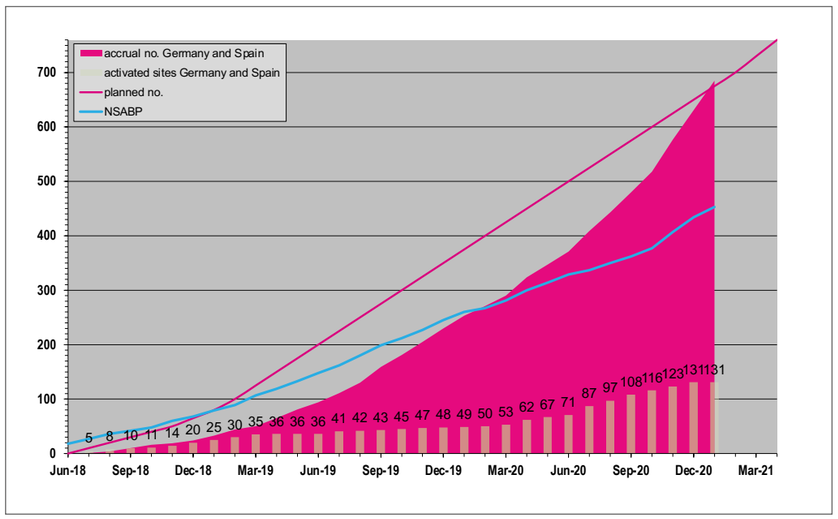


Figure 2: GeparDouze recruitment as of 31st December 2020

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:
NSABP Foundation Inc

STUDY CHAIR:
Prof. Dr. Christian Jackisch
Department of Obstetrics and Gynecology
Sana Klinikum Offenbach

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. With the subsequent protocol amendment (approved in Germany in February 2020) in- and exclusion criteria were updated, investigational medicinal product was provided as capsules and tablets, and drug handling (including drug dispensation and accountability, drug administration and dose modification) was modified.

Translational research

Translational research will be performed to compare progression-free survival based upon investigator assessment of progression between

PATINA
A COLLABORATIVE STUDY SPONSORED BY ALLIANCE FOUNDATION TRIALS, LLC

CONTACT:
Ursula Holdefer
Clinical Project Management
patina@GBG.de

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.

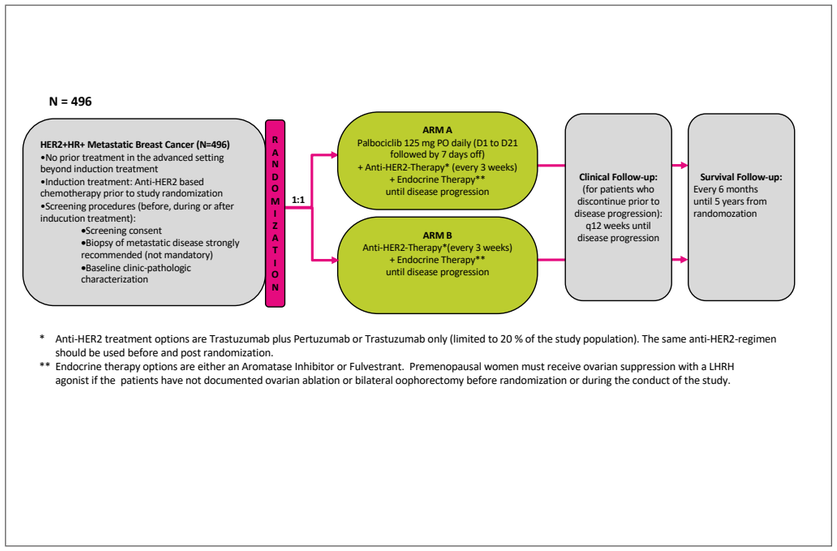


Figure 1: PATINA study design

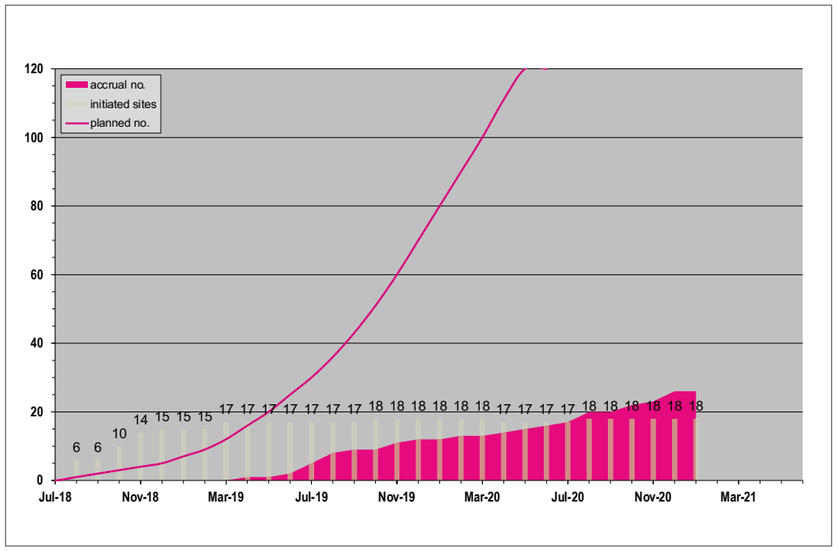


Figure 2: PATINA recruitment as of 31st December 2020

Study report

The PATINA worldwide recruitment started in July 2017 and in Germany in July 2018, respectively. As of 31st December 2020, there are 26 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.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

BREAST CANCER TRIALS

FONDAZIONE MICHELANGELO

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SPONSOR:
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INTERNATIONAL STUDY CHAIR:
Otto Metzger MD
Alliance Foundation Trials

COORDINATING INVESTIGATOR GERMANY:
Prof. Christoph Mundhenke
Klinikum Bayreuth, Klinik für Gynäkologie und Geburtshilfe, Bayreuth

GBG 93: PADMA

CONTACT:
Konstantin Reißmüller
Clinical Project Management
padma@GBG.de

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).

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.

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 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

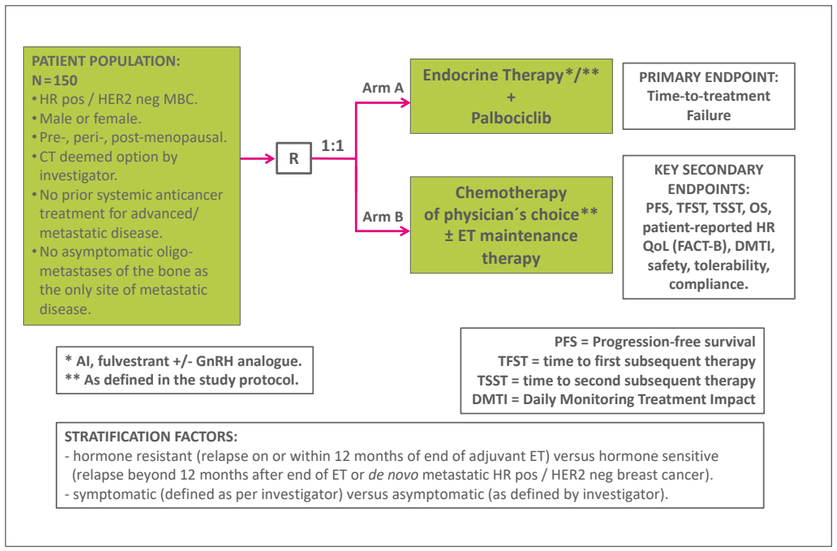

Figure 1: PADMA study design

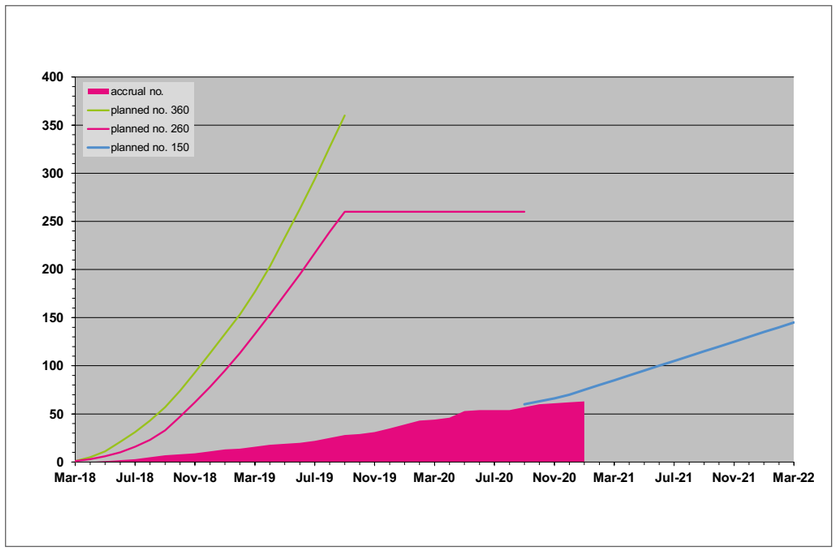

Figure 2: PADMA recruitment as of 31st December 2020

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. With amendment 2 of the study protocol the number of planned patients was reduced again and study duration prolonged. In addition, a molecular screening is offered to the patients included in the study to identify molecular changes of therapeutic relevance within the context of precision medicine (for more details see section Translational Research).

Study report
The PADMA recruitment started in March 2018 in Germany. As of 31st December 2020, there are 63 patients enrolled in the study. The end of the study (i.e. last visit of the last patient randomized) is estimated for 2023.

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:
GBG Forschungs GmbH

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

COORDINATING INVESTIGATOR:
PD Dr. Marc Thill
Klinik für Gynäkologie und Geburtshilfe, Agaplesion Markus Krankenhaus, Frankfurt am Main

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

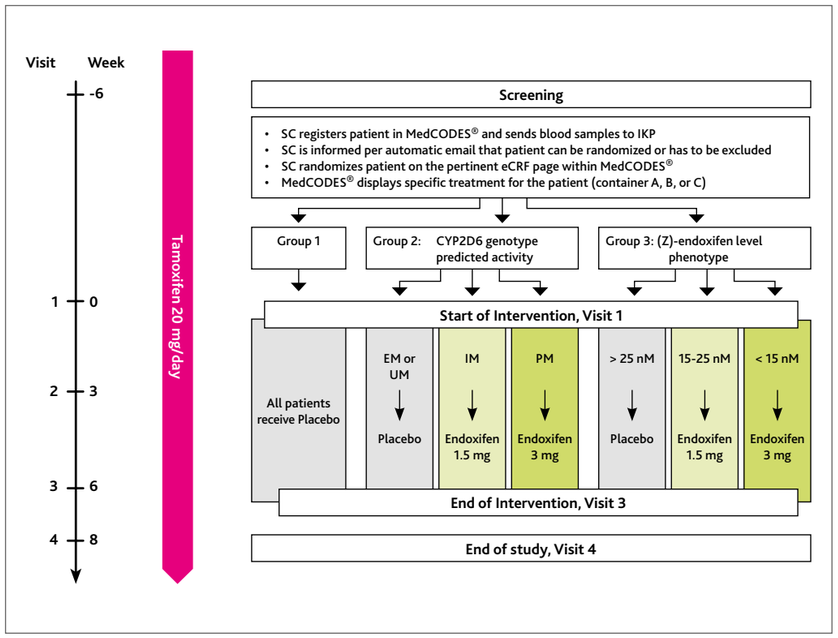

Figure 1: TAMENDOX study design

CONTACT:
Konstantin Reißmüller
Clinical Project Management
tamendox@GBG.de

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 (20 mg/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 (40-300 mg 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 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.

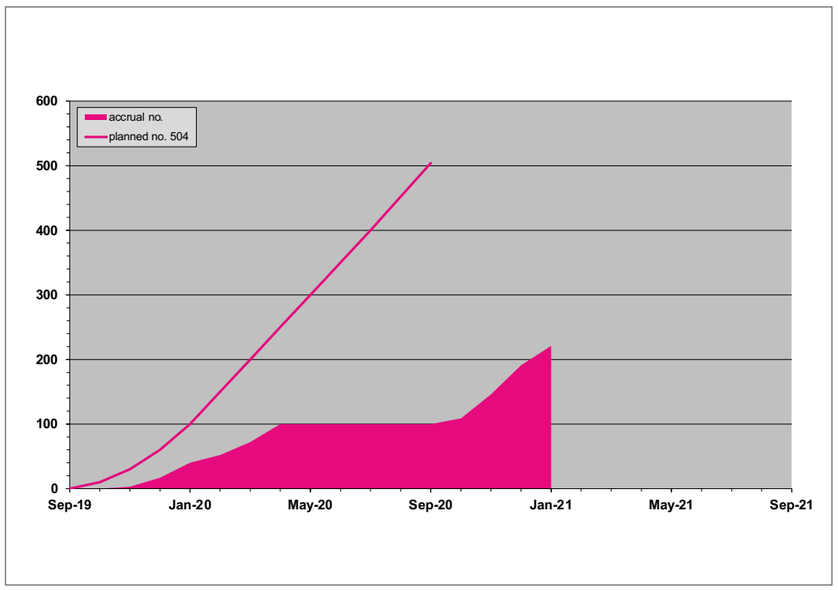

Figure 2: TAMENDOX recruitment as of 31st December 2020

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.

With the first amendment of the study protocol an interim analysis was implemented. The results of 129 analyzed patients will fix which two of the three intervention groups are remaining. Approximately up to 375 patients will be analyzed in the second stage of the adaptive design. The primary endpoint is reached if in one or both intervention groups the proportion of patients with steady state (Z)-endoxifen plasma concentration > 32 nM is significantly higher compared to control group.

Study report

The TAMENDOX study started recruitment on 4th September 2019 and the first patient was randomized on 1st October 2019. As of 31st December 2020, there are 221 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.

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:

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

GBG 85: AURORA

Aiming to Understand the Molecular Aberrations in Metastatic Breast Cancer

NCT02102165

CONTACT:
Dr. Bärbel Felder
Clinical Project Management
aurora@GBG.de

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. The analysis focused on patients with paired samples (primary and metastases) and showed increased number of mutations in the metastatic samples [1]. Recent data on the characterization of gene fusions in a large cohort of patients with metastatic breast cancer was reported at the ASCO 2020. The analysis of paired primary and metastatic tumor samples showed a significant increase of gene fusion burden in metastatic compared to corresponding primary samples, involving relevant breast cancer genes, such as ESR1, ERBB2, NF1 and FGFR1. Presence of gene fusions was associated with shorter overall survival and time-to-relapse in HR+ patients [2]. Additional integrative analyses of matched samples collected within the AURORA program are ongoing.

The goal of 1,000 patients has been reached in August 2020. Nevertheless, recruitment is ongoing and an amendment is planned for Q1 2021.

Publications

1. 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.

2. Benelli M, Biagioni C, Fimereli, et al. Characterization of gene fusions in paired primary and metastatic samples of breast cancer in the AURORA molecular screening program. Cancer Res. 2020;80(16 Suppl): Abstract nr 2488.

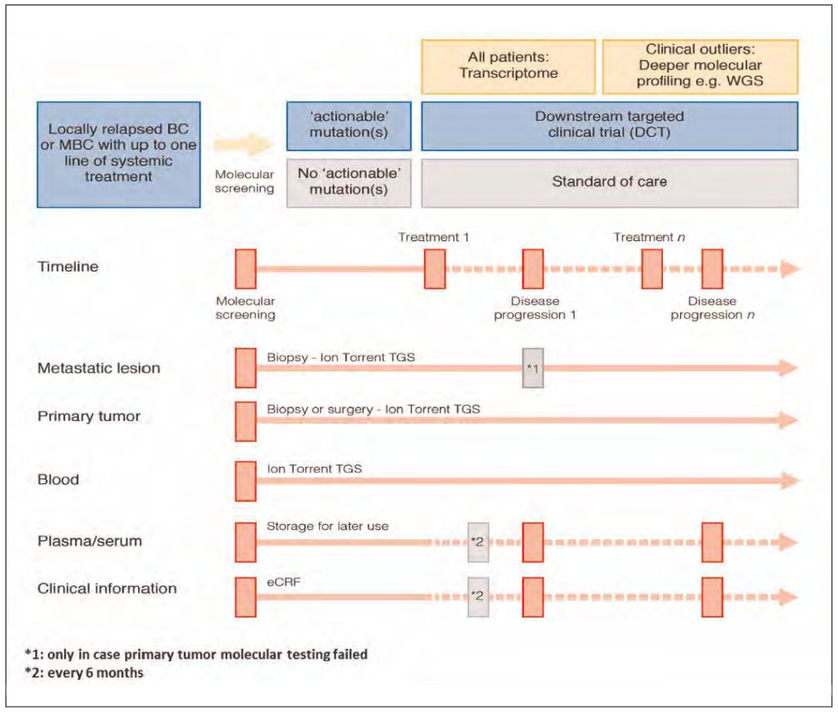

Figure 1: Schematic of the AURORA molecular screening program

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 biomaterial in a timely manner.

COLLABORATING STUDY GROUPS:

SPONSOR:
Breast International Group (BIG)

COORDINATING INVESTIGATOR:
Piccart Martine, MD,PhD
BIG chair and Head of Oncology Department
Institute Jules Bordet, Brussels, Belgium

COORDINATING INVESTIGATOR (GERMANY):
Prof. Dr. Sibylle Loibl
GBG Forschungs GmbH

GBG 79: Brain Metastases in Breast Cancer (BMBC)

CONTACT:
Birgit Raasch
Clinical Project Management
brainmet@GBG.de

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 December 2020, 3,252 patients have been registered and 455 tissue samples have been received. Registration of patients is ongoing.
A retrospective analysis including 882 patients from the BMBC registry with available data of three Graded Prognostic Assessment (GPA)-scores (original-GPA, breast-GPA and updated breast-GPA scores), was recently conducted. The results presented at ESMO breast 2020 revealed that several clinical parameters as well as the GPA-scores were significantly associated with overall survival. However, all GPA-scores showed only a moderate diagnostic accuracy in predicting overall survival in the cohort analyzed [1].
Another retrospective analysis aiming to characterize a cohort of breast cancer patients with asymptomatic brain metastases at diagnosis (N=580) as well as to compare the overall survival (OS) of patients with and without neurological symptoms of brain metastases in the overall cohort of 2,589 patients with brain metastases from BMBC registry was recently published. The findings demonstrated that asymptomatic patients have less severe metastatic brain disease and despite less intensive local brain metastasis therapy still have a better outcome, especially for HER2-positive patients compared to patients with symptomatic brain metastases, although a lead time bias of the earlier diagnosis cannot be ruled out. In addition, this analysis is of clinical relevance in the context of potential trials examining the benefit of early detection and treatment of brain metastases [2].

Publications

1. Riecke K, Mueller V, Neunhöffer T, et al. 149P Predicting prognosis of breast cancer patients with brain metastases in the BMBC registry: Comparison of three different prognostic scores. Ann Oncol 2020;31, suppl. 2.

2. Laakmann E, Witzel I, Neunhöffer T, et al. Characteristics and Clinical Outcome of Breast Cancer Patients with Asymptomatic Brain Metastases. Cancers (Basel). 2020; 12:2787.

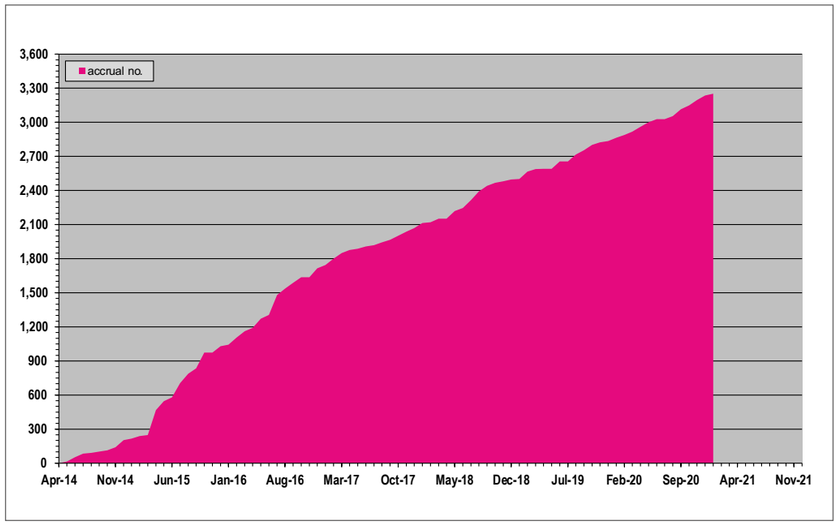

Figure 1: BMBC recruitment as of 31st December 2020

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:

SPONSOR:
GBG Forschungs GmbH

STUDY CHAIRS:
PD Dr. Isabell Witzel
and
Prof. Dr. Volkmar Müller
Universitätsklinikum Hamburg-Eppendorf,
Klinik und Poliklinik für Gynäkologie

GBG 29: Breast Cancer in Pregnancy (BCP)

CONTACT:
Dr. Ioannis Gkantiragas
Clinical Project Management
bcp@GBG.de

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.

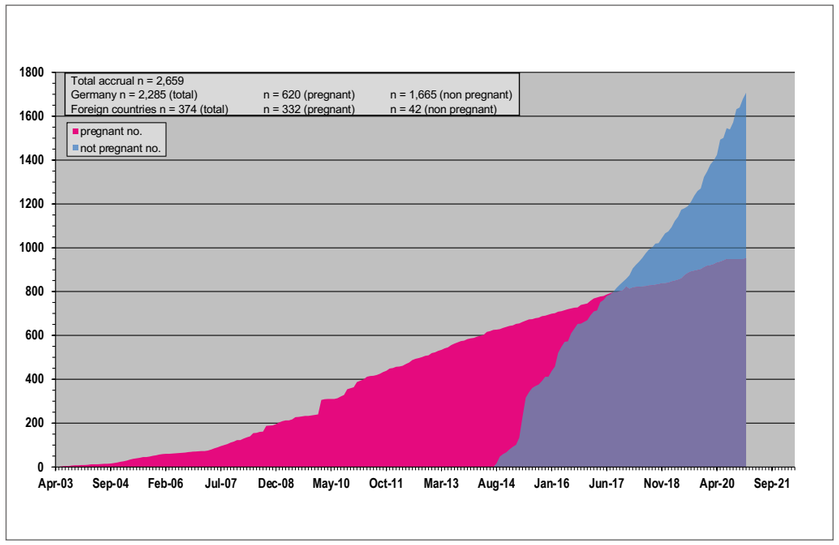

Figure 1: BCP recruitment as of 31st December 2020

Study report

As of 31st December 2020, a total of 2,659 patients have been registered, 2,285 in Germany (620 pregnant and 1,665 non pregnant women).
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. Reported treatments of these young breast cancer patients reflect the modern oncological management. The prognostic relevance of young age by itself could not be shown for patients with HER2-positive and triple-negative breast cancer. However, a trend towards inferior disease-free survival in the group of patients ≤34 years and HR-positive/HER2-negative breast cancer has been suggested [1].
An evaluation of the outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls in cooperation with INCIP (International Network on Cancer, Infertility and Pregnancy) will be presented shortly.

Publications

1. Seiler S, Schmatloch S, Reinisch M, et al. Cancer Management and Outcome of young patients (pts) with breast cancer (BC) diagnosed at 40 years (yrs) or younger. 34. Deutsche Krebskongress 2020, poster.

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

COLLABORATING STUDY GROUPS:

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

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

Completed Studies

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

CONTACT:
Dr. Ioannis Gkantiragas
Clinical Project Management
desiree@gbg.de

DESIREE is a multicenter, double-blind, randomized phase II trial that has recruited 160 patients from 29 sites in Germany within approximately 60 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 compared 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 aimed 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 were: 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 10mg 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 at a later time.

Study report
Between June 2015 and October 2020, a total of 160 patients have been enrolled in the DESIREE study. The end of study and analysis of the primary and secondary objectives is expected in Q2 2021.

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 providing the remaining biomaterial in a timely manner.

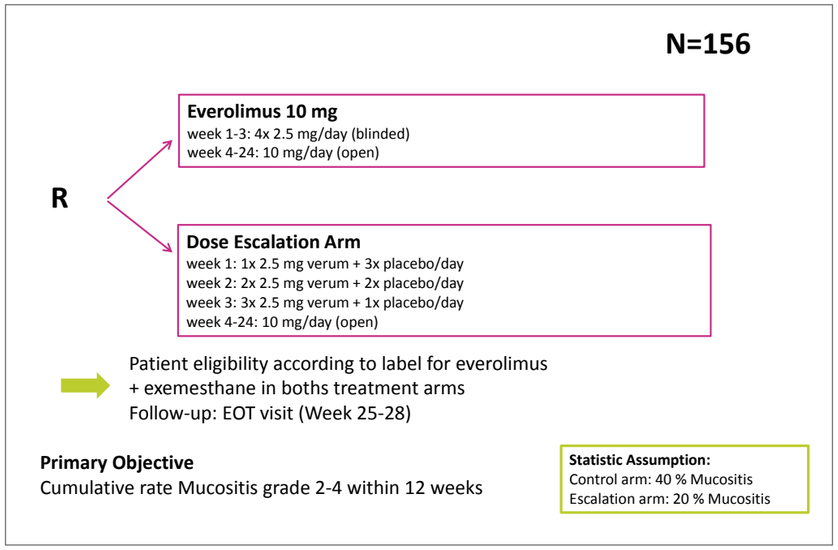

Figure 1: DESIREE study design

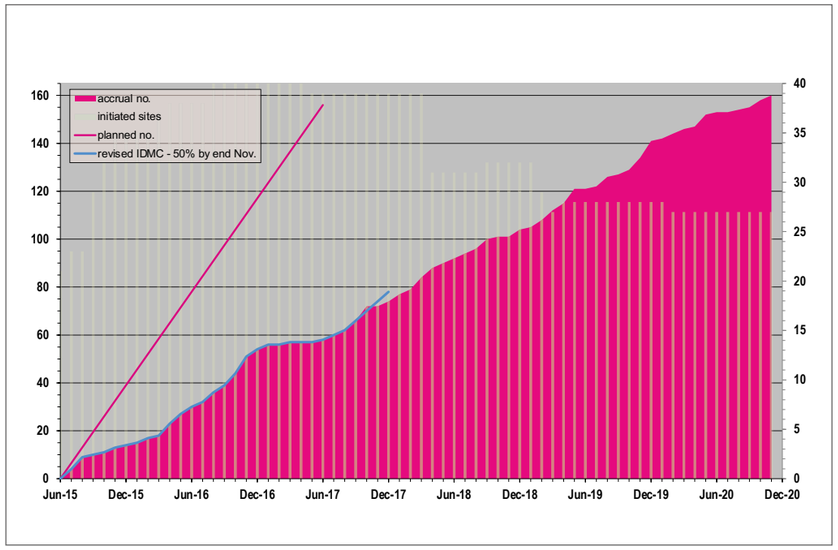

Figure 2: DESIREE recruitment as of 27th October 2020

COLLABORATING STUDY GROUPS:
GBG GERMAN BREAST GROUP

SPONSOR:
GBG Forschungs GmbH

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

GBG 84: GeparOcto

CONTACT:
Konstantin Reißmüller
Clinical Project Management
geparocto@GBG.de

A randomized phase III trial comparing two dose-dense, dose-intensified approaches (ETC and PM(Cb)) for neoadjuvant treatment of patients with high-risk early breast cancer

NCT 02125344

GeparOcto is a multicenter, prospective, randomized open-label phase III study that has recruited 961 patients from 57 sites in Germany within 18 months. Moreover, a total of 123 patients have been randomized for a substudy on supportive anemia treatment.

Background

Two regimen are currently considered to be among the treatments with the highest efficacy in patients with high-risk early stage breast cancer: sequential treatment of high dose epirubicin, taxane, and cyclophosphamide (ETC) concomitantly with or without a dual HER2-blockade mainly based on the AGO ETC adjuvant study (Moebus et al. J Clin Oncol 2010), and weekly treatment with paclitaxel/non-pegylated liposomal doxorubicin with dual HER2-blockade or carboplatin (PM(Cb)) based on the GeparSixto study (von Minckwitz et al. Lancet Oncol 2014). The aim of the GeparOcto study was to compare those two regimens. Moreover, patients with HER2-positive breast cancer have received anti-HER2 treatment with trastuzumab and pertuzumab. In clinical trials, preoperative trastuzumab leads to increased pathological complete response (pCR) rates in the range of 39-62 % (Untch et al. J Clin Oncol 2011; Untch et al. J Clin Oncol 2010; Untch et al. Lancet Oncol 2012; Gianni et al. Lancet 2010). Pertuzumab in combination with trastuzumab has shown impressive activity in combination with docetaxel and/or carboplatin as neoadjuvant treatment in the NeoSphere study (Gianni et al. Lancet Oncol 2012) and in the Tryphaena study (Schneeweiss et al. Ann Oncol 2013).

In addition, the supportive treatment of chemotherapy-induced iron deficiency anemia was investigated. Iron substitution is currently mostly given as an oral supplement in the daily clinical practice. However, parenteral iron substitution is assumed to be more efficient in adjusting iron homeostasis and hemoglobin, as oral preparations are less efficiently absorbed and more frequently cause gastro-intestinal adverse events, leading to non-compliance. The diagnosis and treatment of iron deficiency is, at present, not integrated in the routine medical care of chronic disease, although iron deficiency is a frequent comorbidity in cancer patients and the understanding of iron physiology and pathology has recently gained major insights.

The neoadjuvant GeparOcto study compared a sequential, dose-dense, dose-intensified (idd) ETC (epirubicin, paclitaxel, cyclophosphamide) treatment vs. weekly PM (Cb) (paclitaxel, liposomal doxorubicin, carboplatin) treatment in patients with high-risk operable or locally advanced breast cancer with the addition of trastuzumab and pertuzumab in HER2-positive patients. Moreover, the use of parenteral ferric carboxymaltose versus physician's choice for the treatment of chemotherapy-induced anemia in patients with iron deficiency will be compared.

Study design and objectives:

GeparOcto primarily aimed to compare the pCR (ypT0/is ypN0) rates between the two treatment arms. The secondary objective of the study was to assess the pCR rates per arm separately for the stratified subpopulations. Further objectives were to determine pCR according to other definitions, the response rates of the breast tumor and axillary nodes based on physical examination and imaging tests, the breast conservation rate, toxicity and compliance, loco-regional invasive recurrence free survival (LRRFS), distant-disease-free survival (DDFS), invasive disease-free survival (IDFS), and overall survival (OS) in both arms and according to stratified subpopulations, regional recurrence free survival (RRFS) in patients with initial node-positive axilla converted to negative at surgery (ypN0) and treated with sentinel node biopsy alone, pCR rate and local recurrence free survival (LRFS) in patients with a clinical complete response and a negative core biopsy before surgery and to correlate response (complete vs. partial vs. no change) measured by the best appropriate imaging method after 6 weeks of treatment with pCR.

For those patients randomized for the supportive anemia treatment the primary objective was to compare the frequency of patients reaching hemoglobin (Hb) levels ≥ 11 g/dl 6 weeks after treatment start of a first episode of anemia grade ≥ 2 (Hb < 10g/dl) between patients receiving supportive treatment for iron deficiency with parenteral ferric carboxymaltose versus physician's choice (no supportive treatment, oral iron substitution, erythropoiesis-stimulating agent, or both).

Study report

GeparOcto randomized a total of 961 patients between December 2014 and May 2016 and of those, 123 patients were enrolled in the anemia treatment substudy. A total of 945 patients started treatment (470 in the idd ETC group and 475 in the PM (Cb) group). Primary endpoint pCR (ypT0/is ypN0) was comparable overall and in subgroups [1]. Survival results were recently presented at the ESMO 2020. No difference was found in invasive disease-free and overall survival following neoadjuvant chemotherapy between intense dose-dense epirubicin, paclitaxel, and cyclophosphamide, and weekly paclitaxel/liposomal doxorubicin (plus carboplatin in TNBC) in the high-risk breast cancer population. The subgroup of HR-positive/HER2-negative breast cancer, however, significantly benefitted from treatment with intense dose-dense epirubicin, paclitaxel, and cyclophosphamide, supporting the concept of effective therapy beyond pCR in luminal breast cancer patients [2]. Results of the supportive anemia treatment substudy did not find a difference in efficacy between treatments for chemotherapy-induced anemia [3].

Publications

1. Schneeweiss A, Möbus V, Tesch H, et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto-GBG 84): A randomised phase III trial. Eur J Cancer. 2019;106:181-192.

2. Schneeweiss A, Möbus V, Tesch H, et al. Survival analysis of the randomized phase III GeparOcto trial comparing neoadjuvant chemotherapy (NACT) of iddEPC versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer, TNBC) (PM(Cb)) for patients (pts) with high-risk early breast cancer (BC). Ann Oncol 2020; Vol. 31, Suppl.4, S303-S304, Abstract nr. 160.

3. 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. 34. Deutsche Krebskongress 2020, poster.

We are thanking all participating centers for their commitment and efforts.

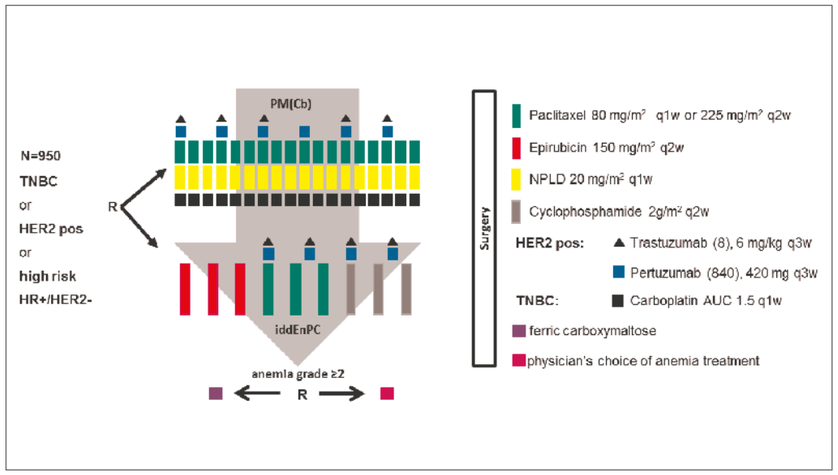

Figure 1: GeparOcto study design

COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

STUDY CHAIR:
Prof. Dr. Andreas Schneeweiss
Nationales Centrum für Tumorerkrankungen, Heidelberg

STUDY CO-CHAIRS:
Prof. Dr. Gunter von Minckwitz (TNBC)
German Breast Group, Neu-Isenburg

Prof. Dr. Volker Möbus (HER2-positive BC)
Klinikum Frankfurt Höchst, Frankfurt am Main

GBG 68: GAIN-2

CONTACT:
Konstantin Reißmüller
Clinical Project Management
gain2@GBG.de

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 (iDFS) 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, pathological complete response (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.

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.

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).

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). The trastuzumab substudy has enrolled 226 patients between November 2013 and August 2017.

Recently, safety results and interim analysis of the primary endpoint invasive disease-free survival (iDFS) were presented at ASCO 2020 showing new safety concerns and no difference in iDFS between arms [1]. Results of the GAIN-2 substudy on the preference for different administration routes of trastuzumab were presented at ESMO Breast 2020. While the subcutaneous was preferred over the intravenous regimen, there were no safety signals or differences in compliance regarding the different areas of subcutaneous injection. However, due to higher bioavailability, the thigh remained the preferred site of injection [2].

Publications

1. Möbus V, Lück HJ, Ladda E, et al. GAIN-2: Neo-/adjuvant phase III trial to compare intense dose-dense chemotherapy (CT) to tailored dose-dense CT in patients (pts) with high risk early breast cancer (EBC): results on safety and interim invasive disease-free survival (iDFS). J Clin Oncol 2020; 38, no. 15_ suppl:516.
2. Reinisch M, Untch M, Reimer T, et al. 86P Patients (pts) preference for different administration methods of trastuzumab (T) in pts with HER2+ early breast cancer (BC) treated within the GAIN-2 trial Ann Oncol 2020; 31, suppl. 2.

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.

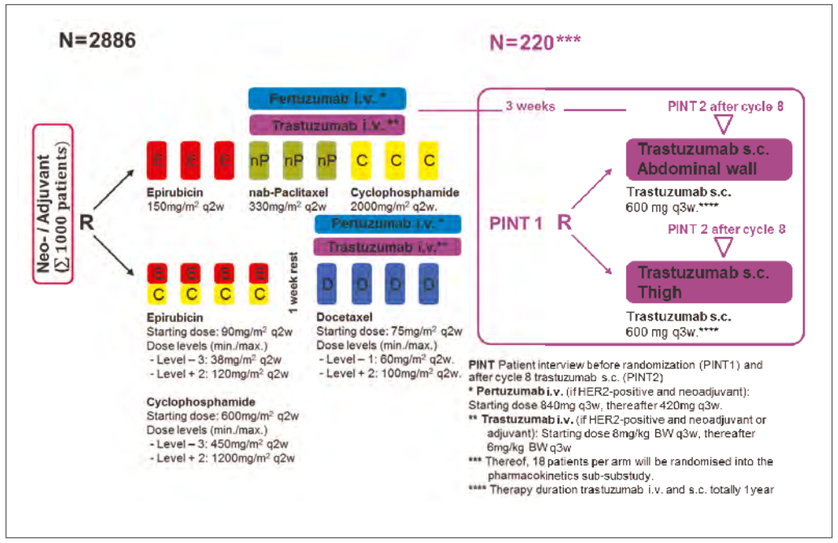

Figure 1: Study design of the GAIN-2 main study and the subcutaneous trastuzumab substudy

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

SPONSOR:
GBG Forschungs GmbH

STUDY CHAIR:
Prof. Dr. med. Volker Möbus
Klinikum Frankfurt Höchst
Frankfurt am Main

Follow-up Activities

Follow-up Activities 2020

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 unaccomplishable task due to the logistic 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 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.

Cooperation with the new data trustee ZKS (Zentrum für Klinische Studien Köln) at the University of Cologne was further established, and data cleaning and exchange optimized. Currently, over 12,000 participants from 20 trials and 330 sites are included in this registry.

In 2020, only a few new patients were included as there are currently no ongoing trials that fit for 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.

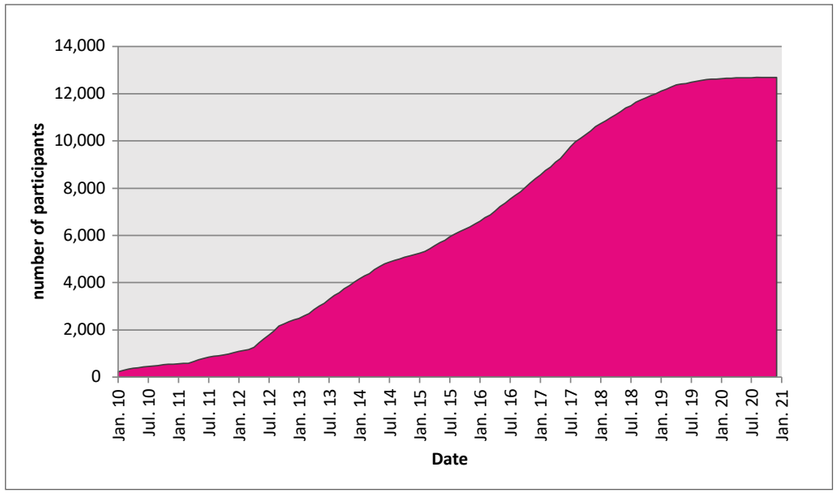

Figure 1: Patient self-reported outcome participants

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	39.4 %
GBG: 24	GeparTrio	2,357	241	44.0 %
GBG: 40	GeparQuattro	1,495	293	51.5 %
GBG: 32	ICE	1,358	198	48.1 %
GBG: 33	GAIN	2,995	1,010	66.6 %
GBG: 36	Natan	693	89	49.9 %
GBG: 44	GeparQuinto	2,572	666	57.1 %
GBG: 66	GeparSixto	588	338	68.0 %
GBG: 52	ICE-2	391	150	58.7 %
GBG: 70	Dafne	65	52	64.7 %
GBG: 69	GeparSepto	1,203	792	74.6 %
GBG: 74	Genevieve	333	205	55.4 %
GBG: 84	GeparOcto	946	732	76.3 %
GBG: 68	GAIN-2	2,858	2,272	77.2 %
GBG: 89	GeparNuevo	174	133	73.5 %
GBG: 90	GeparOla	108	65	50.1 %
GBG: 88	GeparX	801	609	60.1 %
GBG: 75	Insema	5,410	2,888	69.0 %

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 on selected studies that are planned to be analyzed and/or published in the near future.

Neoadjuvant studies

GeparOLA (GBG 90, NCT 02789332)

is a multicenter, prospective, randomized open-label phase II study that has recruited 107 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. Ann Oncol 2020).

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.

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 (Karn et al. Ann Oncol 2020).

It is planned to analyze and publish time-to-event endpoints for GeparNuevo in 2021. Therefore, we would encourage all participating sites to provide follow-up data for their patients.

GeparX (GBG 88, NCT 02682693)

is a multicenter, prospective, 2x2 randomized, open-label phase IIb study that has recruited 780 patients.

The study investigated efficacy and safety of adding denosumab to anthracycline/taxane-containing neoadjuvant chemotherapy and preference for weekly or 2/3 weeks nab-paclitaxel schedules for primary breast cancer. The addition of denosumab to neoadjuvant chemotherapy did not increase the pCR rate while the weekly schedule of nab-Paclitaxel resulted in a significantly higher pCR rates than given d1,8 q22 in early breast cancer. Weekly nab-Paclitaxel resulted in higher rates of serious adverse events and treatment discontinuations mainly due to adverse events (Blohmer et al. Cancer Res 2020). Among predefined subgroups, particularly patients receiving epirubicin/cyclophosphamide every two weeks and patients receiving denosumab benefitted from the weekly nab-Paclitaxel schedule. A high RANK expression was associated with significantly higher pCR rates, an effect that was pronounced in patients with luminal breast cancer. However, a clinical benefit of denosumab in relation to RANK expression could not be shown (Link et al. Ann Oncol 2020). A substudy investigating a potential eradication of disseminated tumor cells (DTCs) by denosumab included 167 patients. While DTC-eradication was observed at a higher rate after denosumab plus chemotherapy than after chemotherapy alone, the presence of DTCs at baseline or DTC-eradication after denosumab treatment did not influence pCR rates. With regards to breast cancer subtypes, a potential effect of denosumab on DTC-eradication could be observed in TNBC (Wimberger et al. J Clin Oncol 2020).

For timely analysis of time-to-event endpoints, which is planned after 248 iDFS events occurred, we would like to encourage all participating sites to provide follow-up data for their patients or to transfer them to the self-reported outcome register.

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). Surgical results demonstrated that neoadjuvant chemotherapy makes breast-conserving therapy (BCT) possible in half of patients with stages II to III TNBC who would have otherwise required mastectomy. Therefore, the overall percentage of those patients eligible for BCT increases from 76.5 % at diagnosis to 83.8 % after neoadjuvant treatment. However, lower BCT rates among eligible patients and higher bilateral mastectomy rates among patients without gBRCA mutation in North America need further investigation (Golshan et al. JAMA Surg. 2020).

The BRIGHTNESS study is now in follow-up with patients being followed for 10 years. We would encourage all participating sites to provide follow-up data for their patients.

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). 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. Cancer 2020).
Subgroup analyses of adjuvant radiotherapy (ART) versus no-ART; hormone receptor (HR)+ versus HR–/unknown disease and HER2– status on retesting of a surgical specimen were recently presented. No new safety signals were observed with concomitant ART or hormonal therapy. Exploratory HER2 analysis of paired specimens suggests that T-DM1 should not be withheld in patients with HER2– residual disease at surgery. Thus HER2 retesting of residual disease may be unnecessary in this population (Loibl et al. Ann Oncol 2020).

Further analyses are to follow in 2021 for this important study. Especially in terms of potential licensing of T-DM1, good quality of follow-up is essential and we therefore encourage all participating sites to provide follow-up data for their patients.

Post-neoadjuvant studies

Penelope^{B} (GBG 78, NCT 01864746)

is a prospective, international, multicenter, randomized, double-blind, placebo-controlled, post-neoadjuvant phase III study that has recruited 1,250 patients.

The study evaluated the addition of the CDK4/6 inhibitor palbociclib as postneoadjuvant treatment for HER2-negative, hormone receptor-positive patients with high relapse risk after neoadjuvant chemotherapy. The addition of 1 year-palbociclib to endocrine therapy in patients with HER2-/HR+ breast cancer and at high-risk of relapse after neoadjuvant chemotherapy did not improve invasive disease-free survival. No new safety signals were observed (Loibl et al. Cancer Res 2021)

We would like to thank all participating sites for their ongoing dedication and tremendous efforts taken on this important trial. We encourage all participating sites to provide further follow-up data for their patients since analysis of overall survival and an update on invasive disease-free survival is planned.

Adjuvant studies

PALLAS (GBG 87, NCT 02513394)

is a multicenter, prospective, international, randomized, open-label, adjuvant phase III study that has recruited 5,760 patients worldwide.

The trial was designed to determine if the addition of two years of palbociclib to adjuvant endocrine therapy improves invasive disease-free survival (iDFS) over endocrine therapy alone in patients with HR+/HER2- early-stage breast cancer. At the second interim analysis, the futility boundary was crossed. Two years of adjuvant palbociclib with endocrine therapy did not improve iDFS compared to endocrine thearpy alone. Ongoing long-term follow-up and additional clinical and translational analyses will explore the effect of palbociclib in this patient population (Mayer et al. Ann Oncol 2020).

We would like to thank all participating sites for their tremendous efforts taken on this important trial. The follow-up of patients will continue for at least 10 years from trial entry and we encourage all participating sites to provide follow-up data for their patients.

OLYMPIA (GBG 82, NCT 02032823)

is a multicenter, double-blind, parallel group, placebo-controlled, randomized phase III trial that has recruited approximately 1,836 patients.

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 BRCA1/2 mutations and high-risk HER2-negative disease. The Olympia study is now in follow-up and primary endpoint is planned to be analysed in 2021. 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.

It is planned to analyze and publish time-to-event endpoints in 2028. Therefore, we would encourage all participating sites to provide follow-up data for their patients.

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. Diarrhea was more common with pertuzumab than with placebo (von Minckwitz et al. N Engl J Med 2017). At 6-year follow-up there was a modest, but not statistically significant, overall survival benefit for the addition of pertuzumab to chemotherapy plus trastuzumab. This benefit was seen mainly in patients with node-positive disease and was observed regardless of hormone receptor status (Piccart et al. Cancer Res. 2020).
To explore how these overall results translate into absolute treatment benefits for different subpopulations of patients a Subpopulation Treatment Effect Pattern Plot (STEPP) analysis was performed and the results were presented at the SABCS 2020. Patients with node-positive breast cancer benefit from the addition of adjuvant pertuzumab in 6-year iDFS compared to the control group (87.9 % vs 83.4 %). Benefit was seen irrespective of STEPP subpopulation, with the largest gain for lower risk node-positive disease. Patients with node-negative breast cancer treated with trastuzumab and chemotherapy alone have good outcomes (≥ 91.0 % 6-year iDFS for each STEPP subpopulation), which were not further improved by the addition of adjuvant pertuzumab (Gelber et al. Cancer Res 2021).
A translational project on prediction of benefit from adjuvant pertuzumab by BluePrint RNA sequencing, an 80-gene molecular subtyping test that classifies early breast cancer into functional basal, luminal and HER2 type, showed that HER2+ tumors with a single transcriptional HER2 activated pathway are more likely to derive a benefit from pertuzumab compared to tumors with multiple activated mitogenic pathways (Krop et al. Cancer Res 2021).
Additionally, a post-hoc, exploratory sub-analysis on timelines to initiate the APHINITY trial across the globe did not demonstrate a significantly longer time for trial activation in Latin American and Caribbean countries and upper middle income economies compared to other groups (Franzoi et al. Cancer Res 2021).

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.

Surgical studies

INSEMA

INSEMA (GBG 75, NCT 02466737)

a prospective, multicenter, randomized, surgical trial that has recruited 5,542 patients in Germany and Austria.

The trial aims to compare the invasive disease-free survival after breast-conserving surgery between patients who received no axillary surgery versus patients who received sentinel lymph node biopsy and between node positive patients who received sentinel lymph node biopsy alone versus patients with completion of axillary lymph node dissection.
Follow-up for this surgical trial is ongoing and analysis of the primary endpoint invasive disease-free survival is planned for 2024. An integrated radiation therapy quality assurance review was recently published. Assuming ≥ 80 % of prescribed breast dose as the optimal dose for curative radiation of low-volume disease in axillary lymph nodes, at least 50 % of reviewed patients received an adequate dose in level I, even with contemporary 3-dimensional techniques. Dose coverage was much less in axillary levels II and III, and far below therapeutically relevant doses (Hildebrandt et al. Int J Radiat Oncol Biol Phys 2020).

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 providing regular follow-up data or transferring participants to the self-reported outcome register.

Translational Research

Translational Research & Biobanking

Central Pathology and GBG Tumor Bank

The Institute of Pathology at the University of Marburg is hosting GBG's FFPE tumor bank and Central Pathology since May 2019 under the direction of Prof. Dr. Carsten Denkert. The barcode-based biobank management system CentraXX (KAIROS GmbH), hosted by GBG, is fully integrated into laboratory workflows for archiving, sample tracking as well as other important central pathology procedures.

In 2020, several new procedures have been established which support the increasing demands of clinical and scientific testing approaches. The molecular pathology facility has been extended to meet these needs with state-of-the-art Illumina platforms (MiniSeq and NextSeq) and laboratory equipment for standardized and high-quality analyses in diagnostic and research context. For RNA analysis and gene expression profiling the HTG EdgeSeq method was implemented for high-plex RNA analysis with a minimum of biomaterial input.

Digitalization of immunohistochemically stained tumor tissue slides was implemented with Leica and PreciPoint platforms in 2020. Currently, the Institute of Pathology is expanding its infrastructure to answer translational research questions with image analysis, based on a digital slide repository.

Molecular Screening

Patients with locally advanced and metastatic breast cancer may benefit from genomic profiling by identifying actionable alterations within the context of precision medicine. With the latest amendments in the AMICA and PADMA study coming into effect, GBG will offer molecular screening within these trials. Sequencing will take place at the Institute of Pathology at Marburg, where a sequencing pipeline has been implemented to include the molecular testing in GBG trials. Meanwhile, GBG has established a Molecular Tumor Board (MTB), whose members will share their experience to interpret the sequencing results to provide well-founded treatment recommendations.

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 running 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 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. Despite of the difficult situation of the COVID-19 pandemic, the GeparDouze trial is recruiting very well and the stool sample collection is ongoing. The first batch of stool samples has already been sent to the Oncobiome cooperation partners at the University of Trento (Italy), where genomic analyses will take place.

RAD51 predict, a project within the ERA PerMed consortium
This project aims to clinically validate a RAD51 predict test, designed by the experimental therapeutics research group of VHIO (Val d'Hebron) Barcelona, led by Dr. Violeta Serra. RAD51 is a biomarker indicating DNA repair functionality of the tumor. The test is supposed to identify patients who can benefit from therapies with PARP-inhibitors. GBG supports the project by providing the well-characterized clinical cohorts of GeparSixto and GeparOla, thus making a significant contribution to the goal of clinical validation of the test.

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

FURTHER INFORMATION:
Dr. Bärbel Felder
Translational Research
Phone: +49 6102 7480-217
Fax: +49 6102 7480-440
trafo@GBG.de

GBG Study Finder 2021*

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
Operable HER2-positive or triple-negative breast cancer: • cT1c-T3 prior to neoadjuvant systemic therapy (NAST) and • cN0/iN0 • Standard NAST with radiological complete response	**EUBREAST-01** Omission of sentinel lymph node biopsy in patients with radiologic and pathologic complete response in the breast after neoadjuvant systemic therapy. All patients with confirmed breast pCR after lumpectomy will be selected for the single study arm leading to omission of any axillary treatment
(Neo)adjuvant Studies (M0)	
Untreated triple-negative breast cancer: • T2-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-positive / HER2-negative 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 positive breast cancer: • Ongoing hormone therapy with tamoxifen (20 mg)	**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-negative (TNBC) or - HR-positive 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
Non-pCR after NACT • HER2-positive breast cancer - cT4, cN0-3 or cT1-3, cN2-3 at first diagnosis or - cT1-3, cN0-1 at first diagnosis with ypN1-3 after NACT • An interval of ≤12 weeks between the date of last surgery and the date of randomization • At least 16 weeks chemotherapy, including at least 9 weeks of trastuzumab (± pertuzumab) and at least 9 weeks of taxane basedchemotherapy	**TruDy/DESTINY-B05** Arm A: **Trastuzumab deruxtecan** 14 cycles d1 q3w Arm B: Trastuzumab emtansine (T-DM1) 14 cycles d1 q3w

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-negative Breast Cancer	
HER2-negative und HR-positive metastatic breast cancer: • At least 4 cycles of a 1st line mono- or polychemotherapy • Pretreatment with CDK 4/6 inhibitors is allowed	**AMICA** Endocrine maintenance therapy after chemotherapy **+/- ribociclib**
HER2-negative and HR-positive metastatic breast cancer: • 1st systemic therapy for the treatment of metastatic 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.
• Patients with **breast cancer in pregnany** • 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

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

Notes

Notes

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GROUP

Impressum:

GBG Forschungs GmbH
Martin-Behaim-Strasse 12
63263 Neu-Isenburg
GERMANY

www.GBG.de