GBG

GERMAN
BREAST
GROUP

Heilung durch Innovation, Kompetenz und Partnerschaft

Annual Scientific Report

2018

GBG
GERMAN
BREAST
GROUP

Heilung durch Innovation, Kompetenz und Partnerschaft

Annual Scientific Report 2018

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.

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

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

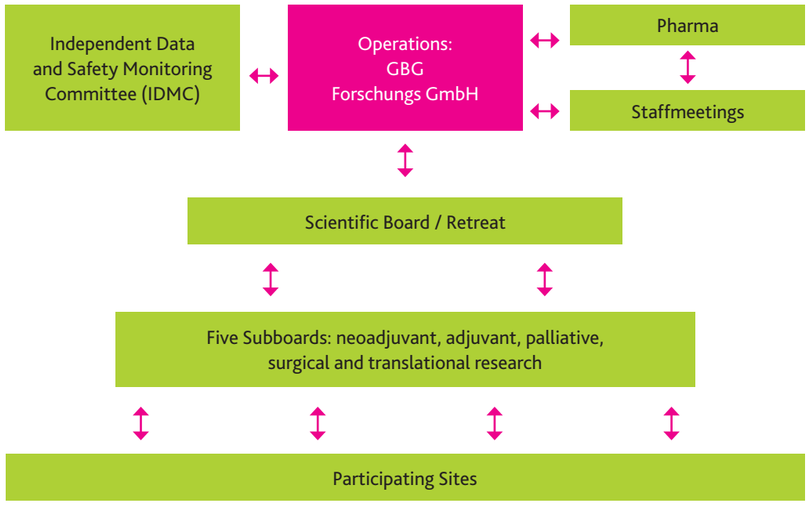


Figure 1: Structure of the German Breast Group

2. Infrastructure of the German Breast Group

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

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

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

The members of our subboards in 2018 are shown below:

Neoadjuvant
Prof. Dr. J. U. Blohmer, Berlin
Prof. Dr. C. Denkert, Berlin
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
Prof. Dr. G. von Minckwitz, Neu-Isenburg
PD Dr. K. Rhiem, Köln
Prof. Dr. A. Schneeweiss, Heidelberg
Prof. Dr. M. Untch, Berlin

Adjuvant
Prof. Dr. W. Janni, Ulm
Prof. Dr. S. Loibl, Neu-Isenburg
Prof. Dr. F. Marme, 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, Freiburg
Prof. Dr. M. Untch, Berlin

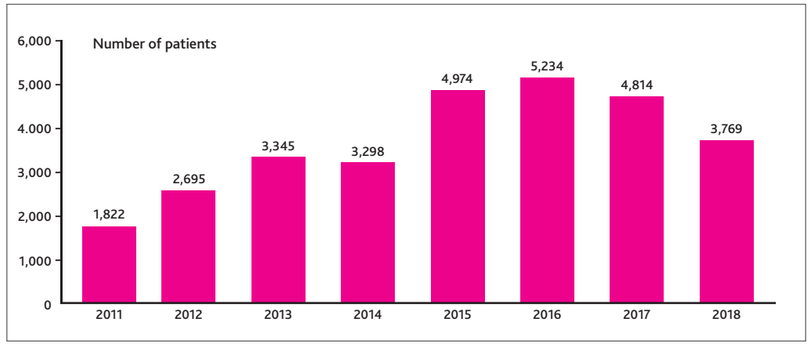


Figure 2: Annual recruitment of patients

Palliative
PD Dr. T. Decker, Ravensburg
Prof. Dr. C. Denkert, Berlin
Prof. Dr. S. Loibl, Neu-Isenburg
Dr. K. Lübbe, Hannover
Prof. Dr. C. Mundhenke, Kiel
Prof. Dr. V. Müller, Hamburg
PD Dr. M. Schmidt, Mainz
Dr. J. Seitz, Heidelberg
Prof. Dr. M. Thill, Frankfurt am Main

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

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

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

The IDMC reviews all GBG sponsored trials regarding:

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

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

3. Cooperations with other study groups

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

ABCSG:
Austrian Breast & Colorectal Cancer Study Group

AFT:
Alliance Foundation Trials

AGO:
Arbeitsgemeinschaft Gynäkologische Onkologie

AGO-B:
Breast Study Group

ANZBCTG:
Australia and New Zealand Breast Cancer Trials Group

BIG:
Breast International Group

BOOG:
Borstkanker Onderzoeksgroep Nederland

CCTG:
Canadian Cancer Trials Group

CECOG:
Central European Cooperative Oncology Grou

CIRG:
Cancer International Research Group

CRUK:
Cancer Research UK

CTI:
Cancer Trials Ireland

CTRU:
Clinical Trials Research Unit

DKG:
Deutsche Krebsgesellschaft

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

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

JBCRG:
Japan Breast Cancer Research Group

NOGGO:
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie

NSABP:
National Surgical Adjuvant Breast and Bowel Project

PrECOG, LLC:
Cancer Clinical Trials Research Company, US

SBG:
Scandinavian Breast Cancer Group

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

UCBG:
French breast cancer intergroup UNICACER

UNICANCER:
UNICANCER Group, France

Universitätsklinikum Hamburg-Eppendorf

Universität Rostock

UZL:
University Hospital of Leuven

WSG:
Westdeutsche Studiengruppe

4. Publications in 2018

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

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

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

Peer-review articles, reviews and congress contributions in 2018 are listed in 4.1., 4.2. and 4.3.

4.1. Peer-reviewed articles in 2018

1. Schneeweiss A, Möbus V, Tesch H, Hanusch C, Denkert C, 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 randomized phase III trial. Eur J Cancer. 2019 (manuscript accepted 2018);106:181-192.

2. Bischoff J, Barinoff J, Mundhenke C, Bauerschlag DO, Costa S-D, et al. A randomized phase II study to determine the efficacy and tolerability of two doses of eribulin plus lapatinib in trastuzumab-pretreated patients with HER-2-positive metastatic breast cancer (E-VITA). Anti-Cancer Drugs 2018 (manuscript accepted 2018).

3. von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2018 Dec 5. [Epub ahead of print]

4. Matikas A, Foukakis T, Moebus V, Greil R, Bengtsson NO, et al. Dose tailoring of adjuvant chemotherapy for breast cancer based on hematologic toxicities: Further results from the prospective PANTHER study with focus on obese patients. Ann Oncol. 2018 Oct 24 [Epub ahead of print]

5. Lambertini M, Moore HCF, Leonard RCF, Loibl S, Munster P, et al. Gonadotropin-Releasing Hormone Agonists During Chemotherapy for Preservation of Ovarian Function and Fertility in Premenopausal Patients With Early Breast Cancer: A Systematic Review and Meta-Analysis of Individual Patient-Level Data. J Clin Oncol. 2018; 36:1981-1990.

6. Loibl S, Weber KE, Timms KM, Elkin EP, Hahnen E, et al. Survival analysis of carboplatin added to an anthracycline/taxane-based neoadjuvant chemotherapy and HRD score as predictor of response - final results from GeparSixto. Ann Oncol. 2018;29:2341-2347.

7. Liedtke C, Kolberg HC, Kerschke L, Görlich D, Bauerfeind I, et al. Systematic analysis of parameters predicting pathological axillary status (ypN0 vs. ypN+) in patients with breast cancer converting from cN+ to ycN0 through primary systemic therapy (PST). Clin Exp Metastasis. 2018;35:777-783.

8. Stevic I, Müller V, Weber K, Fasching PA, Karn T, et al. Specific microRNA signatures in exosomes of triple-negative and HER2-positive breast cancer patients undergoing neoadjuvant therapy within the GeparSixto trial. BMC Med. 2018;16:179.

9. Francis PA, Pagani O, Fleming GF, Walley BA, Colleoni M, et al; SOFT and TEXT Investigators and the International Breast Cancer Study Group. Tailoring Adjuvant Endocrine Therapy for Premenopausal Breast Cancer. N Engl J Med. 2018; 379:122-137.

10. Lambertini M, Di Maio M, Pagani O, Curigliano G, Poggio F, et al. The BCY3/BCC 2017 survey on physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in young breast cancer patients. Breast. 2018;42:41-49.

11. Witzel I, Laakmann E, Weide R, Neunhöffer T, Park-Simon TJ, et al. Treatment and outcomes of patients in the Brain Metastases in Breast Cancer Network Registry. Eur J Cancer. 2018;102:1-9.

12. Nekljudova V, Loibl S, von Minckwitz G, Schneeweiss A, Glück S, et al. Trial-level prediction of long-term outcome based on pathologic complete response (pCR) after neoadjuvant chemotherapy for early-stage breast cancer (EBC). Contemp Clin Trials. 2018 71:194-198.

13. Wu L, Shi W, Long J, Guo X, Michailidou K, et al. A transcriptome-wide association study of 229,000 women identifies new candidate susceptibility genes for breast cancer. Nat Genet. 2018; 50:968-978.

14. Fasching PA, Loibl S, Hu C, Hart SN, Shimelis H, et al. *BRCA*1/2 Mutations and Bevacizumab in the Neoadjuvant Treatment of Breast Cancer: Response and Prognosis Results in Patients With Triple-Negative Breast Cancer From the GeparQuinto Study. J Clin Oncol. 2018; 36:2281-2287.

15. von Waldenfels G, Loibl S, Furlanetto J, Machleidt A, Lederer B, et al. Outcome after neoadjuvant chemotherapy in elderly breast cancer patients - a pooled analysis of individual patient data from eight prospectively randomized controlled trials. Oncotarget. 2018;9(20):15168-15179.

16. Loibl S, Weber K, Huober J, Krappmann K, Marmé F, et al. Risk assessment after neoadjuvant chemotherapy in luminal breast cancer using a clinico-molecular predictor. Clin Cancer Res. 2018; 24:3358-3365.

17. Untch M, von Minckwitz G, Gerber B, Schem C, Rezai M, et al. Survival Analysis After Neoadjuvant Chemotherapy With Trastuzumab or Lapatinib in Patients With Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer in the GeparQuinto (G5) Study (GBG 44). J Clin Oncol. 2018; 36:1308-1316.

18. Engel C, Rhiem K, Hahnen E, Loibl S, Weber KE, et al. Prevalence of pathogenic *BRCA*1/2 germline mutations among 802 women with unilateral triple-negative breast cancer without family cancer history. BMC Cancer. 2018; 18:265.

19. Loibl S, O'Shaughnessy J, Untch M, Sikov WM, Rugo HS, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomized, phase 3 trial. Lancet Oncol. 2018; 19:497-509.

20. Ingle JN, Kalari KR, Wickerham DL, von Minckwitz G, Fasching PA, et al. Germline genome-wide association studies in women receiving neoadjuvant chemotherapy with or without bevacizumab. Pharmacogenet Genomics. 2018;28:147-152.

21. Möbus V, Jackisch C, Lück HJ, du Bois A, Thomssen C, et al. Ten-year results of intense dose-dense chemotherapy show superior survival compared with a conventional schedule in high-risk primary breast cancer: final results of AGO phase III iddEPC trial. Ann Oncol. 2018;29:178-185.

22. Bidard FC, Michiels S, Riethdorf S, Mueller V, Esserman LJ, et al. Circulating Tumor Cells in Breast Cancer Patients Treated by Neoadjuvant Chemotherapy: A Meta-analysis. J Natl Cancer Inst. 2018; 110:560-567.

4.2. Peer-reviewed reviews in 2018

1. Denkert C, Loibl S, Budczies J, Wienert S, Klauschen F. [Standardized determination of tumor-infiltrating lymphocytes in breast cancer : A prognostic marker for histological diagnosis]. Der Pathologe. 2018; 39:520-531.

2. Klauschen F, Müller KR, Binder A, Bockmayr M, Hägele M, et al. Scoring of tumor-infiltrating lymphocytes: From visual estimation to machine learning. Semin Cancer Biol. 2018;52(Pt 2):151-157.

3. Tancredi R, Furlanetto J, Loibl S. Endocrine Therapy in Premenopausal Hormone Receptor Positive/Human Epidermal

Growth Receptor 2 Negative Metastatic Breast Cancer: Between Guidelines and Literature. Oncologist. 2018; 23:974-981.

4. Duchnowska R, Loibl S, Jassem J. Tyrosine kinase inhibitors for brain metastases in HER2-positive breast cancer. Cancer Treat Rev. 2018;67:71-77.

4.3. Congress contributions in 2018

SABCS:
San Antonio Breast Cancer Simposium,
4-8 December 2018, San Antonio, Texas, USA

Geyer Jr. CE, Huang C-S, Mano MS, Loibl S, Mamounas EP, et al. Phase III study of trastuzumab emtansine (T-DM1) vs trastuzumab as adjuvant therapy in patients with HER2-positive early breast cancer with residual invasive disease after neoadjuvant chemotherapy and HER2-targeted therapy including trastuzumab: primary results from KATHERINE. SABCS 2018; GS1-10, oral presentation.

Loibl S, Sinn BV, Karn T, Untch M, Treue D, et al. mRNA signatures predict response to durvalumab therapy in triple negative breast cancer (TNBC)- Results of the translational biomarker programme of the neoadjuvant double-blind placebo controlled GeparNuevo trial. SABCS 2018; PD5-13, poster discussion.

Sinn BV, Loibl S, Karn T, Untch M, Kunze CA, et al. Pre-therapeutic PD-L1 expression and dynamics of Ki-67 and gene expression during neoadjuvant immune-checkpoint blockade and chemotherapy to predict response within the GeparNuevo trial. SABCS 2018; PD5-05, poster discussion.

Seiler S, Schmatloch S, Reinisch M, Neunhöffer T, Schmidt M, et al. Cancer management and outcome of very young non-pregnant patients with breast cancer diagnosed at 40 years or younger– GBG 29. SABCS 2018; P1-17-07, poster.

Huober J, Schneeweiss A, Blohmer J-U, Denkert C, Tesch H, et al. Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy – Results of a pooled analysis based on the GBG meta-database. SABCS 2018; P2-08-01, poster.

Villegas SL, Lederer B, Untch M, Holms F, Ulmer H-U, et al. Similarities between low hormone receptor positive and hormone receptor negative breast cancer: An analysis of 4366 patients from multicenter clinical trials. SABCS 2018; P2-08-10, poster.

Karn T, Denkert C, Sinn BV, Weber K, Nekljudova V, et al. Single-cell profiling identifies hypoxic carcinoma cells as source of an immunosuppressive VEGFA metagene. SABCS 2018; P3-10-01, poster.

Massa C, Schneeweiss A, Karn T, Hanusch CA, Blohmer J-U, et al. Immunomonitoring of triple negative breast cancer patients undergoing neoadjuvant therapy with durvalumab - Results from the prospectively randomized GeparNuevo trial. SABCS 2018; P4-06-01, poster.

Witzel ID, Riecke K, Laakmann E, Weide R, Neunhoeffer T, et al. Validation of different prognostic scores in breast cancer patients with brain metastases of the BMBC registry (GBG-79). SABCS 2018; P4-08-26, poster.

Finn RS, Turner NC, Liu Y, Rugo HS, Loibl S, et al. Biomarker analysis of CDK 4/6 and endocrine pathways in hormone-receptor positive (HR+) advanced breast cancer (ABC) bone only disease patients: A joint analysis of PALOMA-2 and PALOMA-3 studies. SABCS 2018; P6-18-03, poster.

Metzger O, Mandrekar S, Loibl S, Mundhenke C, Seiler S, et al. PATINA: A randomized, open label, phase III trial to evaluate the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy (ET) vs. anti-HER2 therapy + ET after induction treatment for hormone receptor positive (HR+)/HER2-positive metastatic breast cancer (MBC). SABCS 2018; OT3-02-07, poster.

Geyer, Jr. CE, Loibl S, Rastogi P, Seiler S, Costantino JP, et al. A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo: NSABP B-59/GBG 96-GeparDouze. SABCS 2018; OT3-05-01, poster.

Ignatiadis M, McArthur H, Bailey A, Martinez J-L, De Azambuja E, et al. ALEXANDRA/IMpassion030: A phase III study of standard adjuvant chemotherapy with or without atezolizumab in early triple negative breast cancer. SABCS 2018; OT3-05-02, poster.

O'Leary B, Lira ME, Huang S, Deng S, Xie T, et al. Longitudinal ctDNA sequencing using an expanded genomic panel in the PALOMA3 trial of palbociclib plus fulvestrant. SABCS 2018; PD2-02, poster discussion.

Polley M-YC, Dickler MN, Johnston S, Goetz MP, de la Haba J, et al. A clinical calculator to predict disease outcomes in women with hormone receptor-positive advanced stage breast cancer treated with first-line endocrine therapy. SABCS 2018; P2-07-05, poster.

ESMO:
European Society for Medical Oncology,
19-23 October, 2018, Munich, Germany

Untch M, Jackisch C, Schneeweiss A, Schmatloch S, Aktas B et al. Impact of nab-paclitaxel dose reduction on survival of the randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy of weekly nab-paclitaxel (nP) with solvent-based paclitaxel (P) followed by anthracycline/cyclophosphamide for patients with early breast cancer (BC), Ann Oncol 2018;29, suppl_8, mdy270.185, 188PD, poster discussion.

Reinisch M, Seiler S, Hauzenberger T, Schmatloch S, Strittmatter H-J, et al. Final analysis of the Male-GBG54 study: A prospective, randomized multi-centre phase II study evaluating endocrine treatment with either tamoxifen +/- gonadotropin releasing hormone analogue (GnRHa) or an aromatase inhibitor + GnRHa in male breast cancer patients, Ann Oncol 2018;29, suppl_8, mdy424.007, 273PD_PR, poster discussion.

Fasching PA, Laible M, Weber KE, Wirtz RM, Denkert C, et al. Validation of the MammaTyper® pathological complete response (pCR)-score as a predictor for response after neoadjuvant chemotherapy (NACT) in patients with early breast cancer (BC). Ann Oncol 2018;29, suppl_8, mdy269.166, 168P, poster.

Fasching PA, Laible M, Weber KE, Wirtz RM, Denkert C, et al. Evaluation of the MammaTyper® as a molecular predictor for pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) and outcome in patients with different breast cancer (BC) subtypes. Ann Oncol 2018;29, suppl_8, mdy270.222, 227P, poster.

Pohl E, Schneeweiss A, Hauke J, Moebus V, Furlanetto J et al. Germline mutation status and therapy response in patients with triple-negative breast cancer (TNBC): Results of the GeparOcto study. Ann Oncol 2018;29, suppl_8, mdy270.238, 243P, poster.

Loibl S, Metzger O, Mandrekar S J, Mundhenke C, Seiler S et al. PATINA: A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy (ET) vs. Anti-HER2 Therapy + ET after Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer (MBC). Ann Oncol 2018;29, suppl_8, mdy272.357, 369TIP, poster.

Decker T, Denkert C, Lübbe K, Müller V, Mundhenke C, et al. Anti-hormonal maintenance treatment with or without the CDK4/6 inhibitor ribociclib after first line chemotherapy in hormone receptor positive/HER2 negative metastatic breast cancer: A phase II trial (AMICA) GBG 97. Ann Oncol 2018;29, suppl_8, mdy272.352, 364TiP, poster.

Cristofanilli M, Slamon DJ, Ro J, Bondarenko I, Im S-A, et al. Overall survival (OS) with palbociclib plus fulvestrant in women with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC): Analyses from PALOMA-3, Ann Oncol 2018;29, suppl_8, mdy424.009, LBA2_PR, poster.

Lambertini PM, Maio MD, Poggio F, Pagani O, Curigliano G, et al. Physicians' knowledge, attitudes and practice towards fertility and pregnancy-related issues in *BRCA*-mutated breast cancer (BC) patients (pts): Results from the BCY3/BCC 2017 survey. Ann Oncol 2018;29, suppl_8, mdy300.009, 1692P, poster.

Hui R, Pearson A, Cortes Castan J, Campbell C, Poirot C, et al. Lucitanib for the treatment of HR+ HER2- metastatic breast cancer (MBC) patients (pts): Results from the multicohort phase II FINESSE trial, Ann Oncol 2018;29, suppl_8, mdy272.281,289PD, poster discussion.

Day C, Middleton D, Loibl S. Application of CDK4/6 inhibitors in practice: Effect of on-line education on clinician competence and confidence. Ann Oncol 2018;29, suppl_8, 343P, poster.

ECI:
5th European Congress of Immunology, 2-5 September, 2018 Amsterdam, Netherlands
Massa C, Mueller A, Schneeweiss A, Hanusch C, Huober J, et al. Immunomonitoring of triple negative breast cancer patients undergoing neoadjuvant therapy (GBG89, Geparnuevo trial). ECI 2018;P.B1.03.10, poster.

DGS:
Deutsche Gesellschaft für Senologie, 29 June-1 July, 2018, Stuttgart, Germany
Decker T, Barinoff, J, Furlanetto J, Denkert C, Lübbe K, et al. Anti-hormonal maintenance treatment with/without the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in HR+/HER2- metastatic breast cancer: a phase II trial (AMICA) GBG 97. DGS 2018; P073, poster.

Loibl S, Jackisch C, Seiler S, Rastogi P, Blohmer J-U, et al. A Randomized, Double-Blind, Phase III Trial of Neoadjuvant Chemotherapy with Atezolizumab/Placebo in Patients with Triple-Negative Breast Cancer Followed by Adjuvant Continuation of Atezolizumab/Placebo (GeparDouze). DGS 2018; P071, poster.

Thill M, Seiler S, Decker T, Denkert C, Lübbe K, et al. A randomized, open-label, phase IV study evaluating palbociclib plus endocrine treatment versus a chemotherapy-based treatment in patients with hormone receptor-positive, HER2-negative metastatic breast cancer (PADMA). DGS 2018; P072, poster.

Furlanetto J, Thode C, Huober J, Denkert C, Bassy M, et al. Changes in hormone levels (E2, FSH, AMH) and fertility of young women treated with neo-/adjuvant chemotherapy (CT) for early breast cancer (EBC). DGS 2018; P076, poster.

Kümmel S, von Minckwitz G, Vladimirova V, Nekljudova V, Wimberger P, et al. Investigating Densumab as an add-on neoadjuvant treatment for RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-Paclitaxel schedules - 2x2 factorial design (GeparX). DGS 2018; P029, poster.

Reimer T. Update INSEMA-Studie. DGS 2018; oral presentation.

Reinisch M. Erste Daten der MALE Studie: Welche Hormontherapie ist die effektivste beim Mann? DGS 2018; oral presentation.

Noske N. Tumor infiltrating lymphocytes predict better DFS from intense dose-dense (idd) EPC regimen - results from the German Adjuvant Intergroup Node-positive Study (GAIN-1). DGS 2018; oral presentation.

ASCO:
American Society of Clinical Oncology, Annual Meeting 1-5 June, 2018, Chicago, Illinois, USA
Turner CN, O'Leary B, Cutts R, Liu Y, Hrebien S, et al. Genetic landscape of resistance to CDK4/6 inhibition in circulating tumor DNA (ctDNA) analy-sis of the PALOMA3 trial of palbociclib and analy-sis versus placebo and fulvestrant. J Clin Oncol 36, 2018 (suppl; abstr 1001), oral presentation.

Geyer EG, Loibl S, Rastogi P, Seiler S, Costantino PJ, et al. NSABP B-59/GBG 96-GeparDouze: A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in Patients (pts) with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. J Clin Oncol 36, 2018 (suppl; abstr TPS603), TIP.

Telli LM, Metzger O, Timms K, Evans B, Vogel D, et al. Evaluation of homologous recombination deficiency (HRD) status with pathological response to carboplatin +/- veliparib in BrighTNess, a randomized phase 3 study in early stage TNBC. J Clin Oncol 36, 2018 (suppl; abstr 519), poster discussion.

Kummel S, Wimberger P, Von Minckwitz G, Nekljudova V, Denkert C, et al. Investigating denosumab as an add-on neoadjuvant treatment for RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-paclitaxel schedules: 2x2 factorial design (GeparX)—An iterim safety analysis. J Clin Oncol 36, 2018 (suppl; abstr 569), poster.

Loibl S, Untch M, Burchardi N, Huober JB, Blohmer JU, et al. Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxaneanthracycline containing chemotherapy in triple negative breast cancer (TNBC). J Clin Oncol 36, 2018 (suppl; abstr 104), oral presentation.

Kolberg HC, Liedtke C, Bauerfeind I, Fehm TN, Fleige B, et al. Association of clinical/pathological parameters with axillary involvement in early breast cancer in patients with limited sentinel node involvement (< 3 LK) after neoadjuvant chemotherapy (NACT). J Clin Oncol 36, 2018 (suppl; abstr 559), poster.

Noske A, Weber K, Moebus V, Schmatloch S, Weichert W, et al. Tumor infiltrating lymphocytes to predict DFS from intense dose-dense (idd) EPC regimen: Results from the German Adjuvant Intergroup Node-positive study (GAIN-1). J Clin Oncol 36, 2018 (suppl; abstr 527), poster.

Matikas A, Foukakis T, Moebus V, Greil R, Bengtsson NO, et al. Dose tailoring of breast cancer adjuvant chemotherapy aiming at avoiding both over and undertreatment: Results from the prospective PANTHER study. J Clin Oncol 36, 2018 (suppl; abstr 538), poster.

Moebus V, Noeding S, Ladda E, Klare P, Schmidt M, et al. Neo-/adjuvant phase III trial to compare intense dose-dense (idd) treatment with EnPC to tailored dose-dense (dt) therapy with dtEC-dtD for patients with high-risk early breast cancer: Results on pathological complete response (pCR) for patients treated within the neoadjuvant setting. J Clin Oncol 36, 2018 (suppl; abstr 568), poster.

Denkert C, Untch M, Benz SC, Weber K, Golovato J, et al. Signatures of mutational processes and response to neoadjuvant chemotherapy in breast cancer: A genome-based investigation in the neoadjuvant GeparSepto trial. J Clin Oncol 36, 2018 (suppl; abstr 574), poster.

Rocco EG, Gray KP, Munzone E, Fumagalli C, Reforgiato MR, Leone I, et al. Molecular alterations and late recurrence in postmenopausal women with hormone receptor-positive node-positive breast cancer (BC): Results from the "SOLE" trial. J Clin Oncol 36, 2018 (suppl; abstr 517), poster discussion.

AACR:
American Association for Cancer Research, 14-18 April, 2018, Chicago, Illinois, USA
Loibl S, Treue D, Budczies J, Weber K, Stenzinger A, et al. Mutational diversity and therapy response in breast cancer – a sequencing analysis in the neoadjuvant GeparSepto trial. AACR; Cancer R Des 2018;78(13 Suppl):Abstract nr LB-027, poster.

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.

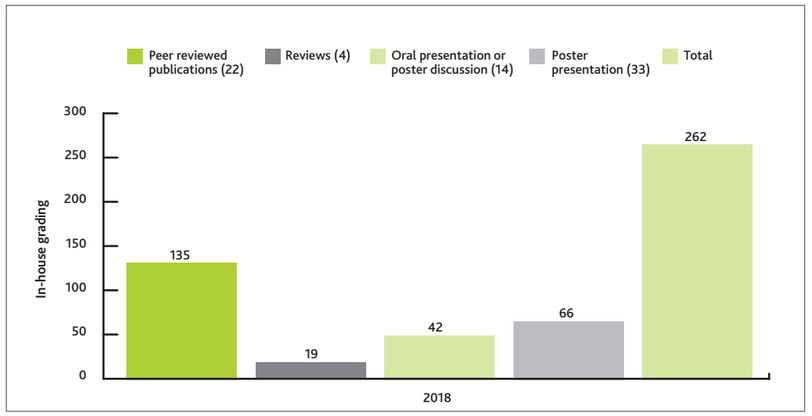


Figure 3: Overview of GBG's in-house grading for publications in 2018

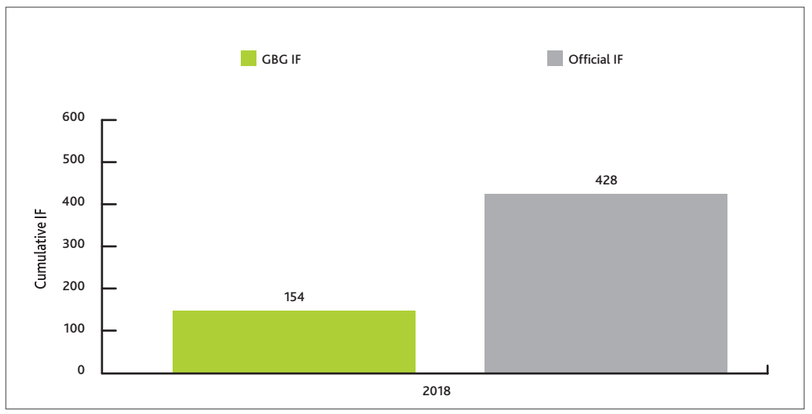


Figure 4: GBG and official Impact Factor (IF) in 2018

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:

GBG 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

GBG 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)

GBG 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

GBG 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

GBG 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

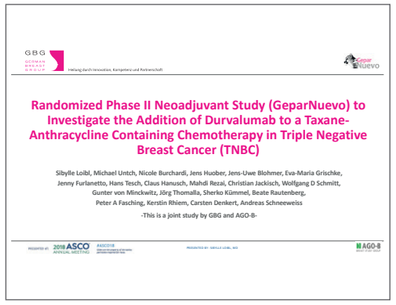
GBG Publications on translational research project

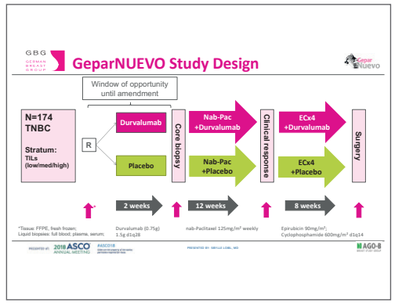
- Project leader (should prepare manuscript)
- Involved team member of this TRAFO project
- TRAFO board / protocol board members*
- Biomaterial provider
- 1-2 local pathologists providing most tumor tissue
- Biometrician
- PI (if involved in TRAFO project)

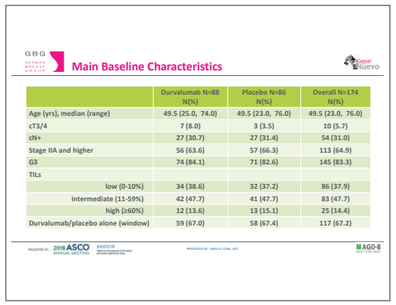
* Subboard and protocol board members will share in general authorships with best biomaterial providers on a 2:1 basis

4.6. Oral and poster presentations

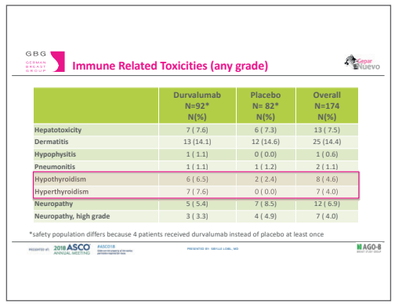
GeparNUEVO study (ASCO 2018)







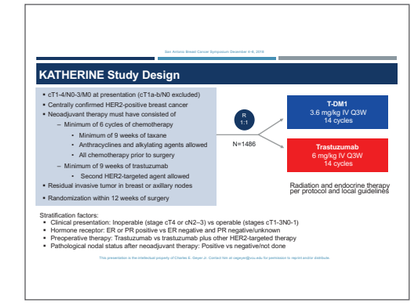
	Durvalumab N=88 N(%)	Placebo N=86 N(%)	Overall N=174 N(%)
Age (yrs), median (range)	49.5 (25.0, 74.0)	49.5 (23.0, 76.0)	49.5 (23.0, 76.0)
cT3/4	7 (8.0)	3 (3.5)	10 (5.7)
cN+	27 (30.7)	27 (31.4)	54 (31.0)
Stage IIA and higher	56 (63.6)	57 (66.3)	113 (64.9)
G3	74 (84.1)	71 (82.6)	145 (83.3)
TILs			
low (0-10%)	34 (38.6)	32 (37.2)	86 (37.9)
intermediate (11-59%)	42 (47.7)	41 (47.7)	83 (47.7)
high (≥60%)	12 (13.6)	13 (15.1)	25 (14.4)
Durvalumab/placebo alone (window)	59 (67.0)	58 (67.4)	117 (67.2)

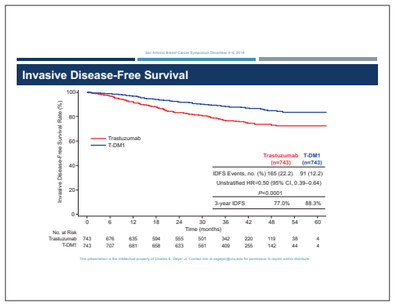


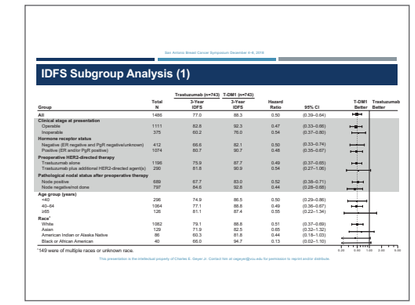
	Durvalumab N=92* N(%)	Placebo N= 82* N(%)	Overall N=174 N(%)
Hepatotoxicity	7 (7.6)	6 (7.3)	13 (7.5)
Dermatitis	13 (14.1)	12 (14.6)	25 (14.4)
Hypophysitis	1 (1.1)	0 (0.0)	1 (0.6)
Pneumonitis	1 (1.1)	1 (1.2)	2 (1.1)
Hyporthyroidism	6 (6.5)	2 (2.4)	8 (4.6)
Hyperthyroidism	7 (7.6)	0 (0.0)	7 (4.0)
Neuropathy	5 (5.4)	7 (8.5)	12 (6.9)
Neuropathy, high grade	3 (3.3)	4 (4.9)	7 (4.0)

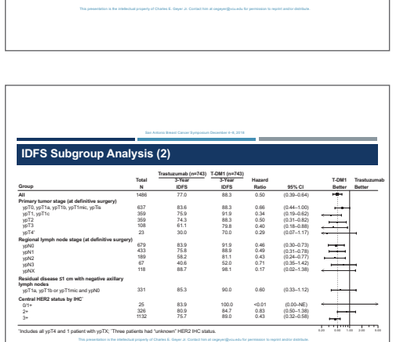
*safety population differs because 4 patients received durvalumab instead of placebo at least once

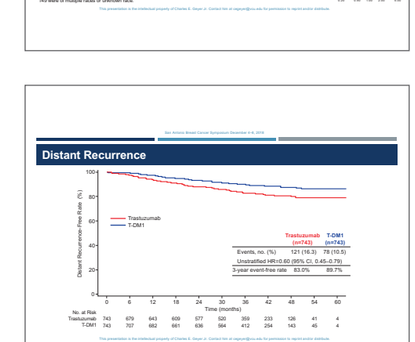
KATHERINE study (SABCS 2018)

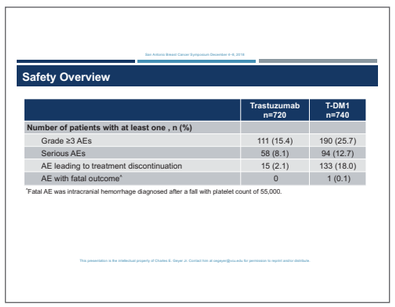






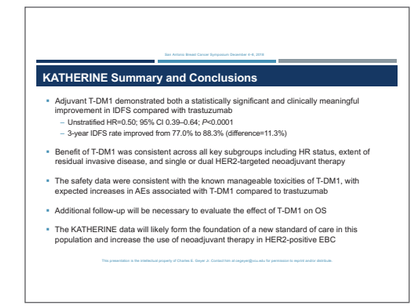






	Trastuzumab n=720	T-DM1 n=740
Number of patients with at least one , n (%)		
Grade ≥3 AEs	111 (15.4)	190 (25.7)
Serious AEs	58 (8.1)	94 (12.7)
AE leading to treatment discontinuation	15 (2.1)	133 (18.0)
AE with fatal outcome*	0	1 (0.1)

*Fatal AE was intracranial hemorrhage diagnosed after a fall with platelet count of 55,000.



Mutational diversity and therapy response in breast cancer – a sequencing analysis in the neoadjuvant GeparSepto trial

Sibylle Loibl[1], Denise Treue[2], Jan Budczies[2], Karsten Weber[1], Albrecht Stenzinger[3], Wolfgang D. Schmitt[2], Wilko Weichert[4], Paul Jank[2], Jenny Furlanetto[1], Frederick Klauschen[2], Thomas Karn[5], Nicole Pfarr[4], Gunter von Minckwitz[1], Annika Lehmann[2], Christian Jackisch[6], Christine Sers[2], Andreas Schneeweiss[7], Peter A. Fasching[8], Christian Schem[9], Michael Hummel[2], Marion van Mackelenbergh[10], Valentina Nekljudova[1], Michael Untch[11], Carsten Denkert[2]

LB-027

[1]German Breast Group, Neu-Isenburg, Germany; [2]Charité-Universitätsmedizin, Berlin, Germany; [3]Universitätsklinikum Heidelberg, Germany; [4]Institut für Allgemeine Pathologie und Pathologische Anatomie, Technische Universität München, Germany; [5]Universitätsklinikum, Frankfurt, Germany; [6]Sana Klinikum Offenbach, Germany; [7]Gynäkologische Onkologie, Nationales Centrum für Tumorerkrankungen Universitätsklinikum, Heidelberg, Germany; [8]Universitätsklinikum Erlangen, Germany; [9]Mammazentrum Hamburg, Germany; [10]Klinik für Gynäkologie und Geburtshilfe Universitätsklinikum Schleswig-Holstein, Kiel, Germany; [11]Helios Kliniken Berlin Buch, Germany

Background

Targeted next-generation sequencing (NGS) enables investigation of key molecular events in breast cancer (BC) and driver genes[1]. Pathological complete response (pCR) rate in the GeparSepto trial (NCT01583426) was significantly higher in patients treated with nab-paclitaxel (NAB-P) instead of paclitaxel (Pac)[2]. In the HER2-positive BC *PIK3CA* mutations predicted lower pCR to a dual anti-HER2 treatment[3]. In this study we evaluated the relevance of mutations and amplifications in 21 cancer genes for response to neoadjuvant chemotherapy (NACT) in the GeparSepto cohort.

Patients and Methods

A total of 851 pretherapeutic formalin-fixed paraffin embedded (FFPE) core biopsies from the GeparSepto trial were analysed by targeted NGS. A panel of 16 genes for mutations and 8 genes for amplifications was used (Figure 1). Associations between the gene status, baseline characteristics and pCR rate were evaluated with Fisher's exact and X^2 tests. Odds ratios (OR) with 95% confidence intervals (CI) and 2-sided p-values are shown.

Objectives

- **Primary objective:** to assess the predictive value of *PIK3CA* mutations for response to NACT.
- **Secondary objective:** to investigate additional mutations and amplifications in the different BC subtypes for response to neoadjuvant chemotherapy.

Table 1. Baseline characteristics

Parameter	Category	analysed setting (n=851)	not analysed setting (n=355)	p-value
Age (years)	≤40	162 (19.0%)	72 (20.3%)	0.857
	>40-50	320 (37.6%)	129 (36.3%)	
	>50	369 (43.4%)	154 (43.4%)	
Tumor stage	cT1	268 (31.7%)	126 (36.0%)	0.187
	cT2	452 (53.5%)	176 (50.3%)	
	cT3	75 (8.9%)	22 (6.3%)	
	cT4 a-d	50 (5.9%)	26 (7.4%)	
Nodal status	cN0	538 (64.4%)	229 (66.2%)	0.592
	cN+	298 (35.6%)	117 (33.8%)	
Grading	G1-2	399 (46.9%)	150 (42.3%)	0.145
	G3	452 (53.1%)	205 (57.7%)	
Treatment	Pac	414 (48.6%)	186 (52.4%)	0.255
	NAB-P	437 (51.4%)	169 (47.6%)	
BC subtype	HER2+	295 (34.7%)	101 (28.5%)	<0.001
	Luminal/HER2-	397 (46.7%)	137 (38.6%)	
	TNBC	159 (18.7%)	117 (33.0%)	

Results

Figure 1. Consort statement

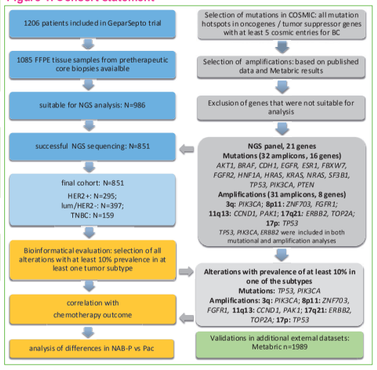


Figure 2. Molecular diversity of genomic alterations in the complete cohort (A) and within the BC subtypes

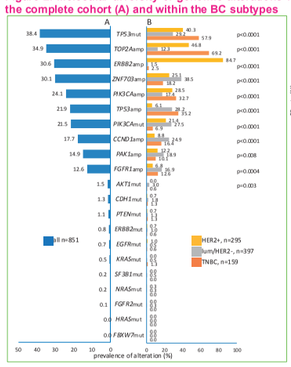
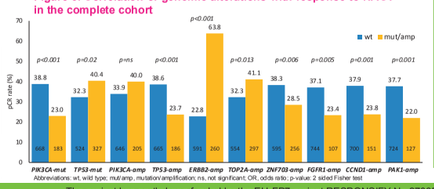


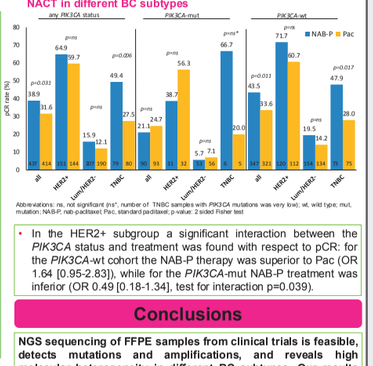
Figure 3. Correlation of genomic alterations with response to NACT in the complete cohort



Abbreviations: wt, wild type; mut/amp, mutation/amplification; ns, not significant; OR, odds ratio; p-value: 2 sided Fisher test

- Overall, the most prevalent mutations (*TP53* and *PIK3CA*) and amplifications (*CCND1, ERBB2, FGFR1, PAK1, TOP2A, TP53, ZNF703* [Figure 2]) were significantly associated with variations in pCR rate (Figure 3).
- *PIK3CA* mutations predicted a significantly lower pCR rate compared to *PIK3CA*-wt BC (OR 0.47 [0.32-0.69], p<0.001) (Figure 3).
- An increased pCR rate was observed in the *PIK3CA*-wt cohort treated with NAB-P compared to Pac (OR 1.52 [1.11-2.08], p=0.009) (Figure 4).

Figure 4. Correlation of *PIK3CA* status with response to NACT in different BC subtypes



Abbreviations: ns, not significant (ns*, number of TNBC samples with PIK3CA mutations was very low); wt, wild type; mut, mutation; NAB-P, nab-paclitaxel; Pac, standard paclitaxel; p-value: 2 sided Fisher test

- In the HER2+ subgroup a significant interaction between the *PIK3CA* status and treatment was found with respect to pCR: for the *PIK3CA*-wt cohort the NAB-P therapy was superior to Pac (OR 1.64 [0.95-2.83]), while for the *PIK3CA*-mut NAB-P treatment was inferior (OR 0.49 [0.18-1.34], test for interaction p=0.039).

Conclusions

NGS sequencing of FFPE samples from clinical trials is feasible, detects mutations and amplifications, and reveals high molecular heterogeneity in different BC subtypes. Our results point to *PIK3CA* as a major mechanism of therapy resistance in BC, which might also be relevant for response to NAB-P vs standard Pac. Hence, NGS holds promise in identify markers of therapy resistance as a basis for individualized and new molecular-targeted BC therapies.

References

1. Nik-Zainal S, Davies H, Staaf J, et al. Landscape of somatic mutations in 560 breast cancer whole-genome sequences. Nature. 2016;534:47-54; 2. Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016;17:345-56; 3. Loibl S, von Minckwitz G, Schneeweiss A, et al. *PIK3CA* mutations are associated with lower rates of pathological complete response (pCR) to anti-HER2 therapy in primary HER2 overexpressing breast cancer. J Clin Oncol 2014; 32:3212-20.

Presented at AACR Annual Meeting 2018 in Chicago– April 14-18, 2018

The project has partly been funded by the EU-FP7 project RESPONSIFY No 278659, TH4-RESPONSE, German Cancer Aid project TransLUMINAL-B and the German Cancer Consortium (DKTK)

Tumor infiltrating lymphocytes predict better DFS from intense dose-dense (idd) EPC regimen – results from the German Adjuvant Intergroup Node-positive Study (GAIN-1)

Aurelia Noske[1], Karsten Weber[2], Volker Möbus[3], Sabine Schmatloch[4], Wilko Weichert[1], Claus-Henning Köhne[5], Christine Solbach[6], Barbara Ingold-Heppner[7], Katja Steiger[1], Volkmar Müller[8], Peter Fasching[9], Thomas Kam[6], Marion van Mackelenbergh[10], Frederik Marmé[11], Wolfgang D. Schmitt[7], Christian Schem[12], Elmar Stickeler[13], Carsten Denkert[7], Sibylle Loibl[2]

[1]Institut für Pathologie, Technische Universität München, Germany; [2]German Breast Group, Neu-Isenburg, Germany; [3]Klinikum Frankfurt-Höchst, Germany; [4]Brustzentrum, Elisabeth Krankenhaus, Kassel, Germany; [5]Universitätsklinik für Innere Medizin – Onkologie und Hämatologie, Oldenburg, Germany; [6]Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Frankfurt, Germany; [7]Institut für Pathologie, Charité – Universitätsmedizin Berlin, Germany; [8]Universitätsklinikum Hamburg-Eppendorf, Germany; [9]Universitätsklinikum Erlangen, Germany; [10]Universitätsklinikum Kiel; [11]Universitätsklinikum Heidelberg, Germany; [12]Mammazentrum Hamburg – Brustklinik am Krankenhaus Jerusalem, Germany; [13]Klinik für Gynäkologie und Geburtsmedizin, Uniklinik RWTH Aachen

Abstract ID: 527
Poster Board #19

Background

Immunogenic infiltrate in breast cancer may influence the prognosis and response to systemic therapies. TILs are predictive for a pathological complete response in neoadjuvant treated breast cancer [1]. Less is known about the predictive role in the adjuvant setting. The association and prognostic role of tumor infiltrating lymphocytes (TILs), PD-1 and PD-L1 expression were investigated in high-risk, node positive breast carcinomas with different intrinsic molecular subtypes. We further evaluated a potential benefit of adjuvant chemotherapy regimens.

Patients and Methods

The prospective adjuvant phase III GAIN-1 trial compared two dose-dense regimens, iddEPC (epirubicin (E), paclitaxel (P), cyclophosphamide (C)) vs. EC-PX (capecitabine (X)) and Ibandronate vs. observation in patients with node-positive primary breast cancer (Figure 1A) [2]. Intrinsic molecular subtypes were defined as following: Luminal A (ER/PR+, HER2 -, Ki67 ≤20%), Luminal B (ER/PR+, HER2+/-, Ki67 ≥21%), HER2+/HR- (ER/PR-), triple-negative (TNBC) (ER/PR-, HER2-). A total of 1318 FFPE tumor samples were available for analysis of TILs by H&E morphology [3], and PD-1, and PD-L1 (SP263) by immunohistochemistry (Figure 1B). The association of immune parameters and their prognostic and potential predictive role were analyzed by Cox regression models. The median FU was 74.3 months (range: 0.1-113.7).

Figure 1 Study design (A) and tumor analysis set (B)

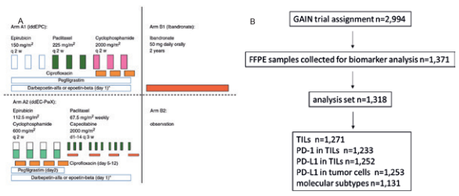


Figure 2 Increased TILs (HE) and PD-1 and PD-L1 positive TILs

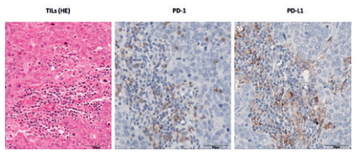
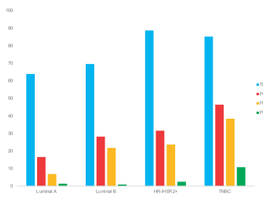


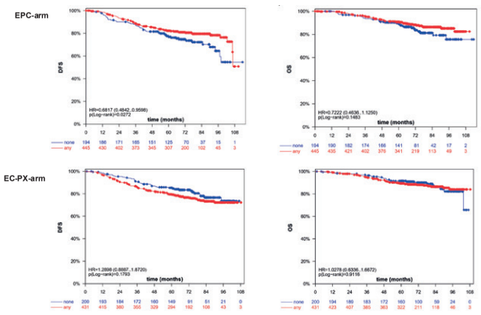
Figure 3 Distribution of TILs, PD-1 and PD-L1 positive TILs and tumor cells (TC) among the molecular subtypes



Results

Increased TILs as well as PD-1 and PD-L1 positive TILs (cut-off ≥1%, each, [4] Figure 2) were significantly associated with higher tumor grade, higher Ki67, ER/PR negative and triple negative breast cancer (each p<0.0001). TILs and PD-L1 positive TILs were slightly more frequent in HER2 positive BC (p=0.0051 and p=0.0036, respectively) (Figure 3).
At multivariate Cox regression analysis with clinical covariables, TILs had a significant positive impact on DFS in the iddEPC-arm (HR=0.57 [0.39-0.84], p=0.0043) but not in the EC-PX-arm (HR=1.26 [0.86-1.87], p=0.2384, interaction p=0.0336) (Figure 4). Especially, HR+/HER2- BC with TILs and treated with iddEPC had a better DFS compared to no TILs (HR=0.59 [0.38-0.93], p=0.0227). PD-1 positive TILs in TNBC were associated with a significant better DFS (HR=0.50 [0.25-0.99], p=0.0457). PD-L1 expression had no impact on patient outcome.

Figure 4 Kaplan-Meier analysis



Conclusions

1. TILs and expression of PD-1/PD-L1 are common in high-grade, highly proliferative, triple negative and in part in HER2 positive breast cancer.
2. TILs predict the benefit from intense dose-dense EPC.
3. The prevalence and prognostic impact of PD-1/PD-L1 seem to play an inferior role in this node-positive breast cancer cohort with adjuvant chemotherapy.

References

1. Denkert C et al. Tumor-infiltrating lymphocytes and prognosis in different subtypes of breast cancer: a pooled analysis of 3771 patients treated with neoadjuvant therapy. Lancet Oncol 2018
2. Moebus V et al. German Adjuvant Intergroup Node-positive Study (GAIN): A Phase III Trial Comparing Two Dose-Dense Regimens (ddEPC vs. ddEC-PwX) in High-Risk Early Breast Cancer Patients. Ann Oncol 2017
3. Salgado R et al. The evaluation of tumor-infiltrating lymphocytes (TILs) in breast cancer: recommendations by an International TILs working group 2014. Ann Oncol 2015
4. Nanda et al. Pembrolizumab in patients with advanced TNBC: Phase Ib Keynote 012. JCO 2016

Presented at ASCO Annual Meeting 2018, Chicago, IL, USA, June 1-5 :

The study was financially supported by German Cancer Aid project TransLUMINAL-B

Investigating denosumab as an add-on neoadjuvant treatment for RANK/L-positive or RANK/L-negative primary breast cancer and two different nab-paclitaxel schedules - 2x2 factorial design (GeparX) – an interim safety analysis

Kümmel S[1], Wimberger P[2], von Minckwitz G[3], Nekljudova V[3], Denkert C[4], Just M[5], Hanusch C[6], Stötzer O[7], Huober J[8], Hofmann M[9], Jackisch C[10], Blohmer J U[4], Vladimirova V[3] , Schneeweiss A[11], Untch M[12], Loibl S[3]
[1]Kliniken Essen Mitte, Essen, Germany; [2]Universitätsklinikum TU Dresden, Germany; [3]German Breast Group, Neu-Isenburg, Germany; [4]Charité-Universitätsmedizin Berlin, Germany; [5]Onkologische Schwerpunktpraxis Bielefeld, Germany; [6]Rotkreuzklinikum München, Germany; [7]Medizinisches Zentrum für Hämatologie und Onkologie München, Germany; [8]Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Ulm, Germany; [9]Klinik für Gynäkologie und Geburtshilfe, Marienhospital Stuttgart, Germany; [10]Sana Klinikum Offenbach, Germany; [11]Nationales Centrum für Tumorerkrankungen, Heidelberg, Germany; [12]Helios Klinikum Berlin-Buch, Berlin, Germany

Abstract ID: 569
Poster Board #61

Background

RANK ligand (RANKL) functions via its receptor RANK. Pharmacologic inhibition of RANKL and osteoclastic bone resorption can prevent or delay bone metastasis in patients with breast cancer (BC)[1] and may improve disease-free survival[2]. In addition, high RANK expression was associated with higher pathological complete response (pCR) rates in the GeparTrio trial[3]. The GeparX study aims to investigate whether denosumab, an antibody targeting RANKL, increases the pCR rate when added to an anthracycline/taxane containing neoadjuvant chemotherapy (NACT) in patients (pts) with primary breast cancer (BC). As in the GeparSepto trial nab-paclitaxel (nP) lead to an increased pCR rate compared to standard solvent-based paclitaxel[4], two different nP schedules (nP weekly vs nP d1,8 q22) are compared.

Patients and Methods

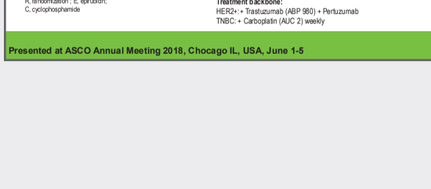
Trial design: GeparX enrolls pts with primary cT1c-cT4d BC, after central assessment of HER2, HR, TILs, Ki67. Study design is shown in Figure 1.

Statistical consideration: Sample size (primary endpoint) planning assumed a pCR improvement by denosumab from 35% to 46% (OR=1.58; 2-sided α=0.10; 92% power) and by different NACT schedule from 36% to 45% (OR=1.45; 2-sided α=0.10; 80% power; overall α=0.20), requiring 778 patients. An interim safety analysis was performed after the first 200 pts have completed nP treatment.

Objectives

Co-primary objectives: to compare the pCR (ypT0 ypN0) rates after NACT+/- denosumab and the pCR rates between nP 125 mg/m² weekly and nP 125 mg/m² d1,8 q22. ***Secondary objectives:*** to assess other pCR definitions for both randomizations; breast conservation rates; toxicity, compliance and survival.

Figure 1: Study design



Results

Figure 2. Consort statement

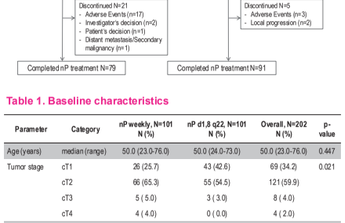


Table 1. Baseline characteristics

Parameter	Category	nP weekly N=101 N (%)	nP d1,8 q22, N=101 N (%)	Overall, N=202 N (%)	p-value
Age (years)	median (range)	50.0 (23.0-76.0)	50.0 (24.0-73.0)	50.0 (23.0-76.0)	0.447
Tumor stage	cT1	26 (25.7)	43 (42.6)	69 (34.2)	0.021
	cT2	66 (65.3)	55 (54.5)	121 (59.9)	
	cT3	5 (5.0)	3 (3.0)	8 (4.0)	
	cT4	4 (4.0)	0 (0.0)	4 (2.0)	
Nodal status*	cN0	61 (60.4)	64 (63.4)	125 (61.9)	0.772
	cN+	40 (39.6)	37 (36.6)	77 (38.1)	
Ki67	≤20%	19 (18.8)	16 (15.8)	35 (17.3)	0.710
	>20%	82 (81.2)	85 (84.2)	167 (82.7)	
LPBC**	≤50%	96 (95.0)	96 (95.0)	192 (95.0)	1.000
	>50%	5 (5.0)	5 (5.0)	10 (5.0)	
BC subtype**	HER2-/HR+	51 (50.5)	51 (50.5)	102 (50.5)	1.000
	TNBC	41 (40.6)	41 (40.6)	82 (40.6)	
	HER2+	9 (8.9)	9 (8.9)	18 (8.9)	
EC**	q2w	40 (39.6)	42 (41.6)	82 (40.6)	0.886
	q3w	61 (60.4)	59 (58.4)	120 (59.4)	

*Clinical nodal status positive (cN+) if, LN biopsy or SNB positive (irrespectively of sonography/palpation) or cN+ by sonography (irrespectively of palpation) and no LN biopsy performed or cN+ by palpation and no sonography and no LN biopsy performed; **stratification factor; LPBC, lymphocyte predominant BC

Table 2. Patients's discontinuation during nP treatment

Patient status	nP weekly N (%)	nP d1,8 q22 N (%)	p-value	With Denosumab N (%)	Without Denosumab N (%)	p-value
All patients	**N=100**	**N=96**		**N=97**	**N=99**	
Completed nP	79 (79.0)	91 (94.8)	0.001	84 (86.6)	86 (86.9)	1.000
Discontinued nP	21 (21.0)	5 (5.2)		13 (13.4)	13 (13.1)	
- Local progressions	0 (0.0)	2 (2.1)		1 (1.0)	1 (1.0)	
- Distant metastasis/ Secondary malignancy	1 (1.0)	0 (0.0)		0 (0.0)	1 (1.0)	
- Patient/investigator decision	3 (3.0)	0 (0.0)		2 (2.1)	1 (1.0)	
- AEs	17 (17.0)	3 (3.1)		10 (10.3)	10 (10.1)	
TNBC*	**N=43**	**N=40**		**N=40**	**N=43**	
Completed carboplatin	31 (72.1)	36 (90.0)	0.052	32 (80.0)	35 (81.4)	1.000
Discontinued carboplatin	12 (27.9)	4 (10.0)		8 (20.0)	8 (18.6)	
- Local progressions	0 (0.0)	1 (2.5)		1 (2.5)	0 (0.0)	
- Distant metastasis/ Secondary malygnancy	1 (2.3)	0 (0.0)		0 (0.0)	1 (2.3)	
- investigator decision	2 (4.7)	1 (2.5)		3 (7.5)	0 (0.0)	
- AEs	9 (20.9)	2 (5.0)		4 (10.0)	7 (16.3)	
HER2+		**Overall, N=18**				
Completed ABP 980		13 (72.2)				
Under ABP 980 treatment		5 (27.8)				
Discontinued ABP 980		0 (0.0)				
Completed pertuzumab		11 (61.1)				
Under pertuzumab treatment		5 (27.8)				
Discontinued pertuzumab		2 (11.1)				
- AE		2 (11.1)				

*3 patients with non-TNBC (two in nP weekly arm and one in nP d1,8 q22 arm) who received carboplatin are included; ABP 980, trastuzumab biosimilar (Amgen)

Table 3. The most frequent AEs during nP treatment

AE	Grade	nP weekly N=100 N (%)	nP d1,8 q22 N=96 N (%)	p-value	With Denosumab N=97, N (%)	Without Denosumab N=99, N (%)	p-value
Any AE	any	100 (100.0)	96 (100.0)	n.a.	97 (100)	99 (100)	n.a.
	3-4	37 (37.0)	37 (38.5)	0.883	37 (38.1)	37 (37.4)	1.000
Any hematological AE	any	98 (98.0)	92 (95.8)	0.438	94 (96.9)	96 (97.0)	1.000
	3-4	17 (17.0)	26 (27.1)	0.120	19 (19.6)	24 (24.2)	0.491
Anemia	any	92 (92.0)	84 (87.5)	0.350	88 (90.7)	88 (88.9)	0.814
	3-4	1 (1.0)	3 (3.1)	0.361	1 (1.0)	3 (3.0)	0.621
Leukopenia	any	85 (85.0)	86 (89.6)	0.395	81 (83.5)	90 (90.9)	0.138
	3-4	2 (2.0)	10 (10.4)	0.017	5 (5.2)	7 (7.1)	0.767
Neutropenia	any	73 (73.0)	69 (71.9)	0.874	69 (71.1)	73 (73.7)	0.750
	3-4	16 (16.0)	23 (24.0)	0.210	18 (18.6)	21 (21.2)	0.721
Any non-hematological AE	any	100 (100.0)	96 (100.0)	n.a.	97 (100)	99 (100)	n.a.
	3-4	22 (22.0)	14 (14.6)	0.200	20 (20.6)	16 (16.2)	0.464
Increased ALAT	any	53 (53.0)	33 (34.4)	0.010	43 (44.3)	43 (43.4)	1.000
	3-4	4 (4.0)	5 (5.2)	0.744	5 (5.2)	4 (4.0)	0.746
Peripheral neuropathy (PNP)	any	67 (67.0)	55 (57.3)	0.186	63 (64.9)	59 (59.6)	0.464
	3-4	4 (4.0)	0 (0.0)	0.121	3 (3.1)	1 (1.0)	0.366
Pneumonia*	any	2 (2.0)	1 (1.0)	1.000	1 (1.0)	2 (2.0)	1.000
	3-4	2 (2.0)	1 (1.0)	1.000	1 (1.0)	2 (2.0)	1.000
Infection other than pneumonia**	any	38 (38.0)	26 (27.1)	0.128	35 (36.1)	29 (29.3)	0.361
	3-4	4 (4.0)	3 (3.1)	1.000	2 (2.1)	5 (5.1)	0.445
Any AESI	n.a.	2 (2.0)	1 (1.0)	1.000	1 (1.0)	2 (2.0)	1.000
Any SAE (overall)	n.a.	18 (18.0)	10 (10.4)	0.155	16 (16.5)	12 (12.1)	0.419
Any SAE in HER2-/HR+	n.a.	10 (10.5)					
Any SAE in TNBC	n.a.	16 (19.3)					
Any SAE in HER2+	n.a.	2 (11.1)					

N, number of patients; AE, adverse event; AESI, AE of special interest; SAE, serious AE; *AESI any grade for HER2+ patients; **AESI grade 3-4 for HER2+ patients

- A total of 202 patients randomized to the denosumab and nP treatment were included in the interim analysis, of them 196 started treatment (Figure 2). Baseline characteristics are shown in Table 1.
- Overall, 13.5% of patients with and 13.1% without denosumab discontinued nP and 21.0 % of patients with nP weekly vs 5.2% with nP d1,8 q22 discontinued nP mainly due to AEs (Table 2).
- 17.0% of patients treated with nP weekly and 27.1% with nP d1,8 q22 reported high grade (grade 3-4) hematological AEs, while 22.0% of patients treated with nP weekly and 14.6% with nP d1,8 q22 had high grade non-hematological AEs (Table 3). During nP treatment overall, 37 SAEs (13 in the HER2-/HR+; 22 in the TNBC and 2 in the HER2+ cohorts) have occurred in a total of 28 patients.

Conclusions

- **The addition of denosumab to NACT does not increase toxicity.**
- **Weekly nP resulted in a higher rate of treatment discontinuations mainly due to non-serious AEs.**
- **The addition of carboplatin resulted in a higher rate of SAEs.**

References

1. Gnant M, Pfeiler G, Dubsky PC et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet 2015; 386:433-43.
2. Del Mastro L et al. Fluorouracil and dose-dense chemotherapy in adjuvant treatment of patients with early-stage breast cancer: an open-label, 2x2 factorial, randomised phase 3 trial. Lancet 2015;385 1863-72.
3. Ibrahim NK et al. Multicenter phase II trial of ABI-007: an albumin-bound paclitaxel, in women with metastatic breast cancer. J Clin Oncol 2005;23:6019-26
4. Möbus V et al. Adjuvant phase III trial to compare intense dose-dense adjuvant treatment with EnPC to dose dense, tailored therapy with dtEC-dtD for patients with high-risk early breast cancer (GAIN-2). J Clin Oncol 2013, 31(suppl; abstr TPS1137)

Presented at ASCO Annual Meeting 2018, Chocago IL, USA, June 1-5

The trial was financially supported by Amgen and Celgene

Neo-/adjuvant phase III trial to compare intense dose-dense (idd) treatment with EnPC to tailored dose-dense (dt) therapy with dtEC-dtD for patients with high-risk early breast cancer: results on pathological complete response (pCR) within the neoadjuvant setting

V. Moebus[1], S. Noeding[2], E. Ladda[3], P. Klare[4], M. Schmidt[5], A. Schneeweiss[6], W. Janni[7], F. Marme[8], T. Reimer[9], S. Schmatloch[10], E. Stickeler[11], M. Untch[12], B. Sinn[13], V. Müller[14], P.A. Fasching[15], G. von Minckwitz[16], J. Furlanetto[16], Nicole Burchardi[16], S. Loibl[16]
1.Klinikum Frankfurt-Höchst; 2.Gynäkologisch-onkologische Praxis Hannover; 3.Praxis Klinikum Neumarkt; 4.Praxisklinik Krebsheilkunde für Frauen, Brustzentrum Berlin; 5.Universitätsfrauenklinik Mainz; 6.Nationales Centrum für Tumorerkrankungen, Heidelberg; 7.Frauenheilkunde und Geburtshilfe, Universitätsklinikum Ulm; 8.Allgemeine Frauenheilkunde und Geburtshilfe, Universitätsklinikum Heidelberg; 9.Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock; 10.Brustzentrum, Elisabeth Krankenhaus Kassel; 11.Frauenheilkunde und Geburtshilfe, Universitätsklinikum Freiburg; 12.HELIOS Klinikum Berlin Buch; 13.Institut für Pathologie, Charité - Universitätsmedizin Berlin; 14.Universitätsklinikum Hamburg-Eppendorf; 15.Universitätsklinikum Erlangen; 16.GBG Forschung GmbH

Abstract ID: 568
Poster Board #60

Background

Sequential administration of single-agent therapies allows high doses and dose-dense intervals. Such intense dose-dense (idd) regimen (q2w) significantly improved recurrence-free and overall survival compared to conventional dosed chemotherapy (q3w).[1,2] nab-Paclitaxel provides a better toxicity profile and higher efficacy compared to solvent-based taxanes and might therefore be preferred in an idd regimen.[3] The primary aim of the GAIN2 study was to compare the 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.[4]
Originally the study was set up as an adjuvant trial. An amendment opened the study for the enrolment of patients in the neoadjuvant setting. Neoadjuvant chemotherapy is as effective as adjuvant chemotherapy in preventing recurrences. **We report pCR rates in the breast per arm (ypT0) in the neoadjuvant cohort.**

Materials and Methods

Trial design: GAIN-2 (GBG 68; NCT01690702) was a multicenter, prospective, randomized, open-label phase III trial . The study design is presented in Figure 1.

Statistical considerations: Sample size was calculated for the primary endpoint IDFS, the neoadjuvant cohort comprises 598 patients. A two-sided continuity corrected χ2-test with α = 0.05 was used to compare pCR rates in patients, who started treatment.

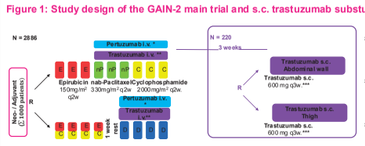
Objectives

Primary objective: to compare IDFS after neo- / adjuvant chemotherapy between the two arms.

Main secondary objectives:

- to compare pCR rates according to different definitions (ypT0 ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0) between arm separately for the stratified subpopulations
- to compare loco-regional invasive recurrence free (LRRFS), local relapse-free survival (LRFS), regional relapse-free survival (RRFS), distant-disease-free (DDFS), and overall survival (OS) between arms and according to predefined subpopulations
- Toxicity and compliance

Figure 1: Study design of the GAIN-2 main trial and s.c. trastuzumab substudy



Results

Figure 2. Consort statement

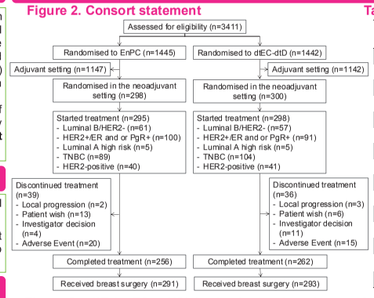


Table 1. Baseline characteristics

Parameter	Category	EnPC (n=295) N (%)*	dtEC-dtD (n=298) N (%)*
Age, years	Median (range)	49.0 (24.0-67.0)	49.0 (20.0-69.0)
cT	cT1-2	272 (92.2)	264 (88.9)
	cT3	11 (3.7)	14 (4.7)
	cT4	12 (4.1)	19 (6.4)
cN	cN0	127 (45.7)	126 (43.9)
	cN1	119 (42.8)	122 (42.5)
	cN2-3	32 (11.6)	39 (13.6)
ER/PgR (central)	ER and/or PgR positive	165 (55.9)	162 (54.4)
HER2 (central)	positive	140 (47.5)	132 (44.3)
Tumor grading	G1	3 (1.0)	3 (1.0)
	G2	105 (35.6)	110 (36.9)
	G3	187 (63.4)	185 (62.1)
Ki67 (central)	>20%	258 (87.5)	263 (88.3)
Histological tumor type	ductal/ductal-lobular invasive	223 (75.6)	217 (72.8)
	lobular invasive/other	72 (24.4)	81 (27.2)

*valid percent

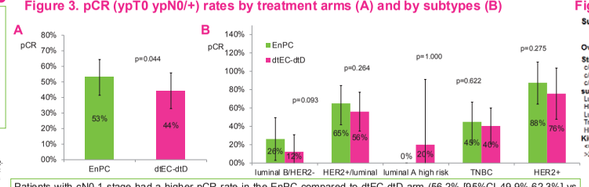
Table 2. Most common SAEs

SAEs	EnPC (N)	dtEC-dtD (N)
Leukopenia	8	13
Neutropenia	17	9
Febrile neutropenia	31	8
Anaemia	5	3
Diarrhoea	7	5
Nausea	4	2
General physical health deterioration	12	6
PSN	2	0
Pneumonitis	0	2
Pyrexia	18	13
Pneumonia	2	6

*Serious Adverse Events

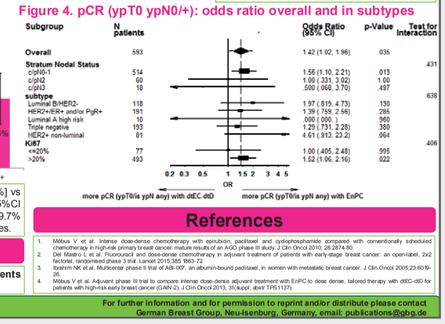
Overall 114 (38.3%) patients in the EnPC and 94 (31.3%) in the dtEC-dtD arm had at least one SAE.
One death in the dtEC-dtD arm was reported during study treatment (sudden death), none in the EnPC arm.

Figure 3. pCR (ypT0 ypN0/+) rates by treatment arms (A) and by subtypes (B)



Patients with cN0-1 stage had a higher pCR rate in the EnPC compared to dtEC-dtD arm (56.2% [95%CI 49.9%-62.3%] vs 44.9% [95%CI 38.7%-51.2%] ; p=0.014) as well as patients with Ki67>20% (54.4% [95%CI 48.0%-60.7%] vs 42.4% [95%CI 36.2%-48.9%]; p=0.010). pCR rate defined as ypT0/is ypN0/+ was 58.3% [95%CI 52.4%-64.0%] in the EnPC arm vs 49.7% [95%CI 43.8%-55.5%] in the dtEC-dtD arm (p=0.043). No significant difference was found within the breast cancer subtypes.

Figure 4. pCR (ypT0 ypN0/+): odds ratio overall and in subtypes



Conclusions

The GAIN-2 trials shows a statistically significant difference in terms of pCR rates within the breast for patients receiving iddEnPC compared to dtEC-dtD as neoadjuvant chemotherapy.

Presented at ASCO Annual Meeting 2018, Chicago, Illinois, USA, June 1-5, 2018

Financial and Drug Supply was provided by by Amgen, Celgene and Roche (only for the HER2-positive substudy)

168P

Validation of the MammaTyper® pathological complete response (pCR)-score as a predictor for response after neoadjuvant chemotherapy (NACT) in patients with early breast cancer (BC)

P.A. Fasching[1], M. Laible[2], K.E. Weber[3], L. Häberle[1], R.M. Wirtz[4], C. Denkert[5], K. Schlombs[2], S. Schmatloch[6], O. Camara[7,8], H.J. Lück[9], J. Huober[10], T. Karn[11], M.T. van Mackelenbergh[12], F. Marmé[13], V. Müller[14], C. Schem[15], E. Stickeler[16], U. Sahin[2], A. Hartmann[17], S. Loibl[3], M. Untch[18]

[1]Department of Gyn/Ob, Universitätsklinik Erlangen, Germany; [2]BioNTech Diagnostics GmbH, Mainz, Germany; [3]German Breast Group (GBG) Forschungs GmbH, Neu-Isenburg, Germany; [4]STRATIFYER Molecular Pathology GmbH, Cologne, Germany; [5]Institute of Pathology, Charite Berlin Mitte, Berlin, Germany; [6]Elisabeth Krankenhaus, Kassel, Germany; [7]Universitätsklinikum Jena, Germany; [8]Hufeland Klinikum, Bad Langensalza, Germany; [9]Gynäkologisch-Onkologische Praxis, Hannover, Germany; [10]Universitätsfrauenklinik Ulm, Germany; [11]Klinik für Frauenheilkunde und Geburtshilfe, Universitätsklinikum Frankfurt, Frankfurt a.M., Germany; [12]Universitätsklinikum Kiel, Germany; [13]Universitätsklinikum Heidelberg, Germany; [14]Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany; [15]Mammazentrum Hamburg, Hospital Jerusalem, Hamburg, Germany; [16]Gynäkologie und Geburtsmedizin, Uniklin & RWTH, Aachen, Germany; [17]Institute of Pathology, University Hospital Erlangen, Germany [18]Gynäkologie und Geburtshilfe, Helios Klinikum Berlin-Buch, Berlin, Germany

Background

Pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) in early breast cancer (BC) is strongly associated with superior long term disease-free survival (DFS). Even though the prognostic impact of pCR may vary for different BC subtypes the achievement of pCR remains an important factor in clinical decision making. Current predictors of pCR like imaging, clinical and histopathological parameters may need improvement before implementation in clinical routine. The MammaTyper® test can be used to predict the probability of pCR after NACT by integrating accurate and reproducible assessment of *ERBB2*, *ESR1*, *PGR* and *MKI67* mRNA into a standardized prediction model[1]. Therefore, the aim of this study was to validate the MammaTyper® pCR-score for predicting pCR (ypT0 ypN0) after NACT in BC.

Patients and Methods

Total RNA was extracted from formalin-fixed paraffin-embedded (FFPE) tumor core needle biopsy samples of BC patients (pts) enrolled in the single arm phase II TECHNO trial[2] and the randomized phase III PREPARE trial[3] (Figure 1). MammaTyper®, a molecular *in vitro* diagnostic RT-qPCR test, was used to assess the mRNA expression of *ERBB2* (HER2), *ESR1* (estrogen receptor, ER), *PGR* (progesterone receptor, PR) and *MKI67* (Ki-67) genes from which a predefined continuous score was calculated. This retrospective analysis was conducted according to predefined objectives and statistics, unless specified otherwise.

In a discovery study samples (n=462) from the Erlangen Neoadjuvant Study Breast (ERNEST-B)[4] were used to develop a score for pCR prediction using MammaTyper® with its 4 markers. The median of this score was used to classify pts into a low or high score group. A score ≤41 predicts a low probability of pCR; score ≥42 predicts a high pCR rate.

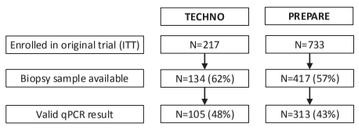


Figure 1: Availability of patients for analysis

Results

Table 1. Characteristics of samples in the analysis (N=418)

Parameter	Category	N (%)
Age	Min, Q1, Median, Q3, Max	23, 41, 48, 55, 67
ER IHC	Negative	138 (39.1%)
	Positive	215 (60.9%)
	Missing	65
PR IHC	Negative	178 (50.6%)
	Positive	174 (49.4%)
	Missing	66
HER2 IHC/ISH	Negative	255 (65.1%)
	Positive	137 (34.9%)
	Missing	26
Tumor grading	G1	7 (2.0%)
	G2	197 (55.0%)
	G3	154 (43.0%)
	Missing	60
T-stage	cT1	39 (9.7%)
	cT2	285 (70.7%)
	cT3	41 (10.2%)
	cT4	38 (9.5%)
	Missing	15
N-stage	cN0	215 (54.8%)
	cN+	177 (45.2%)
	Missing	26
Histological subtype	Ductal invasive	312 (84.8%)
	Lobular invasive	45 (12.2%)
	Other	11 (3.0%)
	Missing	50
Therapy	ddE-ddPAC (±Epo)	150 (35.9%)
	EC-PAC (±Epo)	163 (39.0%)
	EC-PACH	105 (25.1%)
pCR (ypT0 ypN0)	No	356 (85.2%)
	Yes	62 (14.8%)

Performance in all patients: From PREPARE and TECHNO valid qPCR results were available for 418 of 551 pts. Of those 14.8% had a pCR. Analyzing pCR rates according to the pCR score, pts with a low score had a pCR in 3.1% and pts with a high pCR score had a pCR in 25.1% of the cases. Applying the score from the discovery study to TECHNO and PREPARE resulted in an AUC of 0.771 [95%CI 0.715-0.827] (post-hoc analysis).

Performance in subgroups: Focusing on patients with cT1/cT2 tumors pCR rate in pts with a low score was 3.0% and 30.2% in patients with a high score. Corresponding AUC for the score was 0.805 [95%CI 0.747-0.864]. pCR rates according to the pCR score quartiles (quartile cut-offs as determined in the discovery study) for all patients and the cT1/cT2 subgroup are shown in Figure 2, and pCR scores according to molecular subgroups are shown in Figure 3. When only looking at the separation within *ERBB2*- pts who were also *ESR1*+ or *PGR*+ pCR rate was 2.7% in pts with a low score and 17.1% in pts with a high score. In *ERBB2*+ pts who were also *ESR1*+ or *PGR*+ pCR rate was 4.3% in pts with a low score and 25.4% in pts with a high score.

Performance in combination with IHC and clinical parameters: The univariate odds ratio (OR) for binary classification of cT1-2 tumors into low and high according to the cut-off 42 was 13.84 ([95% CI 5.34-35.86], p<0.0001). The binary classifier remained significant in (post-hoc) multivariable analysis including binary IHC results of ER, PR and HER2 (OR=7.55, [95% CI 2.51-22.66], p=0.0003) and also after further adding clinical variables to the model (age, tumor size, nodal status, grading, therapy) (OR=5.58, [95% CI 1.64-19.04], p=0.0060).

Prognosis: In the subgroup of pts with cT1/cT2 tumors and no pCR the mRNA based score (low vs. high) was significantly associated with DFS and overall survival (OS) with samples with low score values having better outcomes (Figure 4).

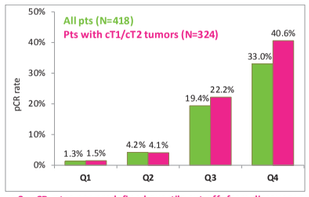


Figure 2. pCR rates per predefined quartile cut-offs from discovery cohort

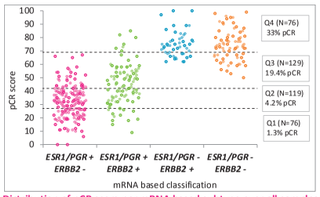


Figure 3. Distribution of pCR score per mRNA based subtype over all samples (N=418)

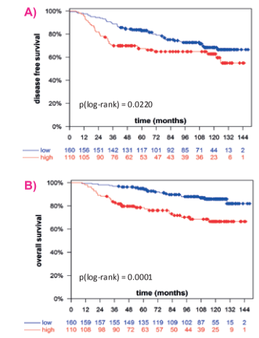


Figure 4. DFS (A) and OS (B) in cT1/cT2 patients with no pCR according to pCR score low/high

Conclusions

Herein we validated a pre-defined score and cut-off based on highly standardized mRNA measurements of *ERBB2* (HER2), *ESR1* (ER), *PGR* (PR) and *MKI67* (Ki-67) by MammaTyper® for prediction of pathological complete response (pCR) after neoadjuvant chemotherapy (NACT) based on the pre-treatment biopsy. The score allows detection of patients with a low probability of pCR for whom a different treatment than NACT or additional postneoadjuvant treatment may be considered.

References

1. Varga et al. Breast Cancer Research 2017
2. Untch et al. Journal of Clinical Oncology 2011
3. Untch et al. Annals of Oncology 2011
4. Wunderle et al. Breast Cancer Res Treat 2018

Presented at: ESMO 2018 Congress, 19-23 October, Munich, Germany

The study was financially supported by BioNTech Diagnostics GmbH

Final analysis of the Male-GBG54 study: A prospective, randomised, multi-centre, phase II study evaluating endocrine treatment with either tamoxifen +/- gonadotropin releasing hormone analogue (GnRHa) or an aromatase inhibitor + GnRHa in male breast cancer patients

273 PD

Mattea Reinisch[1], Sabine Seiler[2,3], Tanja Hauzenberger[4], Sabine Schmatloch[5], Hans-Joachim Strittmatter[6], Dirk-Michael Zahm[7], Christian Thode[8], Christian Jackisch[3], Dominica Strik[9], Volker Moebus[10], Toralf Reimer T[11], Bruno Sinn[12], Elmar Stickeler[13], Frederik Marmé[14], Wolfgang Janni[15], Axel Kamischke[17], Christian Rudlowski[18], Valentina Nekljudova[2], Gunter von Minckwitz[2], Sibylle Loibl[2]

[1]Kliniken Essen-Mitte, Essen, Germany; [2]German Breast Group, Neu-Isenburg, Germany; [3]Sana-Klinikum Offenbach, Germany; [4]Klinikum St. Marien Amberg, Germany; [5]Elisabeth Krankenhaus Kassel, Germany; [6]Rems-Murr-Klinik-Winnenden, Germany; [7]SRH Wald-Klinikum, Gera, Germany; [8]Amedes MVZ Wagnerstibbe für Laboratoriumsmedizin, medizinische Mikrobiologie und Immunologie, Göttingen, Germany, [9]Endokrinologikum Berlin, Germany; [10]Klinikum Frankfurt Höchst , Germany; [11]Universitätsklinikum Rostock, Germany; [12]Institut für Pathologie, Charité Berlin, Germany; [13]Universitätsklinikum Aachen, Germany; [14]Universitätsklinikum Heidelberg, Germany; [15]Universitätsklinikum Ulm, Germany; [16]MVZ Kinderwunschzentrum Münster, Germany; [17]Evangelisches Krankenhaus Bergisch Gladbach, Germany

Background

Over 90% of male patients (pts) with breast cancer (BC) have a hormone receptor (HR) positive BC. Although tamoxifen is recommended as standard of care, there is a lack of data regarding efficacy and safety of the standard endocrine therapy and of alternatives[1]. Due to low incidence of male BC, therapy strategies are extrapolated from principles established for the treatment of female BC and no prospectively randomized study in male BC pts has been conducted so far. The Male study is the first prospective, randomized, multicentre trial presenting data on the effects and safety different endocrine treatment options in male BC pts.

Materials and Methods

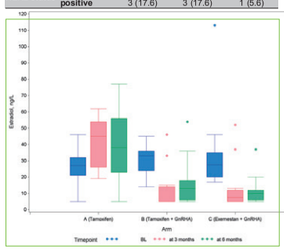
In the phase II Male trial (NCT01638247), pts were randomized to receive either tamoxifen 20 mg/day per os (p.o.) or tamoxifen 20mg/day p.o. + GnRH analogue (a) subcutaneous (s.c.) every 3 months (q3m) or exemestane (AI) 25 mg/day p.o. + GnRHa s.c. q3m for 6 months as (neo)adjuvant or metastatic therapy (figure 6). Male BC pts with a Karnofsky Index ≥60%, normal lipids and no history or evidence of prostate cancer were eligible. The primary objective was the 17-ß-estradiol (E2) suppression in the 3 treatment arms after 3 months therapy. Secondary objectives were to determine the E2 suppression after 6 months, the level of different steroidal hormones testosterone, dihydrotestosterone (DHT), sexual hormone binding globuline (SHBG), FSH, LH, free Androgen Index (FAI). Changes in sexual function (international index of erectile function= IIEF)[2] and health related quality of life in aging men (aging male symptom score= AMS)[3] were measured by validated questionnaires. Reference values of the centrally tested hormonal parameters were presented elsewere[4]. Tissue and blood was collected for translational research.

The sample size of 48 evaluable pts was calculated for the Kruskal-Wallis test to have 80% power to detect at the 5% significance level a difference in median E2 decrease between 3 therapy groups, based on the following assumptions[5]: the mean E2 level at baseline (BL) of 25 ng/L with standard deviation of 8 ng/L, no change with tamoxifen alone after 3 months, 50% decrease with tamoxifen + GnRHa and 80% decrease with AI+ GnRHa. Pts were analysed for hormone changes according to the intent-to-treat principle (as randomized).

Results

Table 1: Main Baseline Characteristics

Parameter n (%)	Category	A tamoxifen n= 17	B tamoxifen + GnRHa n= 17	C exemestane + GnRHa n= 18
Age years	median (range)	59 (37-83)	60 (45-82)	66 (45-80)
Prior CTX	no	11 (64.7)	11 (64.7)	11 (61.1)
	yes	6 (35.3)	5 (35.3)	7 (38.9)
Tumor size	T1	8 (50.0)	6 (35.3)	9 (50.0)
	T2	6 (37.5)	10 (58.8)	7 (38.9)
	T3 + T4	2 (12.5)	1 (5.9)	2 (11.1)
	missing	1	0	0
Nodal status	N0	8 (53.3)	8 (47.1)	9 (50.0)
	N+	7 (46.7)	9 (52.9)	9 (50.0)
	missing	2	0	0
M	M0	15 (88.2)	16 (100)	18 (100)
	M1	2 (11.8)	0 (0.0)	0 (0.0)
	missing	0	1	0
HER2 status	negative	14 (82.4)	14 (82.4)	17 (94.4)
	positive	3 (17.6)	3 (17.6)	1 (5.6)



Median E2 change from BL to 3 / 6 months in ng/L

Arm A	Arm B	Arm C	p-value
+17.0 / +12.0	-23.0 / -19.5	-18.5 / -17.0	<0.001 / <0.001

Figure 1: E2 change at BL to 3 and 6 months treatment (Kruskall-Wallis tests)

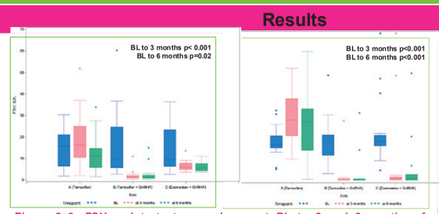


Figure 2+3: FSH and testosterone change at BL to 3 and 6 months of treatment (Kruskall-Wallis test)

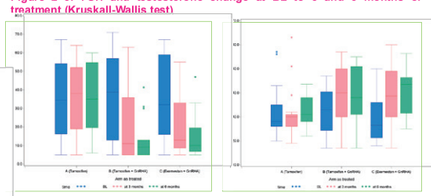


Figure 4+5: Change in erectile function (IIEF) and quality of life (AMS) at BL to and 6 months of treatment

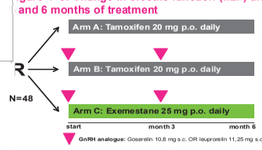


Figure 6: Study design of the Male Study

References

1: Giordano SH, NEJM 2018N Engl J Med. 2018 Jun 14;378(24):2311-2320
2: Rosen R et al., Urology, 1997, 49: 822-830.
3: Heinemann LA et al., Health Qual Life Otcomes. 2003 May 1;1:15.
4: Reinisch M et al., SABCS 2017; PD7-10.
5: Leder BZ et al., Clin Endocrinol Metab, 2004; 89:1174–1180

Conclusions

We describe for the first time treatment effects on hormonal parameters after 3 and 6 months therapy in male BC pts receiving endocrine therapy in a prospective, multicenter, randomized setting.

- GnRHa + tamoxifen or AI led to a comparable reduction of E2, FSH and LH, SHBG and FAI. The changes seen after 6 months therapy support the findings after 3 months therapy.
- Tamoxifen mono (arm A) led to an increase of the plasma E2 concentrations with little impact on FSH and testosterone.
- The main suppression of E2 by AI+ GnRHa was reached after 3 months of therapy and was not further decreased after 6 months of therapy.
- The side effects of tamoxifen on the patients´ erectile function and quality of life were moderate. The combination tamoxifen or AI with GnRHa influenced the well-being and the erectile function in men deeply compared to BL.
- Due to the results of the MALE study, tamoxifen mono should be kept as standard therapy.
- If GnRH + AI or tamoxifen is indicated for men with breast cancer, patients should be informed about the observed changes of erectile function and quality of life.

etween October 2012 and May 2017, 56 pts were randomized within 24 centers in ermany. 50 pts were fully evaluable and comprised the analysis set after 3 months of erapy and 46 pts after 6 months of therapy. The median age was 62 years. The BL aracteristics were well balanced between the 3 treatment groups with no significant anges between the arms[4] (Table 1).

e majority had a T2, N0 BC. The median Body Mass Index was 26.7 kg/m² (range 3.6-49.4). Overall reported SAEs are summarized elsewere[4]. All resolved without equelae, no death was reported. Figure 1-3 describes the changes of the E2, FSH d Testosterone levels at BL to 3 and 6 months of the three different endocrine erapy arms.

e observed a stable decrease of E2 in patients receiving the combination therapy of moxifen or AI with GnRHa for 6 months of therapy. Within the tamoxifen arm (Arm A), e E2 values increased. The changes in FSH and testosterone lead to the E2 suppression in Arm B and C and to the increase in Arm A. FAI and DHT significantly decreased in Arm B and C with little change in Arm A, SHBG slightly increased in Arm , and B and decreases in Arm C after 3 and 6 months therapy.

urthermore, we present results of validated questionnaires (Figure 4+5) regarding the verall health related quality of life in aging men (AMS) and the erectile function of the articipants (IIEF). Tamoxifen hardly influenced the erectile function or the health elated quality of life in men, whereas the combination therapy with GnRHa decreased oth deeply compared to BL.

Presented at: European Society of Medical Oncology Congress 19.-23. October 2018.

Drug supply (Exemestane) was provided by Pfizer, Germany.
The study was sponsored and supported by GBG and the Claudia von Schilling Foundation.

Impact of nab-paclitaxel dose reduction on survival of the randomized phase III GeparSepto trial comparing neoadjuvant chemotherapy of weekly nab-paclitaxel (nP) with solvent-based paclitaxel (P) followed by anthracycline/cyclophosphamide for patients with early breast cancer (BC)

Michael Untch[1], Christian Jackisch[2], Andreas Schneeweiss[3], Sabine Schmatloch[4], Bahriye Aktas[5], Carsten Denkert[6], Christian Schem[7], Hermann Wiebringhaus[8], Sherko Kümmel[9], Kerstin Rhiem[10], Mathias Warm[11], Peter A Fasching[12], Marianne Just[13], Claus Hanusch[14], John Hackmann[15], Jens-Uwe Blohmer[16], Jenny Furlanetto[17], Valentina Nekljudova[17], Gunter von Minckwitz[17], Sibylle Loibl[17]

[1]Helios Clinics Berlin-Buch; [2]Sana Klinikum Offenbach; [3]Nationales Centrum für Tumorerkrankungen Heidelberg; [4]St. Elisabeth Krankenhaus Kassel; [5]Klinik und Poliklinik für Frauenheilkunde Leipzig; [6]Institut für Pathologie, Charité-Universitätsmedizin Berlin; [7]Mammazentrum Hamburg-Brustklinik am Krankenhaus Jerusalem, [8]St. Barbara-Klinik Hamm-Heessen, Hamm; [9]Brustzentrum, Kliniken Essen-Mitte, Essen; [10]Zentrum Familiärer Brust- und Eierstockkrebs, Uniklinik Köln; [11]Brustzentrum im Krankenhaus Köln-Holweide, Köln; [12]Universitätsklinikum Erlangen; [13]Onkologische Schwerpunktpraxis Bielefeld; [14]Klinikum zum Roten Kreuz, München; [15]Marien-Hospital Witten; [16]Klinik für Gynäkologie am Campus Charité Mitte, Berlin; [17]German Breast Group, Neu-Isenburg

188PD

Background

The GeparSepto trial demonstrated a higher pathological complete response (pCR) rate after weekly nP compared to weekly P 80mg/m² (P80) followed by epirubicin/cyclophosphamide (EC) as neoadjuvant treatment in patients with early BC (pCR nP 38% vs. P80 29%, p<0.001).[1] The dose of nP was amended from 150mg/m² (nP150) to 125mg/m² (nP125) weekly during the trial due to the higher rates of toxicities with nP150 compared to P80, especially peripheral sensory neuropathy (PSN).[1,2] In the final safety report the PSN occurred after nP125 was associated with lower frequency and shorter resolution time compared to nP150.[2,3] We report long-term outcome and updated results on PSN resolution of patients treated with nP150 and nP125 in comparison to P80.

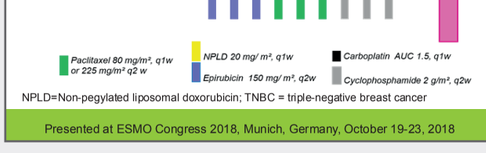
Materials and Methods

Trial design: GeparSepto enrolled patients with primary cT1c and additional high risk or cT2-cT4d BC, after central assessment of HER2, HR, Ki67 and SPARC. Study design is shown in Figure 1.

Statistical consideration: Time-to-event endpoint analysis was planned to be performed on the modified intent-to-treat (mITT) population after 248 events for invasive disease-free survival (iDFS), with 80% power for the log-rank test to detect a hazard ratio (HR) of 0.70, corresponding to an increase in 5-year iDFS from 75% with P80 to 81.8% with nP, with a 2-sided significance level of α=0.05. After the end of the study the protocol was amended in order to collect long-term data on PSN resolution and treatment modalities. Patients who gave their consent to the additional assessments according to this amendment were included in the PSN analysis. Time to resolve PSN might be overestimated as the follow-up data was in part retrospectively collected.

Endpoints: **Primary endpoint** was pCR (ypT0 ypN0). **Main secondary endpoints** were iDFS, overall survival (OS) and resolution of PSN.

Figure 1: Study design



Results

Table1: Baseline characteristics

Parameter	Before amendment P80 N=226 (%)	Before amendment nP150 N=229 (%)	After amendment P80 N=374 (%)	After amendment nP125 N=377 (%)
Age, years, median (range)	48 (26-75)	49 (28-75)	48 (22-76)	50 (21-75)
cT1-3	209 (92.9)	209 (91.7)	354 (94.7)	356 (94.4)
cN+	103 (46.2)	101 (45.5)	162 (44.4)	174 (46.8)
Tumor grade 3	127 (56.2)	123 (53.7)	211 (56.4)	196 (52.0)
Ki67 >20%	136 (60.2)	139 (60.7)	279 (74.6)	279 (74.0)
SPARC positive (IRS 6-12)	40 (17.7)	42 (18.3)	54 (14.4)	55 (14.6)
Breast cancer subtype				
HER2-/HR-	62 (27.4)	64 (27.9)	75 (20.1)	75 (19.9)
HER2-/HR+	110 (48.7)	109 (47.6)	156 (41.7)	159 (42.2)
HER2+/HR+	36 (15.9)	35 (15.3)	113 (30.2)	105 (27.9)
HER2+/HR-	18 (8.0)	21 (9.2)	30 (8.0)	38 (10.1)

- Patients treated with nP150 or nP125 had significantly better iDFS compared to P80. The iDFS rates were lower after nP150 than after nP125 (Figures 2 and 3).
- The 4-year OS did not significantly differ in patients treated with nP150 (88.0%) or nP125 (91.1%) vs P80 (86.1% before and 87.6% after amendment) (nP150, HR 0.89 [95%CI 0.54-1.47], log-rank p=0.640; nP125, HR 0.78 [95%CI 0.49-1.22], log-rank p=0.273).
- After a median follow-up of 220.1 wks [7.7-290] the median time to resolve PSN of grade 2-4 to grade 1 was significantly longer in patients treated with nP150 (12.7 wks) before than with nP125 (6.4 wks) after the amendment (p=0.014), whereas no significant difference was observed in patients treated with P80 (7.0 wks) vs nP125 (p=0.740). The median time to resolve PSN of grade 3-4 to grade 1 did not significantly differ either between nP150 (157.3 wks) and nP125 (32.0 wks) (p=0.200) or between P80 (10.4 wks) and nP125 (p=0.161) (Figure 4).

Figure 2: iDFS before (A) and (B) after the amendment

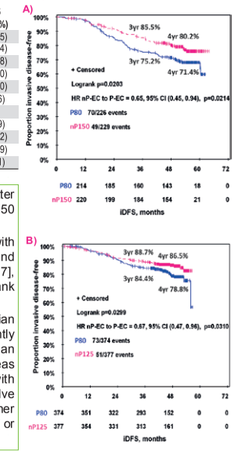


Figure 3: iDFS in subgroups before (A) and (B) after the amendment

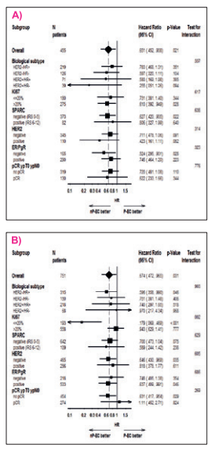
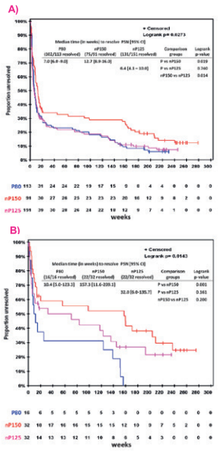


Figure 4: Time to resolve PSN of grade 2-4 (A) and grade 3-4 (B) to grade 1



Conclusions

The nP dose reduction did not compromise the iDFS compared to P80. The lower iDFS rates of nP and P80 before the amendment compared to those after the amendment can be explained by the different risk profile of the two cohorts. The long-term follow-up of PSN of grade 2-4 after nP125 was associated with earlier resolution compared to nP150.

References

1. Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol. 2016;17:345-56; 2. Furlanetto J, Jackisch C, Untch M, et al. Efficacy and safety of nab-paclitaxel 125 mg/m² and nab-paclitaxel 150 mg/m² compared to paclitaxel in early high-risk breast cancer. Results from the neoadjuvant randomized GeparSepto study (GBG 69). Breast Cancer Res Treat 2017;163:495-506.3. Furlanetto J, von Minckwitz G, Jackisch C, et al. Peripheral sensory neuropathy occurrence and resolution: Results from the neoadjuvant randomized GeparSepto study (GBG 69). Cancer Res 2017; 77(4 Suppl):Abstract nr P5-16-03.

Presented at: ESMO 2018 Congress, Munich 19-23 October 2018

The trial was financially supported by Celgene and Roche

Germline mutation status and therapy response in patients with triple-negative breast cancer (TNBC): Results of the GeparOcto study

Esther Pohl-Rescigno[1], Andreas Schneeweiss[2], Jan Hauke[1], Volker Moebus[3], Jenny Furlanetto[4], Carsten Denkert[5], Peter A. Fasching[6], Claus Hanusch[7], Hans Tesch[8], Nana Weber-Lassalle[1], Volkmar Müller[9], Kerstin Rhiem[1], Michael Untch[10], Kristina Luebbe[11], Bianca Lederer[4], Christian Jackisch[12], Valentina Nekljudova[4], Rita K. Schmutzler[1], Eric Hahnen[1], Sibylle Loibl[4]

[1]Center for Familial Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Medical Faculty, University of Cologne and University Hospital Cologne, Cologne, Germany; [2]National Center for Tumor Diseases, University of Heidelberg, Heidelberg, Germany; [3]Department of Gynecology and Obstetrics, Klinikum Frankfurt Höchst, Academic Hospital of the Goethe University Frankfurt, Frankfurt, Germany; [4]German Breast Group (GBG), Neu-Isenburg, Germany; [5]Institute of Pathology, Charité - Universitätsmedizin Berlin, Berlin, Germany; [6]University Hospital Erlangen, Erlangen, Germany; [7]Rotkreuzklinikum, Frauenklinik, Munich, Germany; [8]Hämatologisch-Onkologische Gemeinschaftspraxis, Frankfurt, Germany; [9]Department of Gynecology, Hamburg-Eppendorf University Medical Center, Hamburg, Germany; [10]Department of Gynecology and Obstetrics, Helios Klinikum Berlin-Buch, Berlin, Germany; [11]Diakovere Henriettenstift, Breast Center, Hannover, Germany; [12]Sana Klinikum Offenbach GmbH, Offenbach, Germany.

243P

Background

GeparOcto is a multicenter, prospective, open-label phase III study (NCT02125344) to compare two dose-dense, dose-intensified therapy approaches for the neoadjuvant treatment of primary breast cancer in high-risk patients [1]. In a substudy of GeparOcto, patients with triple-negative breast cancer (TNBC) were randomized to receive treatment with intensified dose-dense epirubicin (E), paclitaxel (P), and cyclophosphamide (C; iddEPC) or weekly paclitaxel/liposomal doxorubicin (PM), plus carboplatin (Cb). Here, we present the data on germline mutation analyses of patients with TNBC and the correlation with pathological complete response (pCR defined as ypT0/is ypN0).

Patients and Methods

Next generation sequencing (NGS)-based germline mutation analysis of *BRCA1, BRCA2,* and 16 further BC predisposition or candidate predisposition genes was carried out in 393 patients with TNBC (iddEPC n=194, PMCb n=199). 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. Validation of CNVs was performed by either multiplex ligation-dependent probe amplification (MLPA) or real-time polymerase chain reaction.

Figure 1. Study design. 393 patients with TNBC were randomized to one of the two treatment arms, iddEPC or PMCb.

NPLD=Non-pegylated liposomal doxorubicin; TNBC = triple-negative breast cancer

Results

Overall, 69 of 393 patients (17.6%) carry pathogenic mutations in the *BRCA1/2* genes. In 324 *BRCA1/2*-negative patients, 30 patients (9.3%) carry mutations in at least one of the 16 additional genes analysed. Of those, 28 carry mutations in one gene (n=2 *BARD1*, n=5 *BRIP1*, n=1 *CHEK2*, n=9 *FANCM*, n=1 *NBN*, n=8 *PALB2*, n=1 *RAD50*, n=1 *RAD51C*) and two patients carry mutations in two genes (*ATM/CHEK2, PALB2/XRCC2*); no mutations were found in *CDH1, MRE11A, PTEN, RAD51D, STK11*, and *TP53*.

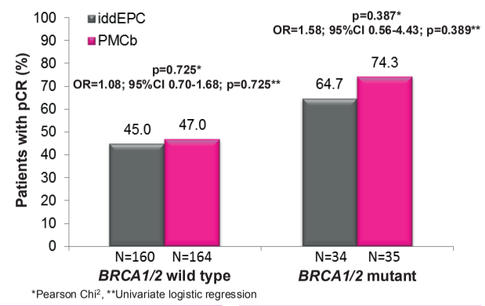
Overall, 69.6% of patients with a *BRCA1/2* mutation had a pCR vs 46.0% of patients without *BRCA1/2* mutation (p<0.001). In the iddEPC group, 64.7% of patients with a *BRCA1/2* mutation had a pCR vs 45.0% without *BRCA1/2* mutation (p=0.037); in the PMCb arm, 74.3% of patients with a *BRCA1/2* mutation had a pCR vs 47.0% without *BRCA1/2* mutation (p=0.003). Comparison of the two study arms, PMCb and iddEPC, did not reveal significantly different response rates for *BRCA1/2*-positive or -negative patients with TNBC, respectively (Figure 2).

Table 1. Subject and baseline characteristics by germline mutation status in *BRCA1/2* (primary definition of mutation status).

Parameter	Category	Wild type N (%)	Mutant N (%)	Overall N (%)	p-value
Biological subtype	TNBC	324 (82.4)	69 (17.6)	393 (100.0)	
Ki67	<60%	156 (84.8)	28 (15.2)	184 (46.8)	0.289
	≥60%	168 (80.4)	41 (19.6)	209 (53.2)	
LPBC	no (<60% TILs)	275 (82.6)	58 (17.4)	333 (84.7)	0.855
	yes (≥60% TILs)	49 (81.7)	11 (18.3)	60 (15.3)	
Grading	G1-2	60 (80.0)	15 (20.0)	75 (19.1)	0.505
	G3	264 (83.0)	54 (17.0)	318 (80.9)	
TS by sonography	≤23 mm	139 (83.7)	27 (16.3)	166 (42.2)	0.594
	>23 mm	185 (81.5)	42 (18.5)	227 (57.8)	
cT	cT1-3	316 (82.3)	68 (17.7)	384 (97.7)	1.000
	cT4	8 (88.9)	1 (1.4)	9 (2.3)	
cN	cN0	243 (83.8)	47 (16.2)	290 (74.7)	0.534
	cN+	79 (80.6)	19 (19.4)	98 (25.3)	
Age	<40 years	59 (65.6)	31 (34.4)	90 (22.9)	<0.001
	≥40 years	265 (87.5)	38 (12.5)	303 (77.1)	
BRCA risk according to family history	no	204 (94.0)	13 (6.0)	217 (55.2)	<0.001
	yes	120 (68.2)	56 (31.8)	176 (44.8)	

LPBC = lymphocyte-predominant breast cancer, TNBC = triple-negative breast cancer

Figure 2. Prediction of response according to mutation status by treatment arm (primary definition).



*Pearson Chi², **Univariate logistic regression

Conclusions

BRCA1/2 germline mutations represent a predictive biomarker for the achievement of pCR following neoadjuvant anthracycline-taxane-containing chemotherapy for TNBC in line with earlier findings [2]. pCR rates in patients with *BRCA1/2* mutation were higher in comparison to *BRCA1/2*-negative patients. There is no evidence for a predictive value of selected non-*BRCA1/2* genes. Among patients with a *BRCA1/2* mutation, no significant higher pCR rate was associated with carboplatin treatment.

References

1. Schneeweiss A. et al. J Clin Oncol. 2017; 35(suppl): abstr 518.
2. Hahnen et al. JAMA Oncol. 2017; 3(10):1378-1385.

Presented at ESMO Congress 2018, Munich, Germany, October 19-23, 2018

The trial was financially supported by Roche, Amgen, Teva, Vifor

PD5-01

Pre-therapeutic PD-L1 expression and dynamics of Ki-67 and gene expression during neoadjuvant immune-checkpoint blockade and chemotherapy to predict response within the GeparNuevo trial

Sinn BV[1], Loibl S[2], Karn T[3], Untch M[4], Kunze C[1], Weber K[2], Treue D[1], Wagner K[5], Hanusch C[6], Klauschen F[1], Fasching PA[7], Huober J[8], Zahm M[9], Jackisch C[10], Thomalla J[11], Blohmer JU[11], van Mackelenbergh M[12], Rhiem K[13], Felder B[2], von Minckwitz G[2], Burchardi N[2], Schneeweiss A[14], Denkert C[1]

[1]Department for Pathology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [2]German Breast Group, Neu-Isenburg, Germany, [3]Department for Gynecology, Universitätsklinikum Frankfurt, Frankfurt, Germany,[4]Helios Klinikum Berlin-Buch, Berlin, Germany,[5]Department of Gynecology Rotkreuzklinikum, München, Germany, [6]Department of Gynecology, Universitätsklinikum Erlangen, Erlangen, Germany, [7]Department of Gynecology, Universitätsklinikum Ulm, Ulm, Germany, [8]Department of Gynecology, Wald-Klinikum Gera, Gera, Germany, [9]Sana Klinikum Offenbach, Offenbach, Germany, [10]Clinic for Hematology and Oncology, Koblenz, Germany, [11]Breast Medical Oncology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [12]Department for Gynecology, Universitätsklinikum Kiel, Kiel, Germany, [13]Department for Gynecology, Universitätsklinikum Köln, Köln, Germany, [14] Department for Gynecology, Universität Heidelberg, Heidelberg, Germany

Background

The GeparNuevo trial showed an increase in the pCR rate to 53% vs 44%; p=0.287 compared to placebo in TNBC with the addition of the anti-PD-L1 antibody durvalumab to a neoadjuvant anthracycline-taxane containing chemotherapy [1]. In a predefined subgroup analysis, a significant increase of the pCR rate was observed for patients that received durvalumab for 2 weeks alone prior to the start of chemotherapy (window phase; 61% vs 41%, P interaction=0.048), while pCR rate was not in patients that did start durvalumab together with chemotherapy.

Patients and Methods

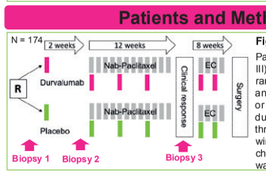


Figure 1: Study design

Patients with triple-negative (Stage I-III) primary breast cancer were randomized to receive anthracycline and taxane-based chemotherapy with or without the PD-L1 inhibitor durvalumab. Biopsies were taken at three times: at diagnosis, after the window phase and after 4 cycles of chemotherapy. The window phase was closed after an amendment.

Patients and Samples

Diagnosis and ER, PR, Ki-67 and HER2-status were confirmed centrally prior to randomization. Negative hormone receptor status was defined as ER staining in < 1% of tumor cells and PR staining in < 10%, negative HER2 status as an IHC score of 0, 1+, or 2+ without amplification (ratio < 2 or < 6 copies/cell) in SISH. Pathologic complete response (pCR) was defined as the absence from cancer in the breast and lymph nodes (ypT0 ypN0).

PD-L1 Immunohistochemistry (Ventana SP263)

We evaluated expression of PD-L1 in 158 cases as percentage of tumor cells with membranous staining and percentage of tumor-infiltrating lymphocytes (TILs) with membranous or cytoplasmic staining (relative to total TILs). We evaluated definitions for positivity as ≥ 1 % and ≥ 25 % of stained tumor cells and/or TILs, respectively.

Targeted RNA Sequencing

162 formalin-fixed, paraffin-embedded pre-treatment biopsies, 79 biopsies after the window phase and 31 biopsies after 4 cycles of chemotherapy were evaluable for profiling of 2559 genes using the HTG EdgeSeq® system (HTG Oncology biomarker panel) that combines a nuclease protection assay with next generation sequencing. Data were processed as recommended by HTG, median normalized within each sample and across the experiment, and log2-transformed. For differential gene expression analyses, data was scale-normalized and linear models were fit after filtering for minimal expression (> 4) and variability (IQR > 1). We used logistic regression analyses to evaluate the predictive value of a predefined gene signature of tumor-infiltrating lymphocytes (CXCL9, CCL5, ICO1, CXCL13) [2], a previously described signature for response to immune-checkpoint inhibition (IFNG, CD274, LAG3, CXCL9) [3] and a metagene for cytotoxic response (PRF1, GZMA). We calculated molecular breast cancer subtypes using the AIMS [4] approach.

Results

Parameter	Category	N	Percent
cT	cT1-2	164	94
	cT3-4	10	6
cN	cN-	120	69
	cN+	54	31
Grade	G2	29	17
	G3	145	83
Ki-67	< 30 %	24	14
	≥ 30 %	150	86
sTILs	< 60 %	149	86
	≥ 60 %	25	14
Arm	Durvalumab	88	51
	Placebo	86	49
Window	yes	117	67
	no	57	33
Response	pCR	85	49
	RD	89	51

Table 1: Baseline characteristics, treatment and response

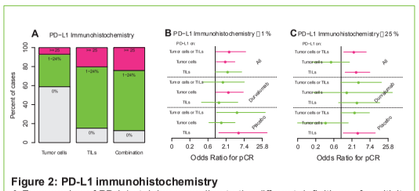


Figure 2: PD-L1 immunohistochemistry

A Frequencies of PD-L1 staining according to the different definitions of positivity. **B** The plot shows the odds ratio (OR) to achieve a pCR for cases defined as positive for PD-L1 in the different compartments. Significant results (P < 0.05) are highlighted in magenta. PD-L1 expression on tumor cells was predictive for response across all patients, within the durvalumab arm and on TILs within placebo-treated patients. **C** Using the 25% definition, PD-L1 was not predictive for response to durvalumab.

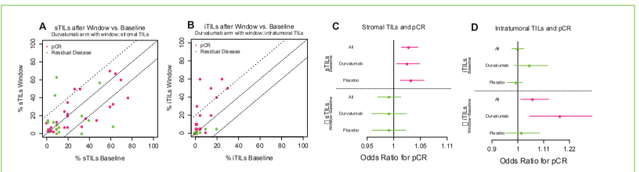


Figure 3 – Tumor-infiltrating lymphocytes (TILs) and response

A Levels of stromal TILs (sTILs) after the window phase are plotted against the corresponding baseline values. Patients in this analysis received durvalumab within the window phase. There was no substantial change in sTILs. **B** The same illustration for intra-tumoral lymphocytes (iTILs) shows increased levels in a subset of patients. **C** Pre-treatment levels of sTILs are predictive for response in both arms, while the dynamic change of sTILs (window vs. baseline) is not. **D** Interestingly, the dynamic change of iTILs is associated with better response to durvalumab, representing a shift of the spatial distribution of TILs. There was no significant association of changes in TILs comparing baseline biopsies and biopsies after four cycles of paclitaxel.

Results

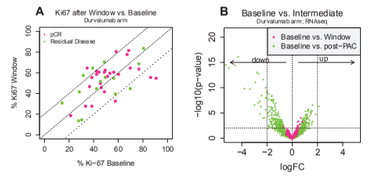


Figure 4 – Ki67 and dynamic changes in global gene expression

A Treatment within the window phase did not lead to significant changes in Ki-67 levels. Its dynamic change was not predictive for response (not shown). **B** Differential gene expression analysis revealed little differences when RNAseq profiles from baseline biopsies and post-window biopsies are compared. –log10 p-values are plotted against the log-fold-change (logFC). In contrast, substantial shifts are seen when baseline profiles are compared to post-paclitaxel biopsies.

Conclusions

- **A definition of ≥ 1 % stained tumor cells for PD-L1 immunohistochemistry is predictive for response to durvalumab**
- **A single dose of durvalumab led to increased intratumoral lymphocytes in some patients. This effect was associated with higher pCR, which might reflect an activated immune response and serve as a surrogate marker for pCR achievement**
- **Little effects on global gene expression are observed after a single dose**
- **Chemotherapy leads to substantial changes in global gene expression. Sequential samples are promising for discovery of resistance mechanisms**

References

1. Loibl S et al. ASCO 2018 Loibl S et al. Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). ASCO 2018

PD2-07

mRNA Signatures Predict Response to Durvalumab Therapy in Triple Negative Breast Cancer (TNBC) – Results of the Translational Biomarker Programme of the neoadjuvant double-blind placebo controlled GeparNuevo trial

Loibl S[1], Sinn BV[2], Karn T[3], Untch M[4], Treue D[2], Sinn HP[5], Weber K[1], Hanusch C[6], Fasching PA[7], Huober J[8], Zahm M[9], Jackisch C[10], Thomalla J[11], Blohmer JU[12], Marmé F[13], Klauschen F[2], Rhiem K[14], Felder B[2], von Minckwitz G[1], Burchardi N[1], Schneeweiss A[15], Denkert C[2]

[1]German Breast Group, Neu-Isenburg, Germany, [2]Department of Pathology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [3]Department for Gynecology, Universitätsklinikum Frankfurt, Frankfurt, Germany, [4]Helios Klinikum Berlin-Buch, Berlin, Germany, [5]Department of Pathology, Universitätsklinikum Heidelberg, Heidelberg, Germany, [6]Department of Gynecology, Rotkreuzklinikum München, München, Germany, [7]Department of Gynecology, Universitätsklinikum Erlangen, Erlangen, Germany, [8]Department of Gynecology, Universitätsklinikum Ulm, Ulm, Germany, [9]Department of Gynecology, Wald-Klinikum Gera, Gera, Germany, [10]Sana Klinikum Offenbach, Offenbach, Germany, [11]Clinic for Hematology and Oncology, Koblenz, Germany, [12]Breast Medical Oncology, Charité-Universitätsmedizin Berlin, Berlin, Germany, [13]Department for Gynecology, Universitätsklinikum Heidelberg, Heidelberg, Germany, [14]Department of Gynecology, Universitätsklinik Köln, Köln, Germany, [15]Department of Gynecology, Universitätsklinikum Heidelberg, Heidelberg, Germany

Background

The GeparNuevo trial showed an increase in the pCR rate to 53% vs 44%; p=0.287 compared to placebo in TNBC with the addition of the anti-PD-L1 antibody durvalumab to a neoadjuvant anthracycline-taxane containing chemotherapy [1]. In a predefined subgroup analysis, a significant increase of the pCR rate was observed for patients that received durvalumab for 2 weeks alone prior to the start of chemotherapy (window phase; 61% vs 41%, p interaction=0.048), while pCR rate was not in patients who started durvalumab together with chemotherapy.

Patients and Methods

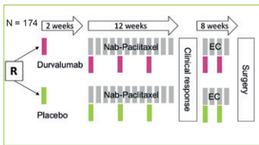


Figure 1: Study design

Patients with triple-negative (Stage I-III) primary breast cancer were randomized to receive anthracycline and taxane-based chemotherapy with or without the PD-L1 inhibitor durvalumab. The window phase was closed after an amendment.

Patients and Samples: Diagnosis and ER, PR, Ki-67 and HER2-status were confirmed centrally prior to randomization. Negative hormone receptor status was defined as ER staining in < 1% of tumor cells and PR staining in < 10%, negative HER2 status as an IHC score of 0, 1+, or 2+ without amplification (ratio < 2 or < 6 copies/cell) in SISH. Pathologic complete response (pCR) was defined as the absence from cancer in the breast and lymph nodes (ypT0 ypN0).

Targeted RNA Sequencing: 162 pre-therapeutic formalin-fixed, paraffin-embedded core biopsies were evaluable for profiling of 2559 genes using the HTG EdgeSeq® system (HTG Oncology biomarker panel) that combines a nuclease protection assay with next generation sequencing. Data were processed as recommended by HTG, median normalized within each sample and across the experiment, and log2-transformed. For differential gene expression analyses, data was scale-normalized and linear models were fit after filtering for minimal expression (> 4) and variability (IQR > 1). We used logistic regression analyses to evaluate the predictive value of a predefined gene signature of tumor-infiltrating lymphocytes (CXCL9, CCL5, ICO1, CXCL13) [2], a previously described signature for response to immune-checkpoint inhibition (IFNG, CD274, LAG3, CXCL9) [3] and a metagene for cytotoxic response (PRF1, GZMA). We calculated molecular breast cancer subtypes using the AIMS [4] approach.

Results

Parameter	Category	N	Percent
cT	cT1-2	152	94
	cT3-4	10	6
cN	cN-	112	69
	cN+	50	31
Grade	G2	28	17
	G3	134	83
Ki-67	< 30 %	22	14
	≥ 30 %	140	86
Lymphocytes	LPBC	24	15
	No LPBC	138	85
Response	pCR	82	51
	RD	80	49
Arm	Durvalumab	83	51
	Placebo	79	49
Window	yes	106	65
	no	56	35

Table 1: Baseline characteristics, treatment and response

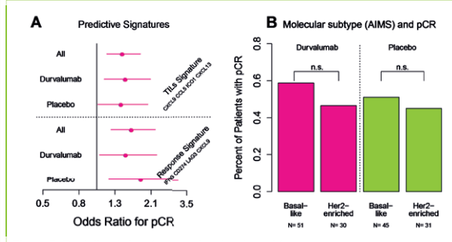


Figure 2: Predefined signatures and molecular subtypes

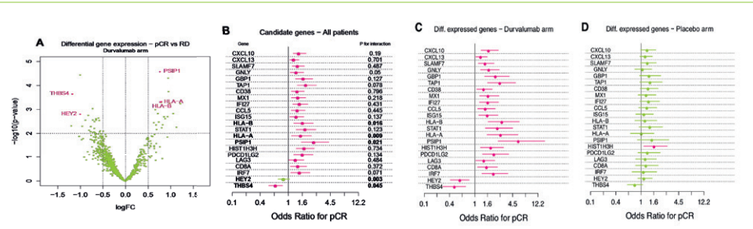


Figure 3: Differential gene expression analysis according to treatment response

A: Differential gene expression analysis according to pCR vs. residual disease (RD) after neoadjuvant treatment with immune-checkpoint inhibition. **B-D:** Logistic regression analysis for treatment response for 20 genes with increased expression (logFC > 0.5 and P < 0.01) and two exemplary genes with decreased expression according to response, **B:** across all patients with interaction P value according to treatment and within **C:** the durvalumab and **D:** placebo arms, respectively. Five genes are significantly predictive and may be interesting markers for response to durvalumab.

- The predefined signatures for TILs and response to immune-checkpoint blockade were predictive for pCR. However, the effect was not specific for the durvalumab arm (**Fig. 2A**). The cytotoxic metagene was not associated with response (not shown).
- The molecular tumor subtype (AIMS) was not predictive (**Fig. 2B**). 4 and 1 cases were classified as normal-like or Luminal A, showing no differences in response (not shown).

Conclusions

- **Predefined signatures reflecting tumor immune response predict response to neoadjuvant chemotherapy, but not specifically to durvalumab**
- **Differential gene expression analysis according to response reveals signatures of immune response**
- **A subset of genes might be specifically predictive for Durvalumab and might serve as a basis to define predictive tests in the future**
- **Further validation is necessary**
- **The basal-like molecular subtype is not associated with response in this study**

References

1. Loibl S et al. Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). ASCO 2018
2. Denkert et al. Tumor-infiltrating lymphocytes and response to neoadjuvant chemotherapy with or without carboplatin in human epidermal growth factor receptor 2-positive and triple-negative primary breast cancers. JCO 2015.
3. Higgs et al. Interferon Gamma Messenger RNA Signature in Tumor Biopsies Predicts Outcomes in Patients with Non-Small-Cell Lung Carcinoma or Urothelial Cancer Treated with Durvalumab. Clin Cancer Res 2018
4. Paquet and Hallett. Absolute assignment of breast cancer intrinsic molecular subtype. JNCI 2014

P2-08-10

Similarities between low hormone receptor positive and hormone receptor negative breast cancer: An analysis of 4366 patients from multicenter clinical trials

Sonia L Villegas[1], Bianca Lederer[2], Michael Untch[3], Frank Holms[4], Hans-Ulrich Ulmer[5], Kurt Diebold[4], Peter A Fasching[6], Karsten Weber[2], Wolfgang D Schmitt[1], Hans Tesch[7], Mahdi Rezai[8], Frederik Marmé[9], Bruno Sinn[1], John Hackmann[10], Andreas Schneeweiss[8], Andrea Tannapfel[11], Valentina Nekljudova[2], Carsten Denkert[1], Sibylle Loibl[2]

[1]Institute of Pathology, Charité Universitätsmedizin Berlin, Berlin, Germany; [2]German Breast Group (GBG Forschungs GmbH), Neu-Isenburg, Germany; [3]HELIOS Klinikum, Berlin, Germany; [4]Institut für Pathologie, Charité-Universitätsmedizin Berlin, Germany; [5]Centrum für Hämatologie und Onkologie Bethanien Frankfurt, Germany; [6]Klinikum zum Roten Kreuz München, Germany; [7]Hämatologisch-Onkologische Schwerpunktpraxis Salat/Stötzer, München, Germany; [8]Zentrum Familiärer Brust- und Eierstockkrebs, Uniklinik Köln, Germany; [9]Medical Center, Luisenkrankenhaus, Düsseldorf, Germany; [10]Universitäts Klinikum Frankfurt, Germany; [11]Brustzentrum Universitätsklinikum Erlangen, Germany; [12]Sana-Klinikum, Offenbach, Germany. [13]German Breast Group, Neu-Isenburg, Germany; [14]HELIOS Klinikum Berlin Buch, Germany

Background

Currently, patients with breast cancer (BC) with hormone receptor (HR) immunohistochemical expression between 1-9% are eligible to receive endocrine therapy[1]. However, recent data suggest that these tumors express a basal-like molecular phenotype associated with triple negative BC (TNBC) rather than luminal phenotype associated with HR positive BC[2-3].

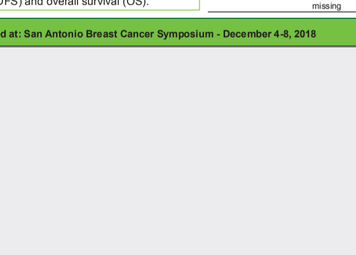
Here we aimed to determine the differences between strong HR positive, low HR positive and negative HR BC, in regard to responsiveness to neoadjuvant chemotherapy (NACT) and disease-free survival (DFS) in large cohorts from German Breast Group (GBG) clinical trials.

Patients and Methods

In this retrospective analysis of data from women treated for BC in three neoadjuvant clinical trials in Germany (GeparQuinto, GeparSixto, GeparSepto), we compared patients with three HR phenotypes: low positive (ER and/or PR 1-9%), strong positive (ER or PR 10-100%), and negative (ER and PR <1%), regarding pathological complete response (pCR, ypT0 ypN0) and DFS. Hormone receptor status was centrally evaluated. Administrated neoadjuvant regimes have been published[4-6]. Pearson´s chi-squared test was performed to compare the three HR phenotypes and baseline clinico-pathological parameters. Survival probabilities were calculated with the Kaplan-Meier method and were compared using the log-rank test.

A logistic regression model for endpoint pCR was performed on pooled data from all trials. Cox regression was used to model DFS. The models were adjusted by age, tumor and nodal status, grading, Her2 status, histological type, and clinical trial. The survival model was additionally adjusted by pCR after NACT. Statistical evaluation was carried out using SPSS Statistics 19 (IBM Corporation, Somers, NY, USA). All tests were two-sided, and p-values <0.05 were considered as significant.

Figure 1. Study Profile



* Immunoreactive Score[7]

Results

Table 1. Comparison of baseline clinico-pathological characteristics of patients/tumors among HR phenotypes from GBG neoadjuvant clinical trials

Parameter and Category	HR negative (n=1658) No. of patients (%)[a]	Low HR+ (n=145) No. of patients (%)[a]	Strong HR+ (n=2455) No. of patients (%)[a]	p value[b] Chi2	p value[c] Chi2
≤40 years old	373 (22.5)	28 (19.3)	433 (17.6)		
41-50 years old	599 (36.1)	59 (40.7)	979 (39.9)		
>50 years old	686 (41.4)	58 (40.0)	1043(42.5)	0.003	0.489
Premenopausal	961 (58.3)	81 (55.9)	1468 (60.0)		
Postmenopausal	686 (41.7)	64 (44.1)	978 (40.0)	0.399	0.561
cT1	426 (25.8)	32 (22.1)	506 (20.7)		
cT2	875 (53.1)	79 (54.5)	1337 (54.8)		
cT3	192 (11.7)	16 (11.0)	326 (13.3)		
cT4	155 (9.4)	18 (12.4)	273 (11.2)	0.006	0.554
cN0	901 (55.1)	81 (57.0)	1315 (54.5)		
cN1	647 (39.6)	56 (39.4)	1011 (41.9)		
cN2	58 (3.5)	4 (2.8)	74 (3.1)		
cN3	28 (1.7)	1 (0.7)	12 (0.5)	0.009	0.777
Grade 1	25 (1.5)	1 (0.7)	92 (3.8)		
Grade 2	463 (28.0)	50 (34.7)	1491 (60.9)		
Grade 3	1166 (70.5)	93 (64.6)	864 (35.3)	<0.001	0.185
NST	1465 (88.5)	137 (94.5)	2020 (82.4)		
Lobular	30 (1.8)	3 (2.1)	243 (9.9)		
Other	161 (9.7)	5 (3.4)	188 (7.8)	<0.001	0.043
Her2 negative	1216 (73.3)	94 (64.8)	1769 (71.1)		
Her2 positive	442 (26.7)	51 (35.2)	686 (27.9)	0.082	0.027
Ki67 0%-20%	169 (14.7)	19 (16.8)	676 (45.5)		
Ki67 21-100%	981 (85.3)	94 (83.2)	809 (54.5)	<0.001	0.546
Docetaxel	751(45.3)	55 (37.9)	1268 (51.6)		
Paclitaxel	709 (42.8)	64 (44.1)	805 (32.8)		
Nab-Paclitaxel	198 (11.9)	26 (17.9)	382 (15.6)	<0.001	0.063

a: Proportion within HR phenotype group (vertically calculated), b: Comparison across all HR groups, c: Comparison between low HR positive and HR negative groups.
NST=No special histological type;

Figure 2. pCR across HR phenotypes from GBG neoadjuvant clinical trials

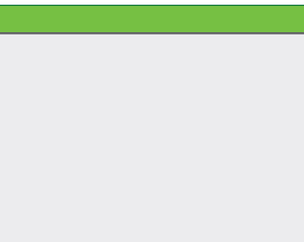


Figure 3. Disease-free Survival stratified by HR phenotypes among patients from GBG neoadjuvant clinical trials (GeparQuinto, GeparSixto, GeparSepto)

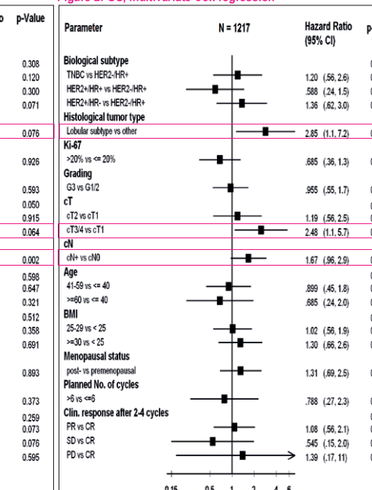


Table 2. Multivariate logistic regression model for prediction of pCR and multivariate cox regression model for DFS from GBG neoadjuvant clinical trials

HR phenotype	pCR (logistic regression) N= 4149			DFS (Cox regression) N=4149		
	Odds ratio	CI 95%	p value	Hazard ratio	CI 95%	p value
Low positive	1		<0.001	1		<0.001
Negative	1.29	(0.88-1.88)	0.195	1.00	(0.73-1.37)	0.983
Strong positive	0.41	(0.28-0.60)	<0.001	0.47	(0.34-0.64)	<0.001

Regression analyses adjusted by age, tumor stage, nodal status, grading, histological type, Her2-status, clinical trial, pCR; CI=confidence interval; DFS=disease-free survival; HR=hormone receptor; pCR=pathological complete response

- Patients median age was 49 years (range 21-78), the majority had clinical tumor stage 2 (54.1%), negative nodal status (54.7%), and Her2 negative tumors (72.4%).
- 145 (3.4%) patients had low HR positive, 2455 (57.6%) strong HR positive and 1658 (39.3%) HR negative tumors (Table 1).
- The pCR rate (ypT0 ypN0) across the studies was 26.2%.
- After NACT, 16.3% of patients with strong HR positive BC achieved a pCR, while among those with HR negative and low HR positive tumors, pCR rates were 40.2% and 37.9%, respectively (p<0.001) (Figure 2).
- In the adjusted logistic regression model, there was no statistically significant difference between low HR positive and HR negative tumors (p=0.195). But strong HR positive tumors had a significantly lower chance of achieving a pCR compared to low HR positives (p<0.001) (Table 2).
- Patients with strong HR positive BC had a better DFS than patients with low HR BC (p<0.001). DFS was not significantly different between patients with HR negative and low HR positive tumors (p=0.983) (Table 2, Figure 3).

Conclusions

- **In patients with low HR positive tumors, response to NACT is very similar to that of patients with HR negative BC.**
- **Patients' long-term outcome with low HR positive tumors is similar to that of patients with HR negative BC.**
- **The biological/clinical behavior of low HR positive BC in the neoadjuvant setting is comparable to that of the HR negative BC.**

We therefore suggest that studies on treatment options for basal-like/TNBC, should include patients with low HR positive tumors. The cut-off of 10% for defining HR positivity may need to be reconsidered.

References

1. Hammond ME, Hayes DF, Dowsett M, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010;28:2784-2795.
2. Yi M, Hua L, Koenig KB, et al. Which threshold for ER positivity? A retrospective study based on 9639 patients. Ann Oncol. 2014;25: 1004-1011.
3. Prabhu JS, Korlimarla A, Desai K, et al. A majority of low (1-10%) ER positive breast cancers behave like hormone receptor negative tumors. J Cancer. 2014;5:156-165.
4. Untch M, Loibl S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. Lancet Oncol 2012;13:135-144.
5. Von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014;15:747-756.
6. Untch M, Jackisch C, Schneeweiss A, et al. Nab-paclitaxel versus solvent-based paclitaxel in neoadjuvant chemotherapy for early breast cancer (GeparSepto-GBG 69): a randomised, phase 3 trial. Lancet Oncol 2016;17:345-356.
7. Remmele W, Stegner HE (1987) [Recommendation for uniform definition of an immunoreactive score (IRS) for immunohistochemical estrogen receptor detection (ER-ICA) in breast cancer tissue]. Der Pathologe 8 (3):138-140

Presented at: San Antonio Breast Cancer Symposium - December 4-8, 2018 by sonia.villegas@charite.de

The project has partly been funded by the Transluminal-B Consortium, Germany.

P2-08-01

Factors predicting relapse in early breast cancer patients with a pathological complete response after neoadjuvant therapy – results of a pooled analysis based on the GBG Meta database

Huober J[1], Schneeweiss A[2], Blohmer JU[3], Denkert C[4], Tesch H[5], Hanusch C[6], Salat C[7], Rhiem K[8], Rezai M[9], Solbach C[10], Fasching PA[11], Jackisch C[12], Mehta K[13], Nekljudova V[13], Seither F[13], von Minckwitz G[13], Loibl S[13], Untch M[14]

[1]Universitätsfrauenklinik Ulm, Brustzentrum, Germany, [2]Nationales Centrum für Tumorerkrankungen, Heidelberg, Germany, [3]Brustzentrum Charité-Universitätsmedizin Berlin, Germany, [4]Institut für Pathologie, Charité-Universitätsmedizin Berlin, Germany, [5]Centrum für Hämatologie und Onkologie Bethanien Frankfurt, Germany, [6]Klinikum zum Roten Kreuz München, Germany, [7]Hämatologisch-Onkologische Schwerpunktpraxis Salat/Stötzer, München, Germany, [8]Zentrum Familiärer Brust- und Eierstockkrebs, Uniklinik Köln, Germany, [9]Medical Center, Luisenkrankenhaus, Düsseldorf, Germany, [10]Universitäts Klinikum Frankfurt, Germany, [11]Brustzentrum Universitätsklinikum Erlangen, Germany, [12]Sana-Klinikum, Offenbach, Germany. [13]German Breast Group, Neu-Isenburg, Germany, [14]HELIOS Klinikum Berlin Buch, Germany

Background

Even though patients with a pathological complete response (pCR) after neoadjuvant chemotherapy have an excellent prognosis, some of these patients will eventually relapse. A better identification of patients with an increased risk of relapse despite a pCR can be helpful in selecting these patients for additional post-neoadjuvant treatment strategies.

The rationale of this retrospective analysis was to identify factors predicting relapse despite a pCR.

Patients and Methods

- A total of 2188 patients with a pCR from the neoadjuvant trials GeparTrio[1], GeparQuattro[2], GeparQuinto[3], GeparSixto[4] and GeparSepto[5] were included. The pCR was defined as ypT0/ypTis ypN0. Patient characteristics are presented in Table 1.
- The potential risk factors biological subtype, histological tumor type, tumor grading, Ki-67, clinical tumor (cT) and nodal (cN) status, planned number of cycles of chemotherapy, menopausal status and clinical response after 2-4 cycles as well as study ID were included in multivariate Cox regression models. The plots represent hazard ratios (HR) with 95% confidence interval (CI).
- The two-sided significance level was set to α=0.05.

Objectives

- Primary objective was disease-free survival (DFS).
- Secondary objectives were distant DFS (DDFS) and overall survival (OS).

Results

Table 1: Patient characteristics

Parameter	Category	N (valid %)
Age	Median (Min,Max)	48 (21, 78)
BMI	<25	1165 (53.3)
	25-29	667 (30.5)
	≥30	355 (16.2)
	missing	1
Menopausal satus	premenopausal	1308 (60.0)
	postmenopausal	871 (40.0)
	missing	9
Histological tumor type	lobular subtype	74 (3.4)
	other	2112 (96.6)
	missing	2
Tumor grading	G1	29 (1.4)
	G2	789 (37.4)
	G3	1293 (61.3)
	missing	77
cT	cT1	431 (19.8)
	cT2	1337 (61.3)
	cT3	227 (10.4)
	cT4	187 (8.6)
	missing	6
cN	cN0	1182 (54.6)
	cN1	879 (40.6)
	cN2	81 (3.7)
	cN3	22 (1.0)
	missing	24
Ki-67	≤20%	259 (19.7)
	> 20%	1056 (80.3)
	missing	873
Biological subtype	HER2-/HR+	414 (19.6)
	TNBC	805 (38.1)
	HER2+/HR+	456 (21.6)
	HER2+/HR-	440 (20.8)
	missing	73
Grading	G1	29 (1.4)
	G2	789 (37.4)
	G3	1293 (61.3)
	missing	77
Planned No. of cycles	≤ 6	516 (23.6)
	> 6	1672 (76.4)
Clin. response after 2-4 cycles	Compl. response	436 (20.2)
	Partial response	1507 (70.0)
	Stable disease	190 (8.8)
	Progress	21 (1.0)
	missing	34

Figure 1: DFS, multivariate Cox regression

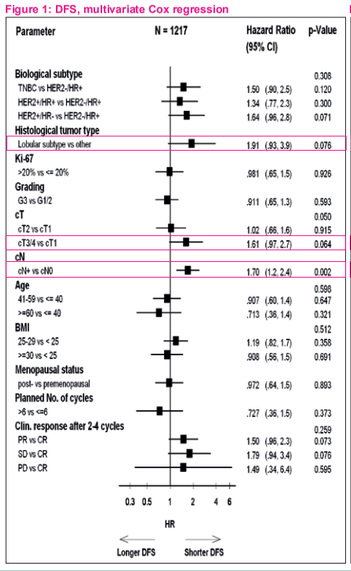


Figure 2: OS, multivariate Cox regression

From 2188 evaluable patients 290 DFS, 197 DDFS and 130 OS events were observed. Location of first relapse was locoregional in 129, distant in 134 and both in 23 patients. 1217 patients were included in multivariate analysis. DFS was significantly different with regard to the initial cN status; a trend for worse DFS was seen in patients with lobular tumor type and initial cT3/4 status (Fig. 1). Similar results were observed for DDFS (data not shown). OS was significantly worse in patients with initial cT3/4 tumors and lobular type; a trend for worse OS was seen in patients with cN+ (Fig. 2). Despite a pCR up to 22% of patients will have a DFS event and up to 15% of patients will die after 60 months (Table 2).

Table 2: DFS and OS rates at 60 months

	DFS rate (95% CI)	OS rate (95% CI)
Overall	86.8% (85.2%, 88.3%)	93.7% (92.4%, 94.7%)
Subgroups		
cT1	87.4% (74.6%, 94.0%)	98.6% (90.4%, 99.8%)
cT2	91.1% (86.6%, 94.1%)	94.9% (91.0%, 97.2%)
cT3/4	90.1% (79.1%, 95.4%)	95.3% (86.0%, 98.4%)
cN0	93.9% (89.5%, 96.5%)	96.8% (92.3%, 98.7%)
cN+	86.3% (79.9%, 90.8%)	94.0% (89.2%, 96.8%)
Lobular tumor type	77.5% (65.3%, 85.8%)	84.5% (73.0%, 91.4%)
Other tumor type	87.2% (85.5%, 88.7%)	94.1% (92.8%, 95.1%)

Conclusions

Initial tumor load (tumor size and nodal status) and histological tumor type remain prognostic factors of long term outcome even when a pCR has been achieved with anthracycline/taxanes based neoadjuvant chemotherapy.

References

1.von Minckwitz G, Kümmel S, Vogel P et al. J Natl Cancer Inst 2008; 2. von Minckwitz G, Rezai M, Loibl S et al. J Clin Oncol 2010; 3. Untch M, Loibl S, Bischoff J, et al. Lancet Oncol 2012; 4. von Minckwitz G, Schneeweiss A, Loibl S. et al., Lancet Oncol. 2014; 5.Untch M, Jackisch C, Schneeweiss A. et al. Lancet Oncol. 2016.

Presented at: San Antonio Breast Cancer Symposium - December 4-8, 2018

San Antonio Breast Cancer Symposium® - December 4-8, 2018
P4-06-01

Immunomonitoring of triple negative breast cancer patients undergoing neoadjuvant therapy with durvalumab - results from the prospectively randomized GeparNuevo trial

Massa C[1], Schneeweiss A[2], Karn T[3], Hanusch C[4], Blohmer JU[5], Fasching PA[6], Jackisch C[7], van Mackelenbergh M[8], Marmé F[2], Müller V[9], Schem C[10], Stickeler E[11], Huober J[12], Weber K[13], Untch M[14], Denkert C[5], Loibl S[13], Mueller A[1], Biehl K[1], Seliger B[1]

[1] Institute of Medical Immunology, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; [2] Universität Heidelberg, Nationales Centrum für Tumorerkrankungen, Heidelberg, Germany; [3] Department of Gynecology and Obstetrics, University of Frankfurt, Frankfurt, Germany; [4] Rotkreuzklinikum, Frauenklinik, München, Germany; [5] Institute of Pathology, Charité University Hospital, Berlin, Germany; [6] Department of Gynecology and Obstetrics, University Hospital Erlangen, Erlangen, Germany; [7] Sana-Klinikum, Offenbach, Germany; [8] Universitätsklinikum Schleswig-Holstein, Klinik für Gynäkologie und Geburtshilfe, Schleswig-Holstein, Germany; [9] Albgemeine Frauenheilkunde und Geburtshilfe, Universitätsklinikum Heidelberg, Germany; [9] Sloah St. Trudpert Klinikum, Pforzheim, Germany; [9] Klinik für Gynäkologie und Geburtshilfe, Klinikum Frankfurt Höchst, Germany; [10] Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock, Germany; [11] Brustzentrum, DRK Kliniken Berlin, Germany; [12] Institut für Pathologie, Charité - Universitätsmedizin Berlin, Germany; [13] Frauenheilkunde und Geburtshilfe, Universitätsklinikum Freiburg, Germany; [14] HELIOS Klinikum Berlin Buch, Germany; [15] Frauenheilkunde und Geburtshilfe, Universitätsklinikum Ulm, Germany
[13] German Breast Group (GBG), Neu-Isenburg, Germany; [14] Breast Cancer Center, Department of Gynecology and Obstetrics, HELIOS Klinikum Berlin Buch, Germany

Background

Background: The GeparNuevo trial is a randomized, double-blind, multi-center phase II trial of neoadjuvant therapy in patients with early-stage triple negative breast cancer (TNBC) investigating the role of durvalumab, an anti-PD-L1 antibody, which blocks PD-L1 binding to PD1 and CD80, in addition to standard anthracycline/taxane based chemotherapy (Loibl S et al. ASCO 2018).

Aim: to determine possible predictive and / or prognostic biomarkers by multicolor flow cytometry monitoring of blood samples taken before and during the different treatment phases

Patients and Methods

Table I. Data of patients evaluated by flow cytometry

	whole trial	with blood evaluation		
	N = 174 (%)	Overall, N=120 (%)	Durvalumab, N=63 (%)	Placebo, N= 57 (%)
Age (yrs), median (range)	50 (23, 76)	50 (23, 76)	50 (25, 66)	50 (23, 76)
cT3/4	10 (5,7)	5 (4,2)	4 (6,3)	1 (1,8)
cN+	54 (31,4)	33 (27,7)	17 (27,4)	16 (28,1)
Stage IIa and higher	113 (64,9)	74 (61,7)	36 (57,1)	38 (66,7)
G3	145 (83,3)	98 (81,7)	52 (82,5)	46 (80,7)
TIL: Low (0-10%)	66 (37,9)	44 (36,7)	24 (38,1)	20 (35,1)
Intermediate (11-69%)	83 (47,7)	61 (50,8)	32 (50,8)	29 (50,9)
High (>=60%)	25 (14,4)	15 (12,5)	7 (11,1)	8 (14,0)
Window treatment	117 (67,2)	63 (52,5)	34 (54,0)	29 (50,9)
Sample T1 / T2 / T3 / T4	-	117 / 51 / 106 / 105	62 / 29 / 55 / 55	55 / 22 / 50 /50

Figure 1. Scheme of GeparNuevo treatment

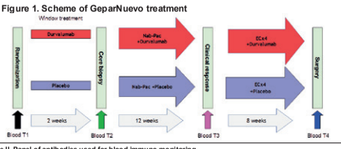


Table II. Panel of antibodies used for blood immuno monitoring

	Abs # (Tu/C tube)	subpopulations and phenotype											
		surface staining						intracellular staining					
Fitc	CD3	gd TCR	CD45	SlanDC	Tim3	CD45	CD45	CD45	IgG2a	CD25	IgG1	CD3z	
Pe	CD16+56	CD56	CCR7	CD56	CXCR3	CD24	IgG2a	CTLA4	IgG2a	FoxP3	IgG2b	perforin	CTLA4
PI5	CD45	CD4	CD4	CD123	CD4	CD19	CD4	CD4	CD4	CD4	CD4	CD4	CD4
Pe-Cy7	CD4	CD28	CD45RA	CD11c	CCR6	IgD	CD19	CD19	IgG1	CCR4	CD56	CD56	
APC	CD19	CD16	CD38	CD16	CD57	CD38	IgG2b	LIR1	IgG1	CD127	CD19	CD19	CD19
APC-H7	CD8	CD8	CD8	CD3+19+20	CD8	CD20	CD8	CD8	IgG2a	CD45RO	CD8	CD8	CD8
BV421		CD45		CD14	CD45	CD27	IgG1	PDL1	CD45	CD45	CD45	CD45	CD45
BV510			HLA-DR	HLA-DR	PD1			PD1		HLA-DR			
BV605		CD3	CD3	CD45	CD3	CD3	CD3	CD3	CD3	CD3	CD3	CD3	CD3

Results

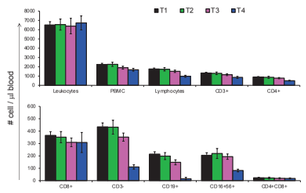


Figure 2. Absolute counts of immune cells in blood along treatment
Blood samples taken at the different time points were evaluated by mean of the multicolor TBNK assay and quantified using the internal bead control of Truecount tubes. Shown are the mean and 95% confidence intervals (CI) of up to 120 patients.

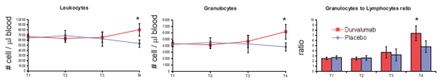


Figure 3. Differences in immune cell counts among treatment arm
Data obtained in Figure 2 were subdivided by treatment arm (Durvalumab vs Placebo). Shown are the populations with significant differences (*) as by Anova test. Granulocytes were calculated as the difference between leukocytes and PBMC.

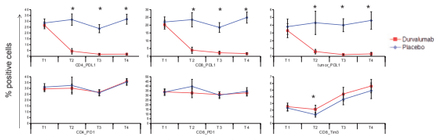


Figure 4. Changes in blood cell phenotype along treatment by arm
Flow cytometric evaluation of blood samples. Shown are percentages of cells positive for different markers at the respective time points in all patients and the two treatment arms. * indicate statistical significance in the Anova test

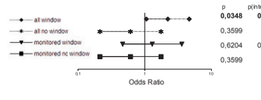


Figure 5. Clinical outcome
Clinical outcome of patients evaluated at T4 for the whole Geparnuevo trial (N =174) and for the subset of patients that underwent blood immunomonitoring. Shown are the odd ratios (OR) with 95% CI together with their statistic value and the Wald interaction test.

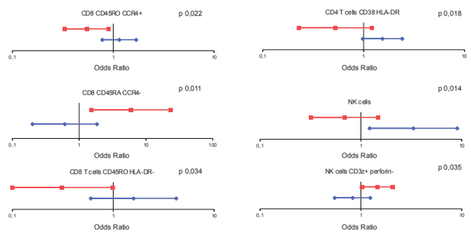


Figure 6. Association of blood biomarkers with clinical outcome
Univariate association between blood biomarkers at T1 and pCR. Shown are the OR with 95% CI for the immunomonitored patients (n=120) together with the significance in the Wald interaction test .

Conclusions

- The treatment induce a reduction in the absolute number of mononuclear cells in the blood:
  - strongest effects are at T4 (i.e. due to EC) and on B (almost total loss) and NK cells (halved);
  - Durvalumab patients at T4 have an increase in granulocytes.
- Treatment with Durvalumab induce a strong reduction in the number of PDL1+ cells, both in T cells and CD45neg (possibly circulating tumor cells), both with and without window treatment:
  - There is no variation in the expression of the receptor PD1 and no (enhanced) upregulation of possible escape mechanisms like Tim-3.
- The window treatment cohort has significant better Odds Ratio for pCR in the whole cohort of the clinical trial, but not in the immunomonitored patients.
- Various subsets of CD4+ and CD8+ T cells as well and NK cells have prognostic significance.

The trial and translational research project were funded by AstraZeneca and Celgene, respectively

Printed by Call4Posters

BCP Breast Cancer in Pregnancy
P1-17-07

Cancer management and outcome of very young non-pregnant patients with breast cancer diagnosed at 40 years or younger – GBG 29

Seiler S[1], Schmatloch S[2], Reinisch M[3], Neunhöffer T[4], Schmidt M[5], Bechtner C[6], Marmé F[7], Wagner M[8], Möbus V[9], Reimer T[10], Kleine-Tebbe A[11], Sinn B[12], Stickeler E[13], Untch M[14], Janni W[15], Seither F[1], Loibl S[1]

[1] German Breast Group, Neu-Isenburg, Germany; [2] Brustzentrum, Elisabeth Krankenhaus Kassel, Germany; [3] Brustzentrum, Kliniken Essen-Mitte, Essen, Germany; [4] Helios Dr. Horst Schmidt Kliniken, Wiesbaden, Germany; [5] Universitätsmedizin Mainz, Germany; [6] Brustzentrum, Klinikum Memmingen, Germany; [7] Allgemeine Frauenheilkunde und Geburtshilfe, Universitätsklinikum Heidelberg, Germany; [8] Sloah St. Trudpert Klinikum, Pforzheim, Germany; [9] Klinik für Gynäkologie und Geburtshilfe, Klinikum Frankfurt Höchst, Germany; [10] Universitätsfrauenklinik und Poliklinik am Klinikum Südstadt Rostock, Germany; [11] Brustzentrum, DRK Kliniken Berlin, Germany; [12] Institut für Pathologie, Charité - Universitätsmedizin Berlin, Germany; [13] Frauenheilkunde und Geburtshilfe, Universitätsklinikum Freiburg, Germany; [14] HELIOS Klinikum Berlin Buch, Germany; [15] Frauenheilkunde und Geburtshilfe, Universitätsklinikum Ulm, Germany

Background

- Breast cancer (BC) diagnosed in young women who are ≤ 40 years is a relatively rare disease. However, it represents the most common cause of cancer-related deaths in this age group.[1]
- Young age at diagnosis is associated with an increased risk of recurrence and worse survival. The prognostic relevance of young age by itself is controversial. Although some data suggest that BC in young women has a unique biology, other studies have shown that BC subtype varies from that in older patients and worse clinicopathological features and more aggressive subtypes are related with inferior survival outcomes.[2,3]
- To date, general concepts concerning oncological management should be driven by clinicopathological tumor characteristics and should adhere to standardized protocols for patients in general.[4]
- Yet, young patients need more individualized care and to date, little is known about the treatment of young women of ≤ 40 years in everyday clinical practice.

Patients and Methods

- BCP (GBG 29/BIG 03-02) is a large multicenter, international, observational study with a prospective and retrospective data collection. BCP was established to investigate the oncological management and outcome of BC in pregnancy. Since 2014 non-pregnant patients who are ≤ 40 years are eligible if diagnosed with histological confirmed invasive BC, independent of the type of treatment as control cohort. All patients receive oncological treatment according to local standards.
- All patients fulfilling the following criteria in June, 2018 were included in the full analysis set: patients must not be pregnant at the time of BC diagnosis and age ≤ 40 years.
- Patient characteristics, clinicopathological tumor characteristics, disease stage, treatment modalities, side effects, and pregnancies were collected from medical records. Actual clinical follow-up data of patients was collected from prospectively included patients.
- Continuous data were summarized as median, minimum and maximum, categorical data (including pathological complete response (pCR) rates) as number and valid percent of patients.
- The three year disease free survival (DFS) and overall survival (OS) rates and the corresponding 95% CIs will be estimated using the Kaplan-Meier method.

Objectives

- The aim of this analysis is to report descriptively baseline characteristics, as well as information on diagnostic procedures, BC therapy, short-term (pCR rates for patients treated with neoadjuvant therapy) and long-term (DFS, OS and pregnancies after diagnosis) outcome for non-pregnant women with an age ≤ 40 years.

Table 1. Patient and tumor characteristics

Parameter	Category	N (valid %)
	Median (min,max)	35 (19,40)
Age	18-29	137 (14.3)
	30-34	267 (27.9)
	35-40	552 (57.7)
	Ductal invasive	815 (86.9)
Histological tumor type	Lobular subtype	38 (4.1)
	Ductal and lobular invasiv	5 (0.5)
	Other	80 (8.5)
Tumor site	Unilateral	938 (98.1)
	Bilateral	18 (1.9)
	cT1	380 (41.5)
cT	cT2	447 (48.9)
	cT3/cT4	85 (9.2)
	cN0	586 (67.0)
cN	cN1	254 (29.1)
	cN2/cN3	34 (3.9)
	M0	868 (93.2)
Metastasis at primary diagnosis	M1	30 (3.2)
	MX	33 (3.5)
	G1	38 (4.1)
Grading	G2	377 (40.7)
	G3	511 (55.2)
Ki-67	<20%	116 (16.8)
	≥20%	576 (83.2)
Hormone receptor (HR) status	HR positive	642 (67.4)
	HR negative	311 (32.6)
	HER2-/HR+	395 (42.7)
	TNBC	235 (25.4)
Biological subtype	HER2+/HR+	222 (24.0)
	HER2+/HR-	73 (7.9)

Figure 1. pCR rates (ypT0 ypN0) according to biological subtype and age groups

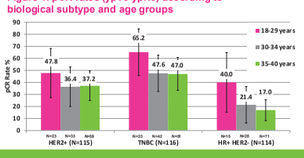


Figure 2. Disease-free survival of young women according to biological subtype and age

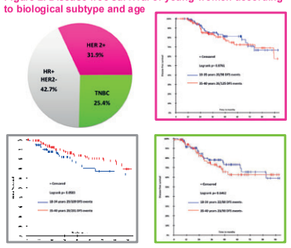
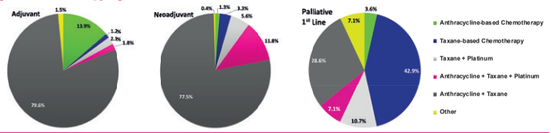


Table 2. Oncological management

Parameter	Category	N (valid %)
Early Breast Cancer		
Chemotherapy	Yes	735 (90.7)
	No	75 (9.3)
Setting of chemotherapy	Neoadjuvant	416 (56.6)
	Adjuvant	319 (43.4)
Endocrine therapy	Tamoxifen	238 (59.9)
	Aromatase inhibitor (AI)	8 (2.0)
	Tamoxifen + GnRH analogue	133 (33.5)
	AI+ GnRHa analogue	15 (3.8)
	Sequential endocrine therapy	3 (0.8)
Anti HER2 therapy	Trastuzumab	123 (65.1)
	Trastuzumab + Pertuzumab	66 (34.9)
	None/missing	106
Breast surgery	Breast conserving surgery	491 (64.5)
	Mastectomy	241 (31.7)
	None	29 (3.8)
Nodal surgery	Sentinel node biopsy	404 (50.3)
	Axillary dissection	340 (42.3)
	None	59 (7.3)
Metastatic Breast Cancer		
1st Line Chemotherapy	Yes	22 (88.0)
	No	3 (12.0)
	Missing	5

Figure 3. Chemotherapy regimes



Results

- From April 2003 until June 2018, 1812 pregnant and non-pregnant patients have been registered. 964 non-pregnant women ≤ 40 years with a median follow-up of 38.7 months (95%CI; 35.2; 41.3) comprised the analysis set.
- The median age at diagnosis was 35 years (range 19-40). Overall, 90.4% of patients had a stage T1-2 at diagnosis and 67.0% had negative lymph nodes. Further patient and tumor characteristics are shown in Table 1.
- At primary diagnosis 95.3% of patients underwent ultrasound, 88.5% mammography, and 23.5% magnetic resonance imaging of the breasts.
- 82.8% of patients with HR+ HER2- early breast cancer (EBC), 99% with triple-negative EBC, and 95.2% with HER2+ EBC received chemotherapy (CT). Most patients (88.0%) with advanced BC were treated in the 1st line mBC setting with CT. 93.4% of patients with endocrine treatment for EBC received tamoxifen; thereof 35.8 % in combination with a GnRH analogue. Further details about oncological management are shown in Table 2. Figure 3 provides an overview of administered CT regimes in EBC and advanced BC.
- Regardless of biological subtype of BC, the highest pCR rates (ypT0 ypN0) were achieved in the cohort of patients age18-29 years; Figure 1 shows the pCR rates according to biological subtype and age groups.
- The 3-year DFS for patients with EBC was 83.1% (95%CI; 79.6%; 86.0%) and the 3-year OS 94.3% (95%CI; 91.9%; 96.0%). The subgroup analysis per biological subtype suggested a trend towards inferior DFS in the group of patients ≤34 years and HR+ HER2−disease (logrank p=0.0583; Figure 2).
- In multivariate analysis DFS and OS were with significantly worse in patients with EBC and initial cN+ and grade 3 tumors (data not shown).
- 33 patients (3.4%) got pregnant after diagnosis of BC with a median time from diagnosis to birth/termination of 3 years (range 2-7).

Conclusions

- This registry comprises a large cohort of young non-pregnant patients below the age of ≤40 years.
- The reported treatments reflect the modern oncological management of very young patients with almost 91% of all patients receiving neoadjuvant or adjuvant chemotherapy.
- Regardless of biological subtype, the highest pCR rate was achieved in the group of patients <30 years.
- The prognostic relevance of young age by itself could not be shown for patients with HER2+ and triple-negative disease. Yet, similar to previously reported results[5] our data suggest a trend towards inferior DFS in the group of patients ≤34 years and HR+ HER2− disease.
- Registry needs to be continued to get more valid prospective information.

References

1. Ferlay, J. et al. Int J Cancer. 2010; 127: 2893–2917.
2. Azim HA Jr, et al. Clin Cancer Res. 2012 Mar 1;18(5):1341-51.
3. Keegan TH, et al. Breast Cancer Res. 2012 Mar27;14(2):R55.
4. Partridge AH, et al. Breast. 2014 Jun;23(3):209-20.
5. Loibl S, et al. Breast Cancer Res Treat. 2015 Jul;152(2):377-87.

Presented at: San Antonio Breast Cancer Symposium - December 4-8, 2018

New Study Concepts

Interview with Prof. Dr. Marcus Schmidt, Coordinating Investigator of the ALEXANDRA/IMpassion030 trial in Germany

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

Prof. Dr. Marcus Schmidt
Universitätsfrauenklinik Mainz

ALEXANDRA/IMpassion030 (BIG 16-05/AFT-27/WO39391) is an international, multicenter, randomized, open-label, controlled phase III trial to evaluate the efficacy, safety, and pharmacokinetics of adjuvant treatment with atezolizumab plus paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide (atezolizumab + T-AC/EC) compared with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide alone (T-AC/EC) in patients with stage II-III triple-negative breast cancer (TNBC).

Primary objective: to evaluate the invasive disease-free survival (iDFS) of adjuvant atezolizumab + T-AC/EC compared with T-AC/EC alone in patients with TNBC.

1. What is the rationale for targeting TNBC with immunotherapeutic agents?

It is well accepted that the immune system plays an important role in breast cancer growth and progression, but also in tumor elimination. Tumor associated antigens (TAAs) can be recognized by the immune system and can evoke an immune response leading, under certain conditions, to tumor rejection. TNBC is known to be more immunogenic compared to other breast cancer subtypes with tumor-infiltrating lymphocytes (TILs) playing an important prognostic and predictive role. Furthermore, TNBC has higher levels of a programmed cell death-ligand 1 (PD-L1) expression. Therapeutic blockade of the PD-L1 expression using immune checkpoint inhibitors (ICPi) like atezolizumab is expected to activate and to enhance tumor-specific T-cell responses, resulting in an improved antitumor activity. Thus, the ICPi like atezolizumab might tilt the balance in favor of the immune system especially in TNBC.

2. What are the advantages of combining atezolizumab with chemotherapy in patients with TNBC?

Used as a single agent, ICPi have only modest activity in TNBC. A reason for this might be that the mutational load in breast cancer is considerably lower compared with other malignant tumors like melanoma or non-small cell lung cancer (NSCLC). Chemotherapy has the potential to increase the mutational load and thereby generating more neoantigens in TNBC. Thus, combining ICPi like atezolizumab with chemotherapy is a promising approach. A recently published double-blind, randomized phase III study IMpassion 130 confirmed the clinical efficacy of atezolizumab in combination with nab-paclitaxel in previously untreated metastatic or unresectable locally advanced TNBC patients. The results of the study showed that the atezolizumab therapy combined with nab-paclitaxel significantly prolonged progression-free survival. Moreover, atezolizumab significantly prolonged overall survival in patients with PD-L1-positive tumors.

3. Are there any clinical data concerning safety profile of atezolizumab in TNBC?

In the pivotal phase III study (Impassion 130), adverse events (AE) occurred more often in the atezolizumab–nab-paclitaxel group. Grade 3 or 4 AE including serious adverse events (SAE) were also increased in patients treated with atezolizumab. Moreover, grade 3 or 4 AEs of special interest with a potential immune-related cause were also increased in patients receiving atezolizumab (7.5 %w vs. 4,4 %w). Discontinuation of atezolizumab due to AEs was also increased (6.4 % vs. 1.4 %). However, these toxicities were manageable and consistent with the known safety profile of atezolizumab.

4. What are the future perspectives for treatment of TNBC?

As outlined above, the combination of atezolizuamab with taxane-containing chemotherapy showed a remarkable efficacy in advanced TNBC. As a next logical step, atezolizumab combined with chemotherapy is investigated in early TNBC (Impassion 030). An exciting further study concept might be the combination of atezolizumab with poly-ADP-ribose-polymerase (PARP) inhibitors in TNBC harbouring a BRCA mutation since DNA damage should lead to increased immunogenicity.

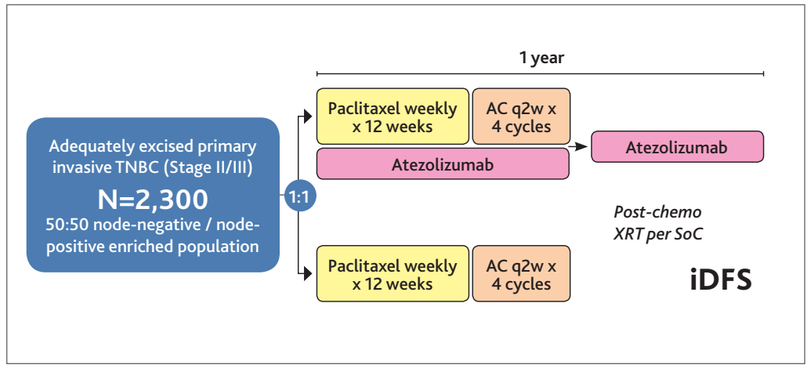


Figure 1: Study design of the ALEXANDRA/IMpassion030 study

Interview with Prof. Dr. Sibylle Loibl, International Principal Investigator of the GeparTreize trial

A phase III, randomized, open-label study investigating the addition of durvalumab to an anthracycline-taxane based chemotherapy in early-stage triple-negative breast cancer

Prof. Dr. Sibylle Loibl
Chair of the
German Breast Group,
GBG Forschungs GmbH,
Neu-Isenburg

GeparTreize is an international, multicenter, prospective, randomized, open-label, parallel-group phase III trial to evaluate the potential incremental efficacy and safety of neoadjuvant and adjuvant administration of durvalumab in early-stage triple-negative breast cancer (TNBC). Patients will be randomized to receive either a sequential regimen of weekly paclitaxel (with or without carboplatin weekly or once every three weeks, at the discretion of the investigator) followed by epirubicin/cyclophosphamide (EC) or doxorubicin/cyclophosphamide (AC) administered once every two or three weeks with durvalumab (IMP arm) or alone (non-IMP arm) in the neoadjuvant setting. Patients will then undergo surgery 3-6 weeks after the last chemotherapy application. Following recovery from surgery, patients will continue for another 12 months adjuvant therapy with durvalumab vs. no treatment.

Co primary objectives/endpoints:

1) To compare pathological complete response (pCR) in the breast and axillary lymph nodes (pCR=ypT0/ypN0) rates between TNBC patients treated with durvalumab concurrently given to chemotherapy (weekly paclitaxel +/- carboplatin followed by EC or AC) vs. chemotherapy alone.
2) To compare event-free survival rates between TNBC patients treated with durvalumab concurrently given to chemotherapy (weekly paclitaxel +/- carboplatin followed by EC or AC) followed by adjuvant treatment with durvalumab vs. no study treatment (observation).

1. Could you consider the new immunotherapeutic approaches including checkpoint inhibitors and neoadjuvant immunotherapy as encouraging for the future treatment of triple-negative breast cancer (TNBC)?

To date no targeted agents are available to treat early-stage TNBC and chemotherapy is currently the only available systemic treatment option. TNBC often has a high amount of tumor infiltrating lymphocytes (TILs) correlating with improved outcome as well as an increased mutation frequency compared to other breast cancer subtypes. A combination of immune checkpoint inhibitors with chemotherapy for the treatment of TNBC holds great promise as shown in GeparNuevo. In this phase II trial conducted with early-stage TNBC patients, the addition of durvalumab, a fully human monoclonal antibody targeting programmed cell death ligand-1 (PD-L1), to anthracycline/taxane based chemotherapy increased the pCR rate by absolute 9 %, although this was not statistically significant.
Additionally, results from the phase II I-SPY2 trial suggested an increase in pCR by adding pembrolizumab from 20 % with paclitaxel-EC alone to 60 % with pembrolizumab plus standard therapy. The phase Ib KEYNOTE-173 study demonstrated a pCR rate with the addition of pembrolizumab of 50 % in the non-carboplatin cohort and 58 % in the carboplatin cohort. As no final conclusion can be drawn from these results, the combination of immunotherapy with chemotherapy should be further investigated in TNBC.

2. Could you further discuss the use of PD-1/PD-L1 inhibitors prior to start of chemotherapy for early-stage TNBC?

In the GeparNuevo study there was a cohort of patients who received durvalumab as a single agent 2 weeks prior to start of chemotherapy (window). Interestingly, in this cohort a statistically significant higher pCR rate was observed in comparison to patients without induction therapy. These findings suggest that induction therapy with durvalumab seems to be beneficial for early-stage TNBC.

3. What needs special attention in the design of the GeparTreize study?

The GeparTreize is a prospective, randomized, open-label, phase III trial aiming to evaluate the efficacy and safety of durvalumab in addition to standard neoadjuvant chemotherapy after a priming dose of durvalumab followed by adjuvant therapy with durvalumab in TNBC. Patients will be randomly assigned to receive durvalumab plus neoadjuvant chemotherapy or chemotherapy alone. A sequential regimen of weekly paclitaxel with or without carboplatin followed by an anthracycline in combination with cyclophosphamide will be administered as neoadjuvant treatment. Moreover, the administration of carboplatin and anthracycline (doxorubicin or epirubicin) schedule is at the discretion of the investigator. Thus, with regard to chemotherapy, the study is designed to be as open as possible. Following surgery patients in the durvalumab arm will continue for another 12 months adjuvant therapy with durvalumab.

4. Are there any biomarkers identified that can be used to predict response to immune-checkpoint inhibitors in TNBC?

It was demonstrated that immune components such as stromal TILs are predictive and prognostic in TNBC. Biomarker exploratory analysis in the GeparNuevo showed a trend for increased pCR rates in PD-L1-positive tumors, which was significant for PD-L1-positive tumor-cells in the durvalumab arm (p=0.045) and for PD-L1-positive immune-cells in the placebo arm (p=0.040). We hope that GeparTreize could answer the question whether PD-L1 is an appropriate biomarker to select patients benefitting from PD-L1 inhibitors and the best way to assess it.

5. What are your expectations regarding the outcome of this trial?

Based on the very challenging design of GeparTreize trial we expect that the addition of durvalumab to neoadjuvant/adjuvant chemotherapy will result in a meaningful increase of pCR rate that could be translated into a survival benefit without a significant increase of toxicity.

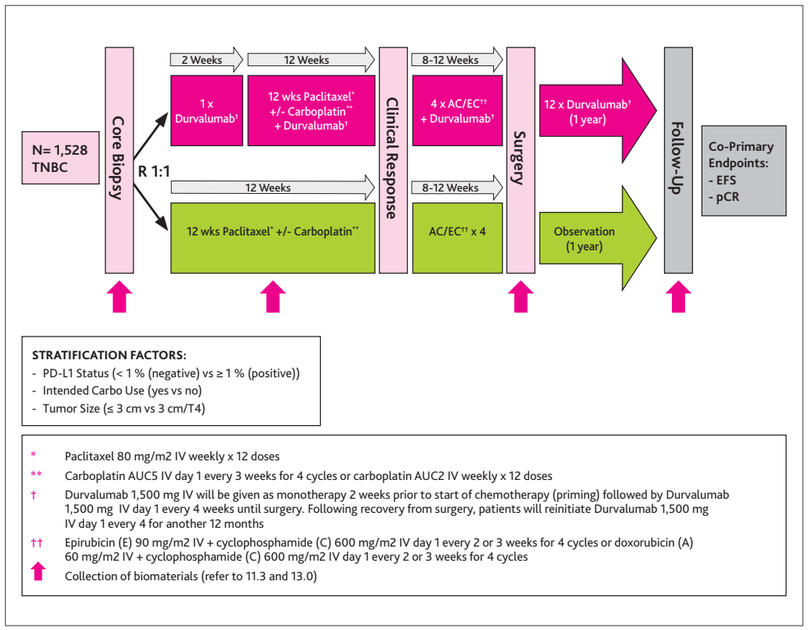


Figure 1: Study design of the GeparTreize study

Recruiting Studies

GBG 91: TAMENDOX

CONTACT:
Dr. Mathias Uhlig
Clinical Project Management
tamendox@GBG.de

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

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

Background

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

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

Independent clinical studies demonstrated that genetically determined low (Z)-endoxifen levels predict higher relapse rates in pre- and postmenopausal women (Madlensky et al. Clin Pharmacol Ther 2011; Saladores et al. Pharmacogenomics J 2015; Helland et al. Breast Cancer Res 2017). The available evidence has recently been addressed by the Clinical Pharmacogenetics Implementation Consortium (CPIC®) (Goetz et al. Clin Pharmacol Ther 2018).

The concept TAMENDOX study is based on a different novel approach which pursues the supplementation of standard adjuvant tamoxifen (20mg/d) with only low doses of (Z)-endoxifen (up to 3 mg/d). In collaboration with Bayer, the doses used in this study have been calculated and validated by physiology-based pharmacokinetic (PBPK) modeling (Dickschen et al. Front Pharmacol 2012; Dickschen et al. Springerplus 2014). (Z)-endoxifen concentrations as found in normal metabolizers (EM) can be attained by IM and PM patients in this way. Evidence from in vitro modeling experiments of a premenopausal setting have already demonstrated that breast cancer cell killing can be improved by adding endoxifen to standard tamoxifen (Maximov et al. J Natl Cancer Inst 2014).

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

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

The TAMENDOX trial is designed to show that (Z)-endoxifen supplementation in IM and PM patients will increase their steady state plasma concentrations of (Z)-endoxifen to the level found in patients without compromised metabolism, i.e. EM or ultrarapid metabolizers (UM). The trial is not designed to evaluate outcome measures of (Z)-endoxifen supplementation in tamoxifen treated patients.

Study design and objectives

TAMENDOX aims to evaluate the supplementation of tamoxifen with low dose (Z)-endoxifen to overcome the impaired bioactivation of tamoxifen to its active metabolite (Z)-endoxifen in patients with compromised CYP2D6 activity.

Pre- and postmenopausal women with ductal carcinoma in situ (DCIS) or Stage I, IIA, IIB or IIIA invasive BC who have received at least three months standard tamoxifen treatment before baseline visit are eligible.

Tamoxifen treatment (20 mg/day) for at least three months in premenopausal and postmenopausal patients is mandatory prior to the start of the study, and will be continued during intervention period without change of dosage. During the intervention, a daily oral dose of (Z)-endoxifen or placebo will be given according to CYP2D6 genotype or (Z)-endoxifen plasma concentrations (phenotype): group 1 (control group) will receive placebo independent of CYP2D6 genotype or (Z)-endoxifen plasma concentration; group 2 will receive (Z)-endoxifen dosed according to CYP2D6 "genotype" (i.e. genotype predicted IM or PM activity) or placebo (genotype predicted EM / UM), and group 3 will receive (Z)-endoxifen dosed according to (Z)-endoxifen steady state plasma concentrations (phenotype) at screening (i.e. ≤ 15 nM or > 15 and ≤ 25 nM) under tamoxifen treatment with 20 mg/day or placebo (> 25 nM). The intervention period will be 6 weeks to assure steady-state levels.

Primary objective is to increase (Z)-endoxifen steady-state concentrations in patients with compromised CYP2D6 activity to levels observed in patients with full CYP2D6 activity. The target concentration is > 32 nM.

Secondary objectives are 1) to increase (Z)-endoxifen steady state concentrations in patients with CYP2D6 genotype predicted PM activity to levels observed in patients with full CYP2D6 activity by supplementation with 3 mg/day (Z)-endoxifen (> 32 nM); 2) to increase (Z)-endoxifen steady state concentrations in

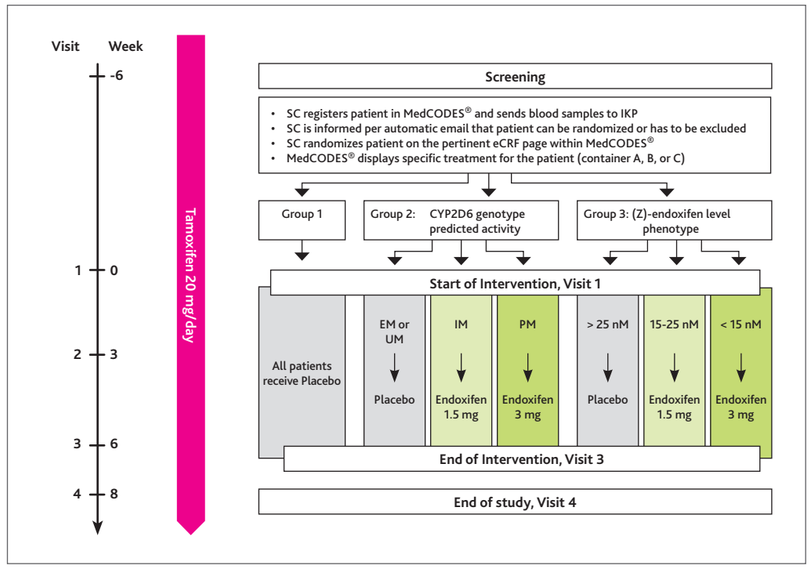


Figure 1: TAMENDOX study design

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

patients with CYP2D6 genotype predicted IM activity to levels observed in patients with full CYP2D6 activity by supplementation with 1.5 mg/day (Z)-endoxifen (> 32 nM); 3) to increase (Z)-endoxifen steady state concentrations in patients with basal (Z)-endoxifen plasma levels ≤ 15 nM to levels observed in patients with full CYP2D6 activity by supplementation with 3 mg/day (Z)-endoxifen (> 32 nM); 4) to increase (Z)-endoxifen steady state concentrations in patients with basal (Z)-endoxifen plasma levels > 15 nM and ≤ 25 nM to levels observed in patients with full CYP2D6 activity by supplementation with 1.5 mg/day (Z)-endoxifen (> 32 nM); 5) to assess safety of low dose (Z)-endoxifen supplementation; 6) to assess and compare steady state plasma levels of tamoxifen, desmethyltamoxifen, 4-hydroxtamoxifen, and possible other tamoxifen metabolites between the intervention groups and control group.

Study report:
TAMENDOX study protocol is expected to be approved by the regulatory authorities in the QI/2019. 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 planned to last up to one year.

GBG 96: GeparDouze

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

NCT03281954

GeparDouze (NSABP B-59) is an international, multicenter, prospective, randomized, double-blind, phase III trial that will recruit 1,520 patients from up to 120 sites in approximately 4 countries within about 33 months.

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

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

GeparDouze

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

This will allow for collection of safety data related to co-administration of atezolizumab with radiation therapy on a blinded, placebo-controlled trial.

Patients will be 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 region (North America; Europe), tumor size (1.1-3.0 cm; > 3.0 cm), EC/AC (q2w; q3w), and nodal status (positive; negative). Patients with primary cT1c-cT3 TNBC and centrally assessed hormone receptor-status, HER2-status, Ki-67, and stromal tumor-infiltrating lymphocytes (sTILs) on core biopsy can be enrolled.

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

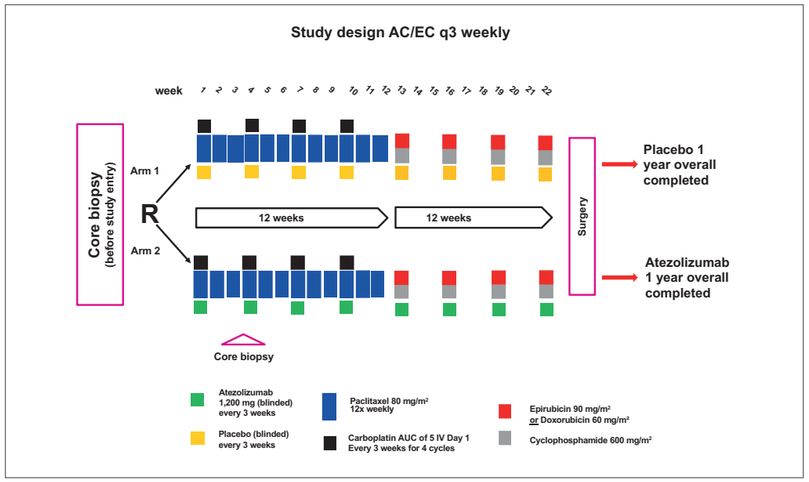


Figure 1: GeparDouze study design

Study report:

GeparDouze recruitment started in December 2017. As of 31st December, there are 33 patients enrolled in the study. Follow-up of an additional 39 months after completion of accrual is planed to obtain 298 EFS events. The expected study duration is approximately 72 months [1-3].

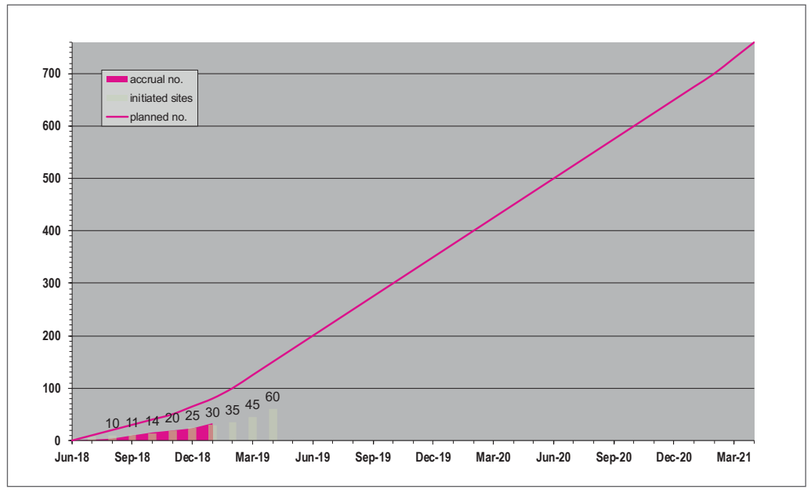


Figure 2: GeparDouze recruitment as of 31st December 2018

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

Publications

1. Geyer CE, Loibl S, Rastogi P et al. NSABP B-59/GBG 96-GeparDouze: A randomized double-blind phase III clinical trial of neo-adjuvant chemotherapy (NAC) with atezolizumab or placebo in Patients (pts) with triple negative breast cancer (TNBC) followed by adjuvant atezolizumab or placebo. J Clin Oncol 2018; 36.15_suppl, TPS603.
2. Loibl S, Jackisch C, Seiler S et al. A Randomized, Double-Blind, Phase III Trial of Neoadjuvant Chemotherapy with Atezolizumab/Placebo in Patients with Triple-Negative Breast Cancer Followed by Adjuvant Continuation of Atezolizumab/Placebo (GeparDouze). 38. Jahrestagung Deutsche Gesellschaft für Senologie 2018; TIP-poster.
3. Geyer CE, Loibl S, Rastogi P et al. A randomized double-blind phase III clinical trial of neoadjuvant chemotherapy (NAC) with atezolizumab or placebo in patients (pts) with Triple Negative Breast Cancer (TNBC) followed by adjuvant atezolizumab or placebo: NSABP B-59/GBG 96-GeparDouze. SABCS 2018; TIP-poster.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

NSABP National Surgical Adjuvant Breast and Bowel Project PARTNERS IN CANCER RESEARCH

SPONSOR:
NSABP Foundation Inc

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

GBG 97: AMICA

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

CONTACT:
Viktoria Tierbach
Clinical Project Management
amica@GBG.de

NCT03555877

AMICA is a multicenter, prospective, randomized open-label, controlled phase II study that will recruit 150 patients from 20-30 sites in Germany within approximately 14 months.

Background

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

Study design and objectives

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

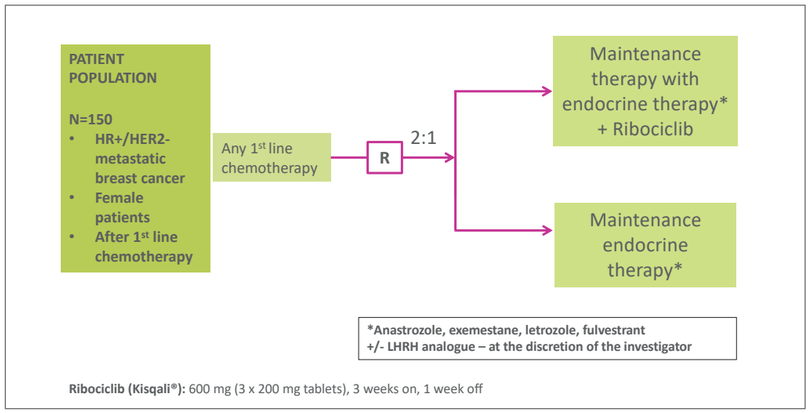


Figure 1: AMICA study design

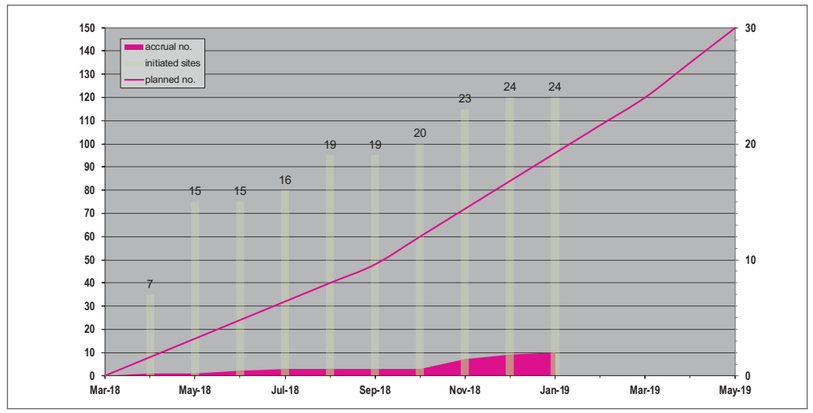


Figure 2: AMICA recruitment as of 31st December 2018

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.

An amendment of the study protocol (approved on 5th November, 2018) includes the following changes: a) inclusion of patients who had previously received a CDK4/6 inhibitor; b) permission of using herbal medication during study therapy; c) permission of surgery for primary tumor at the discretion of the investigator; d) exclusion of tamoxifen, one of the possible endocrine therapies, due to new data reported from the MONALEESA-7 trial [2].

Study report:

AMICA recruitment started in March 2018. As of 31st December 2018, there were 10 patients enrolled in the study. The expected study duration is 21 months.

Publications:

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

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

SPONSOR:
GBG Forschungs GmbH

COORDINATING INVESTIGATOR
Prof. Dr. Thomas Decker
Gemeinschaftspraxis
Onkologie Ravensburg

GBG 93: PADMA

CONTACT:
Dr. Mathias Uhlig
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 130 sites worldwide 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. In addition, we assume that patient reported outcome (PRO) as measured by FACT-B, and a novel composite endpoint of well-being and healthcare utilization as measured by daily monitoring treatment impact (DMTI) will be improved with palbociclib + ET vs. CT regimen.

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

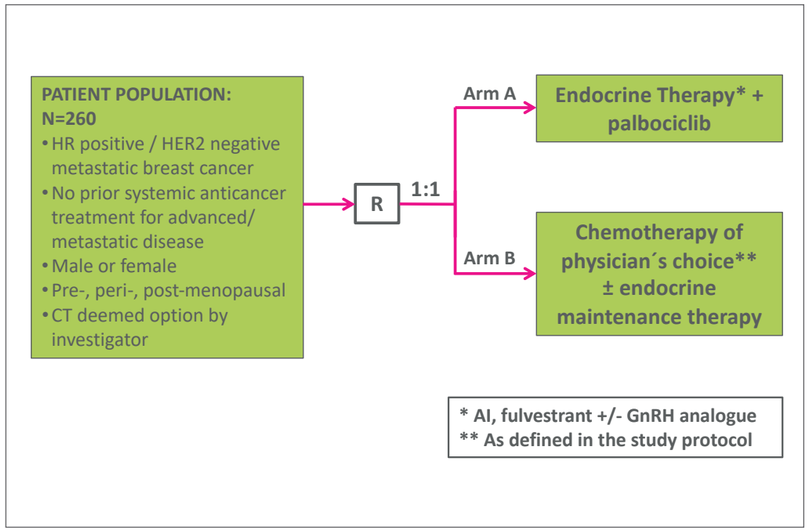


Figure 1: PADMA study design

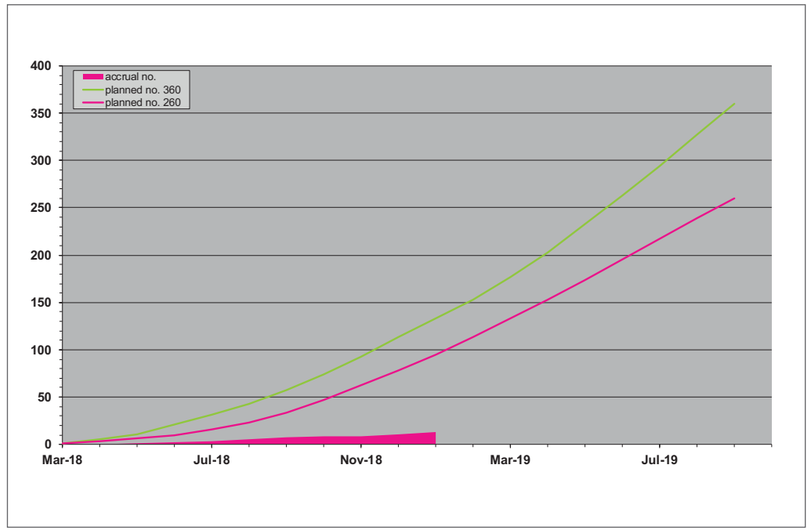


Figure 2: PADMA recruitment as of 31st December 2018

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

Study report:
PADMA recruitment started in March 2018 in Germany (worldwide start is expected in QI/2019). As of 31st December 2018, there are 13 patients enrolled in the study. The end of the study (i.e. last visit of the last patient randomized) is estimated for 2021 [1-3].

Publications:

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

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

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 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.

Translational research
Translational research will be performed to compare progression-free survival based upon investigator assessment of progression between patients in the two treatment arms in the subset of patients with tumors bearing a *PIK3CA* mutation. *PIK3CA* genotype will be assessed in circulating cell-free DNA (cfDNA). The exploratory objectives are to evaluate PFS and OS in genomically-defined BC subgroups based on pre-specified genomic assays; to evaluate base-

PATINA
A COLLABORATIVE STUDY SPONSORED BY ALLIANCE FOUNDATION TRIALS, LLC

CONTACT:
Dr. Mathias Uhlig
Clinical Project Management
patina@GBG.de

line tumor- and blood-based markers as predictors of benefit from the addition of palbociclib to anti-HER2 therapy plus ET; to evaluate tumor- and blood-based markers at the time of disease recurrence for mechanisms of resistance to therapy; to compare serial levels of cfDNA in patients receiving anti-HER2 therapy plus ET versus anti-HER2 therapy plus ET plus palbociclib; to compare mutational profile/copy number variants obtained from tumor tissue to those measured in cfDNA; to determine the trough concentrations of palbociclib when given in combination with trastuzumab plus ET or trastuzumab plus pertuzumab plus ET; to determine trastuzumab and pertuzumab trough concentrations when given in combination with palbociclib plus ET; to explore correlations between palbociclib exposure and efficacy/safety findings in this patient population.

Study report:
PATINA worldwide recruitment started in July 2017, and in Germany in July 2018, respectively. As of 31st December 2018, a total of 93 patients have been enrolled in the study worldwide of which there is currently no patient from Germany. Enrollment is targeted to be completed by June 2019 and the last patient last visit is expected for June 2024 [1-4].

Publications

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

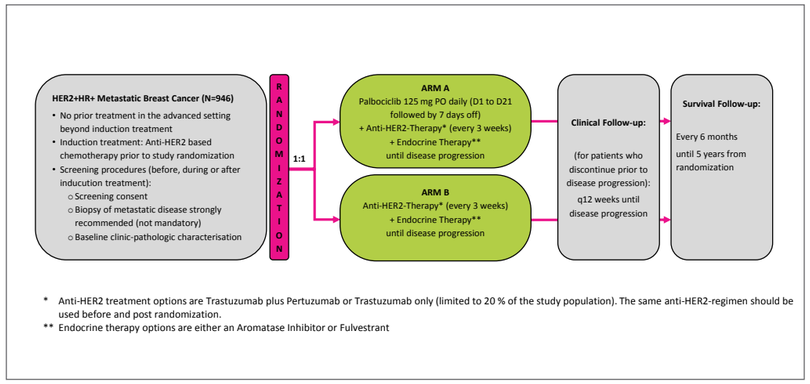


Figure 1: PATINA study design

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP
BREAST CANCER TRIALS
FONDAZIONE MICHELANGELO
PrECOG
SOLTI

SPONSOR:
Alliance Foundation Trials

INTERNATIONAL STUDY CHAIR:
Otto Metzger MD
Alliance Foundation Trials

COORDINATING INVESTIGATOR GERMANY:
Prof. Christoph Mundhenke
UKSH, Klinik für Gynäkologie und Geburtshilfe, Kiel

GBG 95: ULTIMATE

A phase II trial testing durvalumab combined with endocrine therapy in patients with ER+/HER2- breast cancer eligible to neoadjuvant endocrine therapy and who present CD8+ T cell infiltration after 4–6 weeks exposure to immune-attractant

NCT02997995

ULTIMATE (UC-0140/1606; BIG 16-01) is an international, prospective, randomized, open-label, multicenter phase II trial testing aromatase inhibitors in combination with durvalumab in patients with CD8+ T cell infiltration (> 10 % CD8+ T cells in the tumor) that will recruit 240 patients from approximately 35 sites worldwide (8 sites in Germany) within 36 months.

Background
Around 75 % of breast cancers present an estrogen receptor (ER) expression. These patients are sensitive to endocrine therapy (ET). ER-positive breast cancer (BC) includes three groups of patients, i.e. ER-positive/HER2-positive (luminal B HER2); ER-positive/high proliferation (luminal B), ER-positive/low proliferation (luminal A). While the first two groups are sensitive to chemotherapy and ET, the luminal A subtype presents a lower chemosensitivity and a higher endocrine sensitivity. ET and chemotherapy have dramatically improved outcome of ER-positive BC, the mortality rates remain high when the patients present with a T2-4 BC. In a recent meta-analysis, the annual risk of relapse was 3 % and 4 % in patients with T2 and T3/4 BC respectively, translating in a 30 to 40 % risk of relapse at 10 years (Dowsett M et al. Lancet. 2015). This data emphasizes the need to develop new therapies in this group of women. Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) expressed on tumor cells to its receptor programmed cell death 1 (PD-1) expressed on activated T-cells. This may overcome/prevent PD-L1-mediated inhibition/suppression of T-cell activation (Homet M at al. Br J Cancer 2015). Preclinical and clinical evidence has shown that anti-PD-L1 antibodies require CD8+ T-cells on the tumor site to work, and are unlocking an immunosuppressive signaling mediated by PD1 (Tumeh PC et al. Nature 2014). Several studies characterizing the immune landscape of ER-positive/HER2-negative BC have shown that this BC subtype is associated with lower rate of lymphocytic infiltration, especially by CD8+ T-cells. In a study that included 2009 samples, the median infiltration by lymphocytes was 10 in ER-positive/HER2-negative BC as compared to 20 in triple negative BC (Loi S, et al. J Clin Oncol. 2013). In a pooled analysis of four studies, ER-positive/HER2-negative BC presented a lower rate of infiltration by CD8+ T-cells (Ali HR et al. Ann Oncol 2014). Interestingly, while associated with lower infiltration of T-cell, 71 % of ER-positive/HER2-negative BC presented expression of PD-L1 (Arnedos M et al. Ann Oncol 2014, Abst 3510). Finally, analyses from The Cancer Genome Atlas (TCGA) data have suggested that the mutational profile of ER-positive/HER2-negative early BC is not different to the one observed in TNBC (Lefebvre, unpublished data).

Study design and objectives:
The trial includes two sequences: lymphocyte attraction (part 1) and lymphocyte activation (part 2). In the first part of the study patients will receive immune-attractant combined with exemestane for six weeks. After three weeks (+/- 3 days), a tumor biopsy will be performed. Patients having > 10 % CD8+ cells in the tumor after 3 weeks and remain eligible will be included in the second part of the trial i.e. lymphocyte activation. In this second part, patients will receive durvalumab 1,500 mg q4w (equivalent to 20 mg/kg q4w) IV, combined with exemestane (25 mg daily), for six months. The pathological response will be checked by surgery. The second part includes two steps: in the first step 23 patients will be included and if 2 or more of them have a pathological complete response (pCR), additional 33 patients will be included in the second step.
ULTIMATE primarily aims to assess the efficacy of durvalumab combined with exemestane in patients with CD8+ T cells on pathological response at surgery after a lymphocyte attraction phase. Secondary objectives are to evaluate the capacity of several "immune-attractants" approaches to increase CD8+ T cells in the tumor site; to assess the efficacy of six months durvalumab + exemestane combination therapy in ER-positive/HER2-negative BC presenting CD8+ T cells after 4-6 weeks exposure to immune-attractants on secondary endpoints; to evaluate whether durvalumab expands intratumor lymphocytes. Translational research objectives include assessment of the predictive value of mutational load and PD-L1 expression

ULTIMATE

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

COLLABORATING STUDY GROUPS:

SPONSOR:
UNICANCER

INTERNATIONAL STUDY CHAIR:
Prof. Dr. Fabrice André
Institute Gustave Roussy, Villejuif, France

on the efficacy of durvalumab/endocrine therapy; identification of predictive biomarkers for the efficacy of durvalumab/endocrine therapy; comparison of the efficacy of the immuneattractants on the primary endpoint.

Study report:
ULTIMATE recruitment worldwide started in February 2017 (in Germany it is expected to start in QI/2019). Overall trial duration including follow-up will be 3 years.

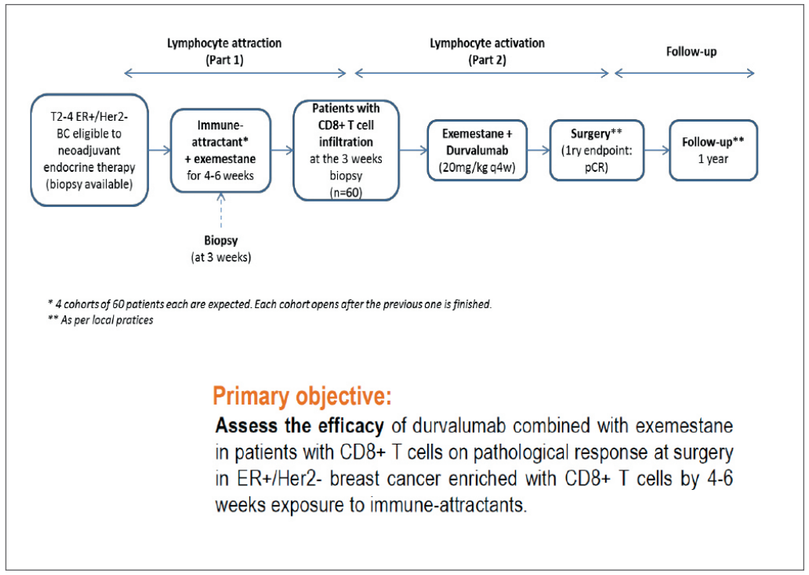


Figure 1: ULTIMATE study design

GBG 88: GeparX

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

NCT02682693

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

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

Study design and objectives
GeparX co-primary aims are to compare the pCR (ypT0 ypN0) rates of neoadjuvant treatment with or without denosumab in addition to backbone treatment consisting of nab-paclitaxel (nP) 125 mg/m² weekly (+ carboplatin [Cb]) followed by epirubicin (E) and cyclophosphamide (C) or nP 125 mg/m² day 1,8 q22 (+ Cb) followed by EC plus anti-HER2 treatment (i.e. trastuzumab/pertuzumab in case of HER2-positive status) and to compare the pCR (ypT0, ypN0) rates of nP 125 mg/m² weekly (+ Cb) followed by EC or nP 125 mg/m² day 1,8 q22 (+ Cb) followed by EC plus anti-HER2 treatment. Cb will be administered concomitantly to nP for patients with triple-negative breast cancer (TNBC).
Secondary objectives are to test for interaction of denosumab treatment with RANK expression, to assess the pCR rates per arm in subgroups and according to RANK immunohistochemical expression (high/low), pCR rates according to other definitions, response rates of the breast tumor and axillary nodes, breast conservation rate, toxicity and compliance as well as to determine loco-regional invasive recurrence free survival, distant-disease-free survival, invasive disease-free survival, event-free survival and overall survival for all treatment arms and according to stratified subpopulations. Further secondary objectives are to compare RANK/L expression and Ki67 from baseline to surgery, to correlate response measured by best appropriate imaging method after the first two cycles of treatment with pCR, to assess mammographic density–changes induced by denosumab and to assess quality of life with a focus on persisting peripheral sensory neuropathy using the FACT-Taxane questionnaire.
In addition, GeparX offers an opportunity to address a range of translational research questions which are summarized below.
An amendment of the study protocol (approved on 27th of July 2017) included the following changes: a) implementation of a HER2-positive substudy in which patients with HER2-positive breast cancer receive trastuzumab biosimilar (ABP 980) in addition to pertuzumab throughout the main trial; after surgery the patients will change to standard Herceptin®; safety and compliance of the patients participating in the substudy will be reported descriptively in treatment arms and b) the GeparPET substudy (designed to investigate whether the presurgical staging with PET-CT in addition to conventional presurgical

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

staging methods can decrease the rate of mastectomy in patients treated with neoadjuvant chemotherapy) has been stopped for futility as recommended by the IDMC based on the interim analysis performed.

Substudies

Pharmacogenetic substudy

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

DTC substudy

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

Substudy on urinary miRNA sampling (UMS)

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

Study report

GeparX recruitment started in February 2017 [1,2]. As of 31st December 2018, there are 702 patients enrolled in the study. An interim safety analysis was performed after the first 200 patients had completed the nab-paclitaxel treatment and the results were presented at the ASCO meeting 2018 [3]. A total of 202 patients randomized to denosumab and nab-paclitaxel treatment (101 patients with weekly and 101 patients with nab-paclitaxel d1,8 q22) were included in the interim analysis, of them 196 started treatment. Overall, median age was 50 (range 23-76) years; 38.1 % of patients were cN+ and 5.0 % had lymphocyte predominant breast cancer (LPBC). 102 patients (50.5 %) had HER2-/HR+, 82 (40.6 %) had triple-negative and 18 (8.9 %) had HER2+ breast cancer. Overall, 13.5 % of patients with and 13.1 % without denosumab discontinued nab-paclitaxel. 21.0 % of patients treated with nab-paclitaxel weekly vs 5.2 % with nab-paclitaxel d1,8 q22 discontinued nab-paclitaxel treatment mainly due to AEs. 17.0 % of patients treated with nab-paclitaxel weekly and 27.1 % with nab-paclitaxel d1,8 q22 reported high grade (grade 3-4) hematological AEs, while 22.0 % of patients treated with nab-paclitaxel weekly and 14.6 % with nab-paclitaxel d1,8 q22 had high grade non-hematological AEs. During nab-paclitaxel treatment overall, 37 SAEs (13 in the HER2-/HR+; 22 in the TNBC and 2 in the HER2+ cohorts) have occurred in a total of 28 patients. These findings demonstrated that the addition of denosumab to neoadjuvant chemotherapy did not increase toxicity. Moreover, weekly nab-paclitaxel resulted in a higher rate of treatment discontinuations mainly due to non-serious AEs, whereas the addition of carboplatin in TNBC resulted in a higher rate of SAEs. Last patient out is expected for QIII/2019 and results of the primary endpoint for QIV/2019.

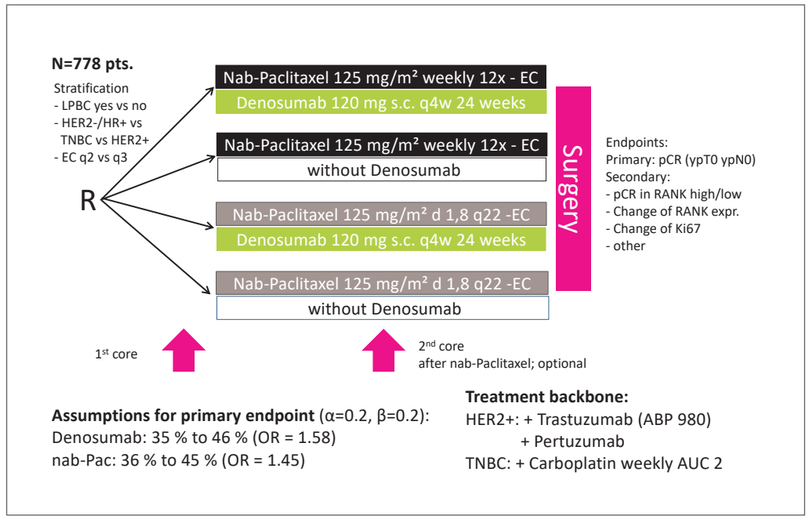


Figure 1: GeparX study design

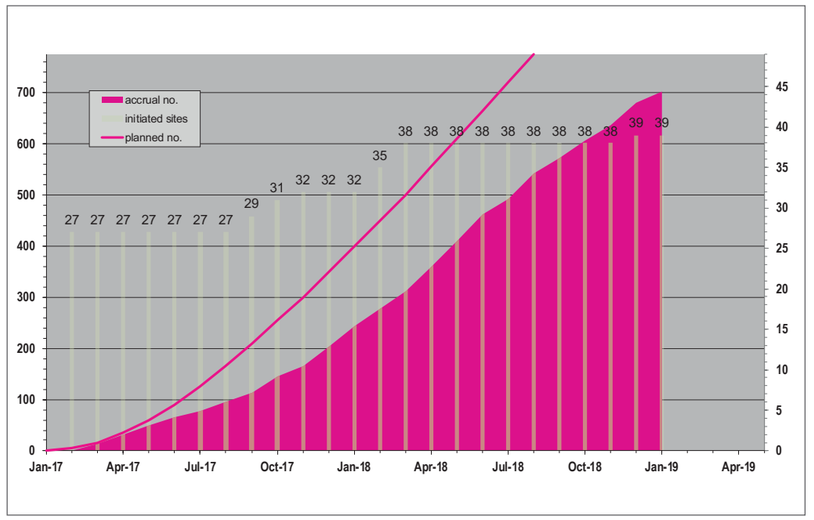


Figure 2: GeparX recruitment as of 31st December 2018

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

Publications

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

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

SPONSOR:
GBG Forschungs GmbH

STUDY CHAIRS:
Prof. Dr. Jens-Uwe Blohmer
Brustzentrum Charité-Universitätsmedizin, Berlin, Germany

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

GBG 87: PALLAS

CONTACT:
Dr. Cornelia Schneider-Schranz
Clinical Project Management
pallas@GBG.de

PALLAS: PALbociclib CoLlaborative Adjuvant Study

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

NCT02513394

PALLAS (ABCSG 42, AFT-05, BIG 14-3) is a multicenter, prospective, international, randomized, open-label, adjuvant phase III study that will recruit 4,600 patients worldwide.

Background

Although many patients with HR-positive (HR+)/HER2-negative (HER2-) breast cancer may be cured of their disease with optimal local and systemic therapy, a significant number of patients with stage II and III disease will experience disease recurrence. Adjuvant endocrine therapy for breast cancer can be extremely effective, particularly with extension beyond 5 years, however disease recurrence can occur, with risk distributed over the decades following initial diagnosis. Methods to improve the efficacy of endocrine therapy, and delay the onset of resistance, are needed.

HR+ breast cancer biologically may demonstrate features suggestive of sensitivity to CDK4/6 inhibition with agents such as palbociclib. Given the demonstrated activity and safety of palbociclib in the first-line treatment of metastatic HR+/HER2- breast cancer, supporting FDA approval, there is interest in whether the benefits of CDK4/6 inhibition may translate into the adjuvant setting. The purpose of the PALLAS study is to determine whether the addition of palbociclib to adjuvant endocrine therapy will improve outcomes over endocrine therapy alone for HR+/HER2- early breast cancer. Assessment of a variety of correlative analysis, including evaluation of the effect of palbociclib in genomically defined tumor subgroups, is planned.

Study design and objectives

PALLAS primarily aims to compare invasive disease-free survival (iDFS) for the combination of at least 5 years endocrine therapy and 2-year palbociclib treatment versus at least 5 years endocrine therapy alone in patients with histologically confirmed HR+/HER2- invasive early breast cancer. Secondary objectives are to compare iDFS excluding second primary cancers of non-breast origin, distant recurrence-free survival (DRFS), locoregional recurrences-free survival (LRRFS), overall survival (OS) and safety between the two arms. The principal translational research objective is to compare baseline tumor tissue to determine whether there is prognostic or predictive utility for defined genomic subtypes (luminal A, luminal B and non-luminal) with respect to iDFS and OS.

Clinical science objectives are to evaluate adherence to oral therapy in patients receiving palbociclib and endocrine therapy, to determine the association of body mass index (BMI) and race with the efficacy of palbociclib and endocrine therapy. Patient reported outcomes objectives are to compare patient-reported quality of life, fatigue, arthralgia, and endocrine symptoms between the two arms overall and by subgroups defined by age at randomization (≤ 50 and > 50) and initial endocrine therapy (tamoxifen and AI) at multiple pre-specified time points. Multiple tissue- and blood-based correlative studies are scheduled throughout the course of the PALLAS trial to evaluate potential markers of response and/or resistance in patients receiving endocrine therapy with palbociclib versus endocrine therapy alone (TRANS-PALLAS). The German Breast Group acts as a local study group for Germany and is responsible for the biobanking organization of the PALLAS study.

Study report

PALLAS started recruitment worldwide in October 2015. In Germany, the study was approved by the Ethics Committee in May 2017 and the recruitment started in October 2017. Two interim efficacy analyses are planned for monitoring the futility and superiority, and are scheduled to occur when 33 % and 67 % of the total number of iDFS events are observed. The expected study duration is 4.8 years [1,2]. Further information about the trial (ABCSG 42/PALLAS) can be found on the ABCSG website:
(https://www.abcsg.org/tag/abcsg-42/)

Publications

1. Mayer E.L, Demichele A.M, Pfeiler G, Barry W, Metzger O, et al. PALLAS: PALbociclib CoLlaborative adjuvant study: A randomized phase 3 trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+/HER2- early breast cancer. Ann Oncol 2017;28: 215TiP.
2. Mayer E, DeMichele A, Gnant M, Barry W, Pfeiler G, et al. PALLAS: PALbociclib CoLlaborative Adjuvant Study: A randomized phase 3 trial of palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for HR+/HER2- early breast cancer. Cancer Res 2018; 78(4 Suppl): OT3-05-08.

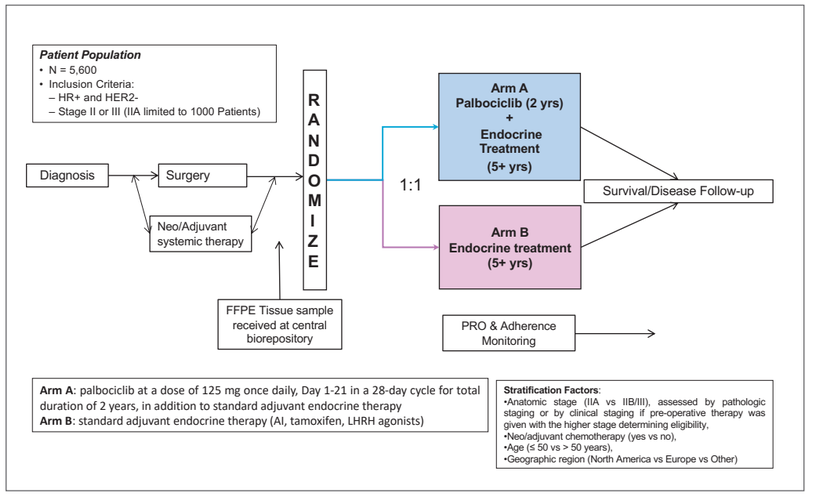


Figure 1: PALLAS study design

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

COLLABORATING STUDY GROUPS:

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

INTERNATIONAL STUDY CHAIRS:
Dr. Erica L. Mayer
Susan F Smith Center for Women's Cancers (US)
Dr. Angela DeMichele
Abramson Cancer Center (US)
Prof. Dr. Michael Gnant
ABCSG (AT)

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

GBG 82: OLYMPIA

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

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

NCT02032823

OLYMPIA (BIG 6-13, NSABP B-55, D081CC0006) is a multicenter, double-blind, parallel group, placebo-controlled, randomized phase III trial that will recruit approximately 1,800 patients from 340 sites in 24 countries within approximately 4 years.

Background

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

Study design and objectives

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

Study report

OLYMPIA started recruitment in September 2014. As of 31st December 2018, a total of 1,679 patients worldwide (179 patients in Germany) have been enrolled in the study. An interim analysis for superiority is planned after 165 iDFS events have been observed from the first 660 patients recruited, which is estimated for approximately 4.5 years after randomization of the first patient. The end of the study (i.e. last visit of the last patient randomized) is estimated for 2028.

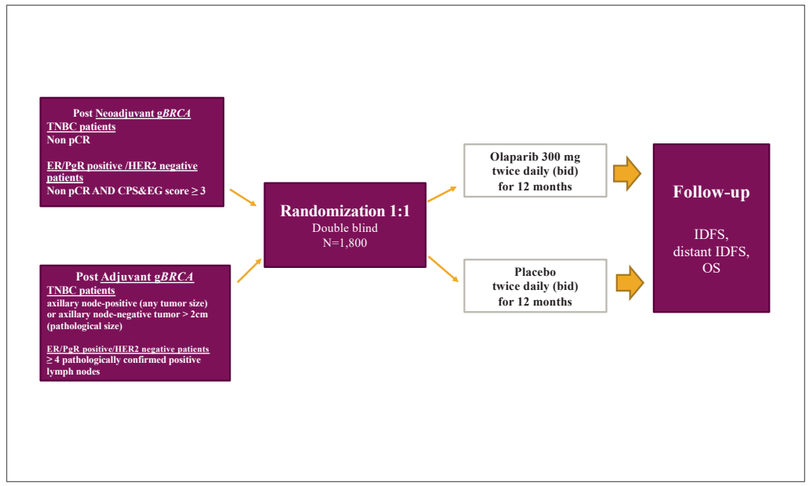


Figure 1: OLYMPIA study design

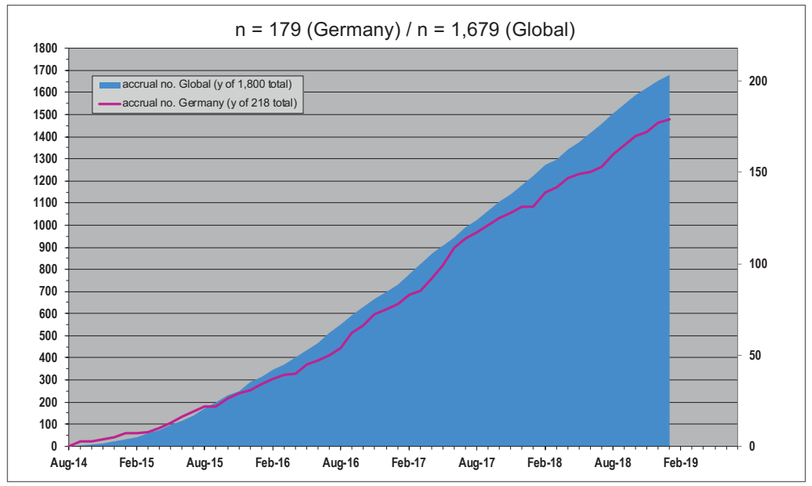


Figure 2: OLYMPIA recruitment as of 31st December 2018

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 OLYMPIA study by recruitment of patients and the timely provision of biomaterial.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

BIG Breast International Group

NRG ONCOLOGY Advancing Research. Improving Lives.™

frontier science

SPONSOR:

AstraZeneca

INTERNATIONAL PRINCIPAL INVESTIGATOR:
Prof. Dr. Andrew Tutt
King's College,
London (UK)

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

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.

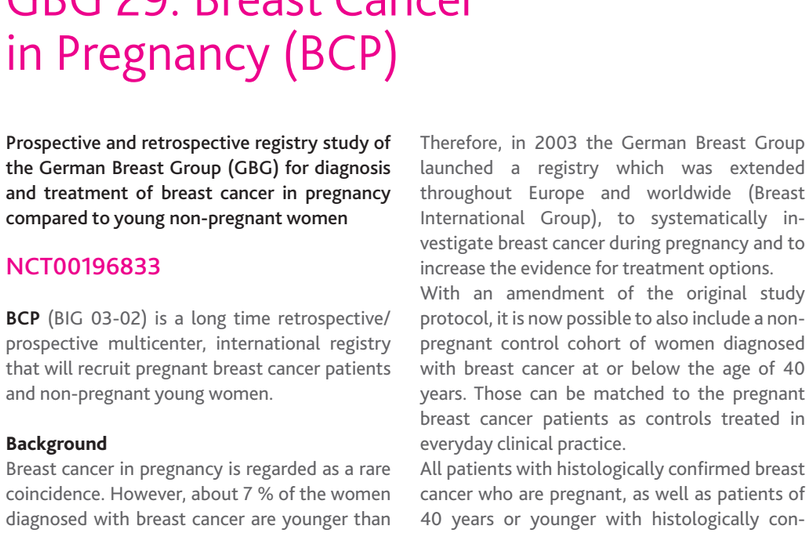


Figure 1: BCP recruitment as of 31st December 2018

Study report

As of 31st December 2018, a total of 1,914 patients have been registered, 1,554 in Germany (512 pregnant and 1024 non pregnant women).
A first analysis of registry data looking at fetal health for up to 4 weeks after delivery included 447 patients and showed that although infants exposed to chemotherapy in utero had a lower birth weight and reported more complications compared to their unexposed counterparts, these differences were not clinically significant. Since none of the infants was exposed to chemotherapy in the first trimester, the differences were most likely related to premature delivery. This led to the conclusion that preterm birth was strongly associated with adverse events and a full-term delivery seems to be of paramount importance. Moreover, a delay of cancer treatment did not significantly affect disease-free survival for mothers with early breast cancer [1].
In a combined analysis of our data with data form the Cancer in Pregnancy registry, Leuven, Belgium, we were able to demonstrate that overall survival was similar for patients diagnosed with breast cancer during pregnancy compared with non-pregnant patients. This information is important for counseling patients and supports the option to start treatment with continuation of pregnancy [2].
We were also able to demonstrate that neoadjuvant chemotherapy for patients with breast cancer during pregnancy results in the same pCR rate if given during pregnancy or after delivery and as in non-pregnant controls. Disease free and overall survival was not different between the three cohorts [3].
The general recommendation derived from the registry data so far is that patients with breast cancer during pregnancy can and should be treated as closely as possible according to patients diagnosed outside pregnancy. Up-to-date guidelines on breast cancer during pregnancy, which also incorporated outcomes from the BCP registry, have been published in 2015 [4].
Little is known about the impact of pregnancy on breast cancer biology at the genomic level. It is believed that breast cancer during pregnancy is biologically not different from breast cancer diagnosed outside pregnancy [5]. Current translational research project aims to compare the mutational pattern as well as the gene expression profile between pregnant and non-pregnant patients with breast cancer. In our preliminary results we showed that overall the mutational landscape does not seem to be different between pregnant patients enrolled in BCP study and no-pregnant controls obtained from The Cancer Genome Atlas (TCGA) database [6,7]. Further analyses using other datasets are currently conducted.
Data from the BCP registry including oncological management, toxicity and survival of young non-pregnant patients with breast cancer diagnosed at the age of 40 years or younger has recently been presented.. From February 2014 until June 2018, 969 non-pregnant patients ≤ 40 years have been registered. The median age at diagnosis was 35 years (range 19-40). Overall, 90.1 % of patients had a stage T1-2 at diagnosis and 67.1 % of patients had negative lymph nodes; 86.7 % of tumors were invasive ductal carcinomas and 4.1 % lobular carcinomas. Grade (G) 3 was reported in 55.5 %; 26.6 % of tumors were luminal A-like (ER- and/or PgR-positive, HER2-negative, G1-2), 40.0 % luminal B-like (ER- and/or PgR-positive, HER2-negative, G3 or ER- and/or PgR-positive, HER2-positive, any G), 7.7 % HER2 positive non-luminal-like, and 25.7 % triple negative breast cancers. 3.8 % of young non-pregnant patients had metastatic disease at primary diagnosis [8].

Publications

1. Loibl S, Han SN, von Minckwitz G, et al. Treatment of breast cancer during pregnancy: an observational study. Lancet Oncol 2012; 13(9):887-96.
2. Amant F, von Minckwitz G, Han SN, et al. Prognosis of women with primary breast cancer diagnosed during pregnancy: results from an international collaborative study. J Clin Oncol 2013; 31(20):2532-9.
3. Loibl S, Han S, Mayer K, et al. Neoadjuvant chemotherapy for patients with breast cancer during pregnancy (BCP). J Clin Oncol 2014; 32:5s (suppl; abstr 1071).

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

4. Loibl S, Schmidt A, Gentilini O, et al. Breast Cancer Diagnosed During Pregnancy: Adapting Recent Advances in Breast Cancer Care for Pregnant Patients. JAMA Oncol 2015; 1(8):1145-53.
5. Loibl S, Han SN, Amant F. Being Pregnant and Diagnosed with Breast Cancer. Breast Care (Basel). 2012; 7(3):204-209.
6. Loibl S, Pfarr N, Weber K, et al. Comparison of the mutational landscape of breast cancer during pregnancy and non-pregnant controls. Ann Oncol 2017; 28(suppl_1):Abstract nr 10P.
7. Loibl S, Pfarr N, Weber K, et al. Comparison of the mutational landscape of breast cancer during pregnancy and non-pregnant controls. Cancer Res 2017;77(4 Suppl):Abstract nr P2-03-09.
8. Seiler S, Schmatloch S, Reinisch M et al. Cancer Management and Outcome of very young non-pregnant patients with breast cancer diagnosed at 40 years or younger – GBG 29. SABCS 2018; Abstract nr P1-17-07.

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

GBG 79: Brain Metastases in Breast Cancer (BMBC)

BMBC

CONTACT:
Udo Pfeil
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 of December 2018, 2,501 patients have been registered and 355 tissue samples have been received. Registration of patients is ongoing.
First analysis of treatment patterns and clinical outcome in 1,105 breast cancer patients with brain metastases (BM) from the BMBC registry has confirmed our previous findings [1,2] and has shown that HER2-positive patients had the longest median survival with 12.1 months (95 % CI, 10.2–13.7) compared to 5.5 months (95 % CI, 4.1–7.1) for luminal primary tumors and 4.1 months (95 % CI, 3.1–4.8) for triple-negative patients ($p < 0.001$) [3]. Median overall survival (OS) of patients with BM diagnosed between 2000 and 2006 was 7.2 months (95 %CI, 5.3-9.6) compared to 6.7 months (95 % CI, 5.5-8.1) of patients diagnosed between 2007 and 2012 ($p=0.848$). However, we could not observe improvement of survival over the study period and the time intervals in any tumor subtype. Hence, larger patient cohorts are needed to detect the survival difference.
A subproject has retrospectively analyzed clinical data, CT and MRI scans obtained from 300 breast cancer patients with BM in 4 centers participating in the BMBC registry in Germany [4]. Patients with hormone receptor (HR)-positive or HER2-positive status had a significantly lower number

of BM at diagnosis. HER2-positive patients treated with trastuzumab before the diagnosis of BM demonstrated a lower incidence of intracranial metastases. Patients with HER2-positive breast cancer had a higher number of cerebellar metastases compared to HER2-negative patients, whereas patients with triple-negative breast cancer developed more often leptomeningeal disease. These findings suggest a different tumor cell homing to different brain regions depending on molecular subtype and treatment.

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

Publications

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

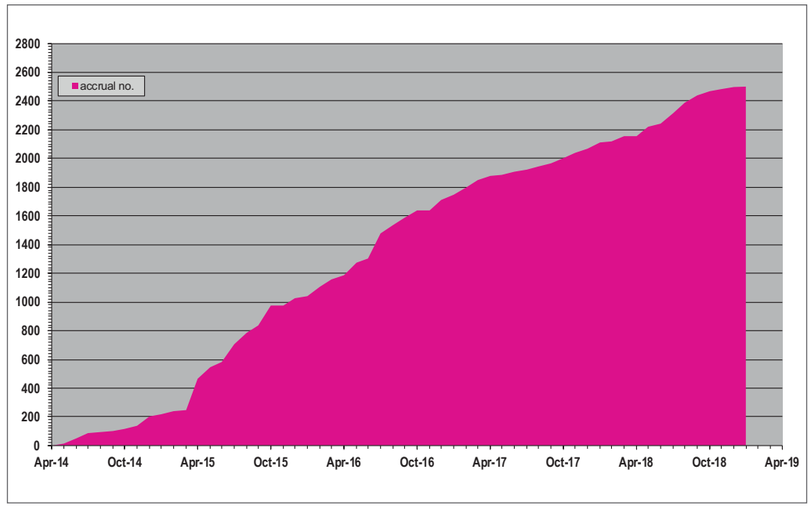


Figure 1: BMBC recruitment as of 31st December 2018

We encourage all study centers and practices to enter eligible patients into the registry.
We thank all participating sites that have entered their patients into the registry and have contributed to this important research so far.

We would like to kindly remind all sites to provide biomaterial which is urgently needed to answer translational research questions.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

Universitätsklinikum Hamburg-Eppendorf

TRAFO

SPONSOR:
GBG Forschungs GmbH

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

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 will recruit 156 patients from 60 sites in Germany within approximately 24 months.

Background
The BOLERO-2 study demonstrated an enormous benefit for patients who received everolimus in addition to exemestane and who progressed during/after a non steroidal aromatase inhibitor (NSAI) (Baselga N Engl J Med 2012), which led to approval of everolimus in this indication. However, experience from routine use has shown a high rate of intolerability of this innovative treatment approach especially during the first 12 weeks of treatment. Most common side effect is mucositis/stomatitis which is considered the leading cause for treatment discontinuation not related to tumor progression.
This outside clinical trial experience is contrary to findings from BOLERO-2, where the number of patients still taking full-dose (10 mg) of everolimus at 4, 8, and 12 weeks is 77.8 %, 75.6 %, and 75.6 %, respectively. These findings are in concordance with non-interventional studies.
In the non-responder part (setting III) of the neoadjuvant GeparQuinto study, everolimus was given as salvage treatment in combination with paclitaxel for patients without response to 4 cycles epirubicin/cyclophosphamide +/- bevacizumab. A dose-escalation schema was successfully used to improve tolerability of everolimus together with the cytotoxic agents (von Minckwitz Ann Oncol 2011; von Minckwitz Ann Oncol 2014).
The palliative DESIREE study compares the cumulative rate of mucositis/stomatitis grade 2-4 (WHO's oral toxicity scale (OTS) at 12 weeks after start of treatment using a conventional and a dose-escalating schema of everolimus in combination with exemestane in patients with metastatic breast cancer and progression or relapse after non-steroidal aromatase-inhibitor treatment.

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

Study report
DESIREE started recruitment in June 2015. As of 31st December 2018, a total of 105 patients have been included. The end of the study (i.e. last visit of the last patient randomized) was initially estimated for October 2017, but due to the very slow accrual it was recently extended to QIV/2019.

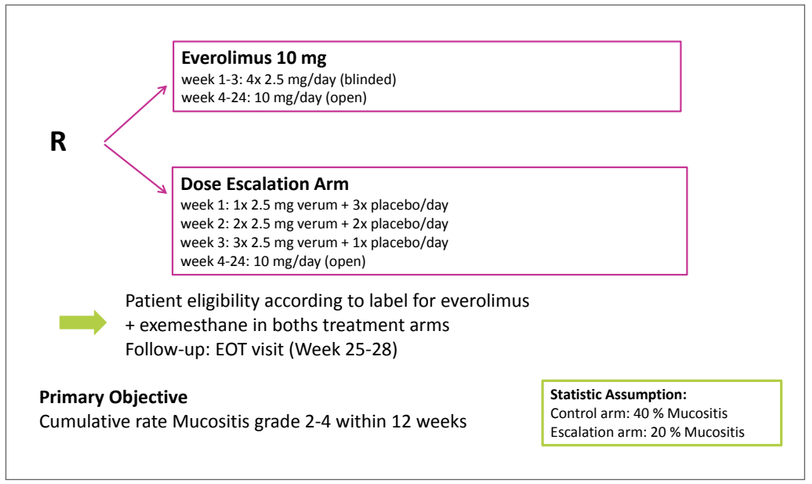


Figure 1: DESIREE study design

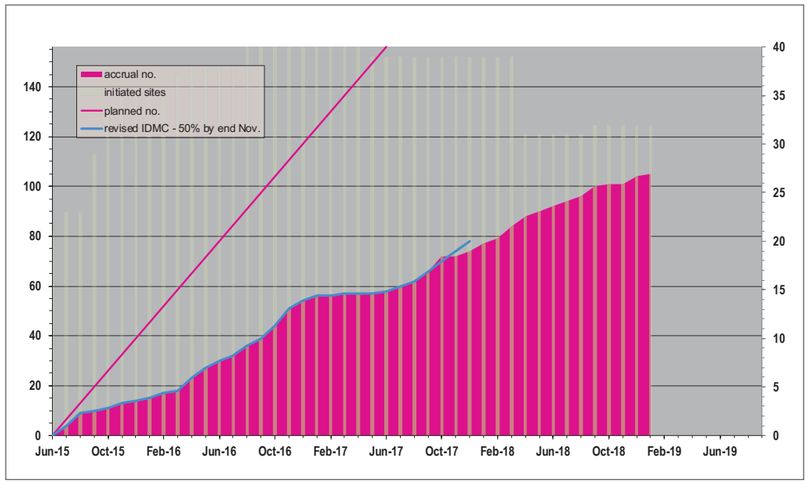


Figure 2: DESIREE recruitment as of 31st December 2018

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

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

SPONSOR:
GBG Forschungs GmbH

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

INSEMA

CONTACT:
Dr. Cornelia Schneider-Schranz
Clinical Project Management
insema@GBG.de

GBG 75: INSEMA

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

NCT02466737

INSEMA is a prospective, multicenter, randomized trial that will recruit 5,940 patients from approximately 150 sites in Germany and approximately 20 sites in Austria.

Background

Although there is no doubt that the presence of lymph node metastases worsens prognosis of a patient, there is a lack of unambiguous evidence to support lymph node dissection. Axillary surgery for breast cancer is now considered as a staging procedure that does not seem to influence breast cancer mortality, since the risk of developing metastases depends mainly on the biological behavior of the primary tumor (seed-and-soil model).

Women with breast cancer have benefitted greatly from a series of carefully conducted randomized controlled trials focusing on axillary surgery. Each successive trial showed that less surgery was better, as outcomes were the same and less surgical intervention resulted in fewer surgical complications (Fisher et al. N Engl J Med 2002; Rudenstam et al. J Clin Oncol 2006; Martelli et al. Ann Surg 2005; Veronesi et al. Ann Oncol 2005; Giuliano et al. Ann Surg 2010; Giuliano et al. JAMA 2011).

A high rate of loco-regional control could be achieved with multimodality therapy, even without axillary lymph node dissection (ALND). Despite increasing evidence disfavoring ALND, it remains part of widely recognized guidelines for breast cancer treatment. The modern approach in breast cancer care, which includes improved imaging, more detailed pathological evaluation, improved planning of surgical and radiation therapy, and more effective systemic treatment, emphasizes the need for ongoing re-evaluation of "standard" local therapy. The postsurgical therapy should be considered on the basis of biologic tumor characteristics rather than nodal involvement.

Study design and objectives

INSEMA is a prospective randomized surgical trial. Patients are randomized into two treatment arms in an 1:4 allocation for the first randomization and in an 1:1 allocation for the second randomization. Duration of recruitment is 4 years. The aim of the trial is to compare the invasive disease-free survival after breast-conserving surgery between patients who received no axillary surgery vs. patients who received sentinel lymph node biopsy (SLNB) and between node positive patients who received SLNB alone vs. patients with completion of ALND. Secondary objectives of the study are to compare the invasive disease-free survival after breast-conserving surgery between patients with no axillary surgery vs. node negative patients, between patients with no axillary surgery vs. node positive patients who received SLNB alone, and between patients with no axillary surgery vs. node positive patients with completion of ALND. Furthermore, the study allows comparison of overall survival, locoregional disease-free survival (no tumor in the ipsilateral breast or ipsilateral supraclavicular, subclavicular, internal mammary or axillary nodes), ipsilateral axillary recurrence rate, distant disease-free survival, and quality-of-life between arms as well as the event-free survival in subgroups according to age (< 65 vs. ≥ 65years), grading G1/2 vs. G3), tumor size (≤ 2 vs. > 2cm), and study site (German vs. Austrian sites in randomization 2).

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

An amendment of the study protocol (version 15.09.2016) included the following changes: a) within the inclusion criteria: patients with age at diagnosis ≥ 18 years can be enrolled in the study; histological confirmation of the unilateral primary invasive carcinoma of the breast can be

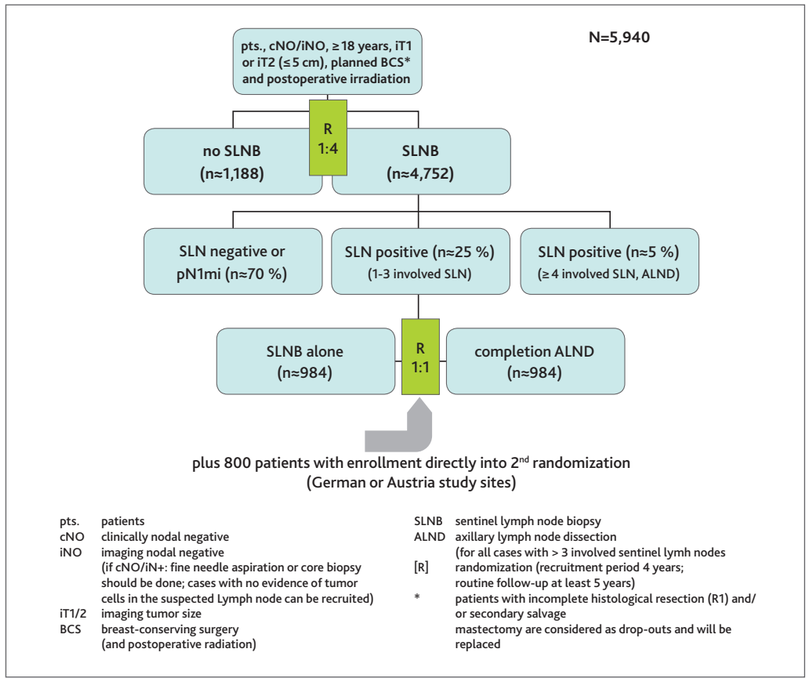


Figure 1: INSEMA study design after amendment 4

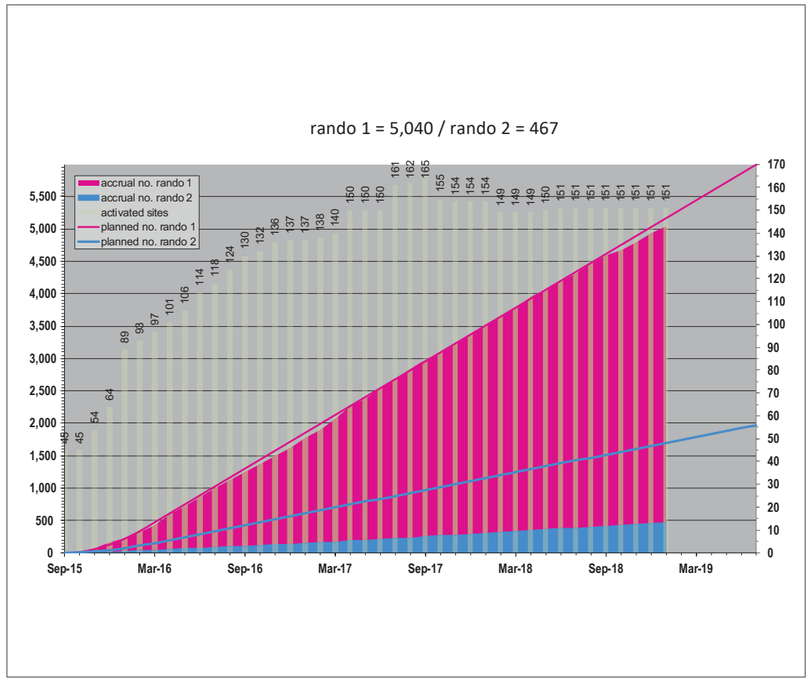


Figure 2: INSEMA recruitment as of 31st December 2018

COLLABORATING STUDY GROUPS:

SPONSOR:
University of Rostock

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

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

Study report

INSEMA recruitment started in September 2015 and is planned for 48 months at 120-150 German and 15-20 Austrian sites. As of 31st December 2018, a total of 5,040 patients from 151 recruiting centres have been enrolled in the first randomization and 467 patients in the second randomization (Figure 2). After a 5 year follow-up, final analysis is planned for 2024.

The first analysis of patient's characteristics was recently published [2]. Of the 1,001 breast carcinomas analyzed, 96.9 % were hormone receptor positive, 8.5 % were HER2-positive and only 5.4 % of all cases were tumor grade 3 (G3). Pathological analysis of 751 SLNBs showed that 83.0 % (n=623) of patients had negative nodal status (pN0), 2.8 % (n=21) micrometastasis (pN1mi), 12.9 % (n=97) 1–2 macrometastases and 1.3 % (n=10) ≥ 3 macrometastases. The case rate of 85.8 % without demonstrable axillary lymph node macrometastasis was significantly above the 70 % predicted at protocolling.

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

Lack of knowledge of nodal status when SLNB is avoided represents a new challenge for the postoperative tumor board. In particular decisions on chemotherapy for luminal-like tumors and irradiation of the lymphatics (excluding axilla) must be guided by tumor biological parameters [2,3].

Publications:

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

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 recruitment of patients and the timely provision of biomaterial.

Studies in Follow-up

GBG 78: Penelope^{B}

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

NCT01864746

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

Background

About one third of hormone receptor (HR)-positive, HER2-normal breast cancer patients with residual disease after neoadjuvant chemotherapy have a substantial risk of relapse (von Minckwitz et al. J Clin Oncol 2012). Those patients can be identified using the validated clinical-pathologic stage–estrogen/grade (CPS-EG) scoring system (Figure 1A), ranging from 0-6 (Jeruss et al. J Clin Oncol 2008; Mittendorf et al. J Clin Oncol 2011).

Palbociclib is an oral, highly selective inhibitor of CDK4/6 kinase activity that prevents cellular DNA synthesis by inhibiting cell cycle progression (Finn et al. Breast Cancer Res 2009). Luminal tumors have shown sensitivity to palbociclib. In a phase II study, palbociclib extended progression free survival in combination with letrozole as first-line hormonal treatment for advanced breast cancer (Finn et al. Cancer Res 2012). Palbociclib has also shown single agent activity in patients with relapsed HR-positive advanced breast cancer (DeMichele et al. Cancer Res 2011). Based on the recent results from the PALOMA-2 (Finn et al. N Engl J Med 2016) and PALOMA-3 trials (Turner et al. N Engl J Med 2015), palbociclib was approved by European Medicines Agency (EMA) for the treatment of HR-positive, HER2-negative advanced or metastatic breast cancer in combination with an aromatase inhibitor as initial endocrine-based therapy in postmenopausal women or in combination with fulvestrant in pretreated patients.

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

Study design and objectives

Penelope^{B} primarily aims to compare invasive disease-free survival (iDFS) between the two treatment arms.

In addition, iDFS excluding second non-breast cancers, overall, distant disease-free and local recurrence-free survival, iDFS per treatment group in patients with luminal-B tumors, compliance and safety, patient reported outcomes (quality of life), health economics, drug-drug interaction-potential for the palbociclib – endocrine combination therapy (in a subset of this patient population) as well as correlations between drug exposure and efficacy and safety findings will be analyzed. The study includes post- as well as premenopausal women and allows the use of different endocrine therapies. Furthermore, the Penelope^{B} study will also address translational research questions, such as the role of biomarkers involved in the CDK4/6 pathway.

Based on the outcome of the first efficacy interim analysis (April 2017), the Independent Data Monitoring Committee (IDMC) has recommended to adapt the patient's number of the trial to a total of 1,250 patients.

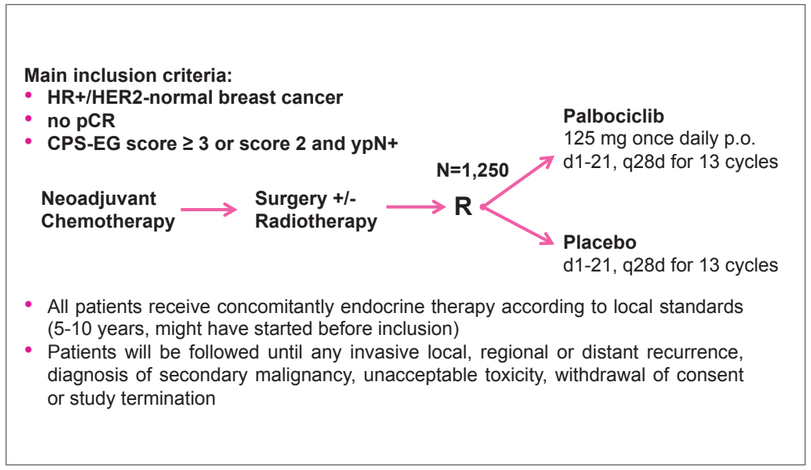


Figure 1: Penelope^{B} study design

Study report

Penelope^{B} started recruitment with the first randomized patient in Germany in February 2014. The first international patient was randomized in Spain in October 2014. The recruitment was closed in December 2017. An efficacy interim analysis will be performed in QII/ 2019. Final analysis on the primary endpoint and secondary efficacy endpoints (except for OS) will be conducted when 290 iDFS events have been observed, which is estimated to occur about 6.5 years after first patient in.

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

CONTACT:
Dr. Mathias Uhlig
Clinical Project Management
penelope@GBG.de

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

BIG Breast International Group

AGO-B BREAST STUDY GROUP

NSABP Partners In Cancer Research

SPONSOR:
GBG Forschungs GmbH

INTERNATIONAL STUDY CHAIR:
Prof. Dr. Gunter von Minckwitz
German Breast Group,
Neu-Isenburg

COORDINATING INVESTIGATOR (GERMANY):
Prof. Dr. Toralf Reimer
Universitätsfrauenklinik
und Poliklinik am Klinikum
Südstadt Rostock

CONTACT:
Dr. Cornelia Schneider-Schranz
Clinical Project Management
gain2@GBG.de

GBG 68: GAIN-2

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

NCT01690702

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

Background

Combined chemotherapy regimens always require compromises regarding the doses of each drug and the treatment intervals due to acute and cumulative toxicities. The sequential administration of monotherapies, however, allows the administration of high doses of single substances and dose-dense intervals. Such intense, dose-dense chemotherapy regimens have shown to improve the survival in early breast cancer patients with high risk of recurrence when compared to conventional dosed chemotherapy (Möbus et al. J Clin Oncol 2010; Citron et al. J Clin Oncol 2003). However, both of these dose-dense regimens tested so far used solvent-based taxanes (paclitaxel and docetaxel) and nowadays outdated comparators.

Nab-paclitaxel, the nanoparticle albumin-bound form of paclitaxel, has shown a better toxicity profile and higher efficacy compared to solvent-based taxanes and might thus be preferred in an intense dose-dense regimen.

It is long known from the NSABP-B18 trial and others that neoadjuvant chemotherapy is as effective as adjuvant chemotherapy in preventing recurrences (Wolmark et al. J Natl Cancer Inst Monogr 2001).

The hypothesis studied by GAIN-2 is that in patients with early node-positive or high-risk node-negative breast cancer, a pre-defined, intense, dose-dense, regimen (EnPC – epirubicin followed by nab-paclitaxel followed by cyclophosphamide) is more effective compared with a dose-dense regimen, where single doses are adjusted depending on individual hematological and non-hematological toxicities (dtEC-dtD - dose-dense, dose-tailored epirubicin and cyclophosphamide followed by dose-dense, dose-tailored docetaxel).

The maximum dose of nab-paclitaxel in this setting has been explored in a run-in phase included in the study design. It has been shown that patients can safely be treated with a biweekly dosage of 330 mg/m2 nab-paclitaxel (Möbus et al. J Clin Oncol 2013) which is now used for the main phase of the study.

Study design and objectives

GAIN-2 primarily aimed to compare invasive disease-free survival after neo-/adjuvant chemotherapy with EnPC or dtEC-dtD in patients with primary node-positive or high risk node negative breast cancer. In addition, overall, distant disease-free, locoregional relapse-free, local relapse-free, regional relapse-free and brain metastasis-free survival, compliance and safety, side-effects of taxanes, pCR rate in patients treated with neoadjuvant therapy and treatment effects by intrinsic subtypes, number of involved nodes and Ki-67 are compared between the two treatment arms. Breast conservation rate between adjuvant and neoadjuvant patients as well as the survival endpoints by pCR will be also assessed.

In addition, GAIN-2 offers the opportunity to address a range of translational research questions, which are summarized bellow.

An amendment of the study protocol (effective as of 1st August 2016) allowed treatment of patients with the same regimens in the neoadjuvant setting. All neoadjuvant patients with HER2-positive disease received trastuzumab and optional pertuzumab at doses and duration in concordance with current treatment guidelines.

Substudies

Substudy subcutaneous trastuzumab

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

Substudy biology of lymph node metastases

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

Substudy on SNP (Single Nucleotide Polymorphisms)

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

Substudy on ovarian function

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

Study report

Between October 2012 and July 2017, a total of 2,887 patients have been enrolled in the main study (2,289 in the adjuvant setting and 598 in the neoadjuvant setting from 136 recruiting sites in Germany) [1,2]. The trastuzumab substudy has enrolled 226 patients between November 2013 and August 2017.

Pharmacokinetic analysis of a s.c. injection of trastuzumab into the thigh or into the abdominal wall in patients with HER2-positive primary breast cancer (BC) treated within the neo-/adjuvant GAIN-2 study showed that bioavailability of s.c. trastuzumab as reflected by peak and total exposure measured in cycle 7 was approximately 30 % higher if the antibody was administered into the thigh; no increased toxicity was observed. Study limitations were that no cross-over design was used and the number of patients who satisfied criteria for per-protocol-set was different in the arms [3].

The first results of the ovarian substudy were presented at the SABCS 2017 [4]. The pooled analysis of 740 breast cancer patients aged ≤45 years treated with anthracycline or taxane-based chemotherapy (CT) within the GeparSixto, GeparSepto, GENEVIEVE and Gain-2 trials showed that nearly 70 % of women regained premenopausal hormone levels of FSH and E2 within 2 years after the end of CT. Despite that, less than one third of the women maintain their fertility potential as predicted by AMH, indicating that AMH is a very sensitive marker for the prediction of fertility function after CT for early breast cancer. Preliminary results of the pCR rates within the breast (ypT0/is ypN0+) for the neoadjuvat setting have been presented at the ASCO 2018. The pCR rate for patients treated with iddEnPC were statistically significantly higher compared to those receiving dtEC-dtD as neoadjuvant chemotherapy (53.3 % [95 %CI 52.4 %-64.0 %] vs 49.7 % [95 %CI 43.8 %-55.5 %]; p=0.043). No significant difference for pCR was found within the breast cancer subtypes [5].

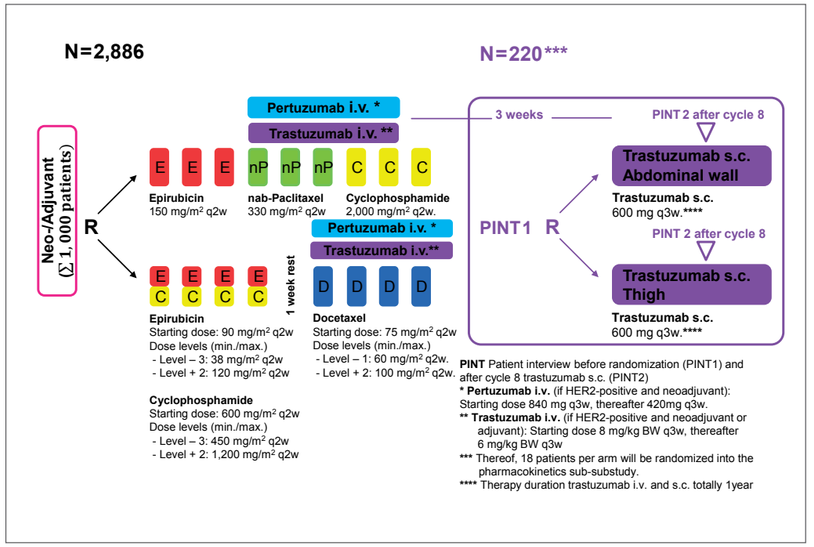


Figure 1: Study design of the GAIN-2 main study and the subcutaneous trastuzumab substudy

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

SPONSOR:
GBG Forschungs GmbH

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

Publications

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

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. We also encourage all participating sites to support the various substudies by providing biomaterials in a timely manner.

GBG 53: PANTHER

A randomized phase III study comparing biweekly and tailored epirubicin plus cyclophosphamide followed by biweekly tailored docetaxel versus three weekly epirubicin plus cyclophosphamide, 5-fluorouracil followed by docetaxel in lymph node positive or high risk lymph node negative breast cancer patients

NCT00798070

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

Background

In the adjuvant setting, a number of trials have demonstrated that the addition of a taxane to chemotherapy regimen leads to a survival gain (Henderson et al. J Clin Oncol 2003; Martin et al. N Engl J Med 2005; Roché et al. J Clin Oncol. 2006), however, relapse risk remains significant especially in lymph-node positive disease. Therefore, various dose and schedule strategies have been investigated. Dose-dense and sequential designs have been shown to improve clinical outcomes (Citron J Clin Oncol 2003; Möbus et al. J Clin Oncol 2010). Long term results confirmed that the sequential use of docetaxel compared with concurrent doxorubicin-docetaxel resulted in a better disease free survival and significantly better overall survival (Oakman et al. Ann Oncol 2013). The dose-dense and tailored epirubicin/cyclophosphamide followed by docetaxel regimen was found to produce manageable feasibility, with an acceptable incidence of grade 4 infection/febrile neutropenia (Margolin et al. Acta Oncol 2011). All patients received granulocyte colony stimulating factor (G-CSF) support and prophylactic ciprofloxacin. G-CSF has the capacity to reduce the depth and duration of granulocytopenia and to reduce the risk of granulocytopenic fever and infection and its use is mandatory in dose-dense regimen.
PANTHER aimed to investigate efficacy of a dose-dense and dose-adapted sequence of epirubicin/cyclophosphamide and docetaxel in the adjuvant setting in a cohort of lymph node positive or high-risk lymph node negative patients compared to a standard anthracycline/taxane containing regimen.

Study design and objectives

After surgery, patients were randomized to receive either dose-dense, dose-adapted epirubicin/cyclophosphamide for 14 days followed by 14 days of dose-dense, dose-adapted docetaxel

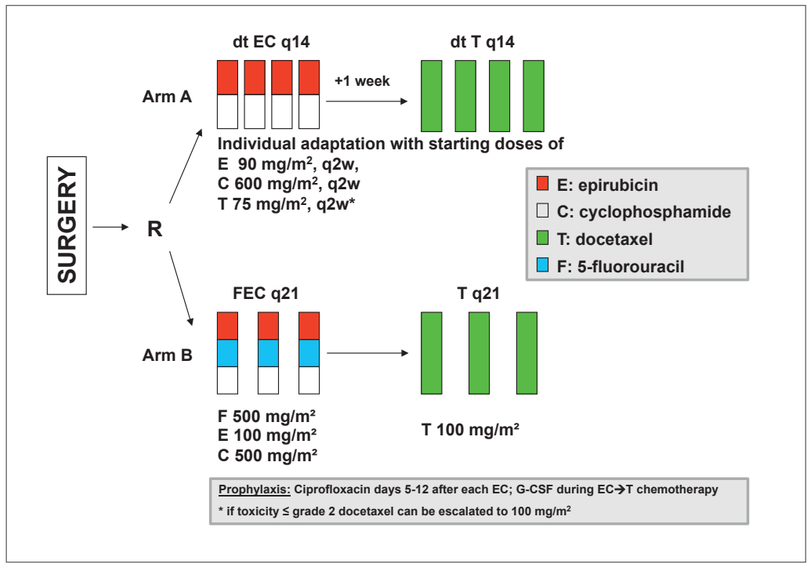


Figure 1: PANTHER study design

PANTHER SBG ABCSG GBG

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

taxel or 5-fluorouracil, epirubicin and cyclophosphamide for 21 days followed by 21days of docetaxel (Figure 1).
PANTHER primarily aimed to compare breast cancer relapse-free survival (BCRFS) between treatment arms. A total of 225 events (overall in the two arms) were therefore needed to detect a five-year breast cancer relapse-free survival difference of 0.710 to 0.790. Secondary objectives of the study are to compare distant disease free survival, event-free survival overall survival, health related quality of life and toxicity and outcome in relation to tumor biological factors and polymorphism patterns between the two treatment arms. Moreover, dose intensity and side effects were analyzed.

Study report
PANTHER trial recruited a total of 2017 patients between February 2007 and September 2011 from 86 sites in Sweden, Germany and Austria. Estimated study completion date is January 2022. The final analysis of the primary endpoint included 2000 patients (1001 in the tailored dose-dense group and 999 in the control group). After a median follow-up time of 5.3 years (interquartile range (IQR), 4.5-6.1 years), 269 BCRFS events were reported, 118 in the tailored dose-dense group and 151 in the control group (HR 0.79 [95 % CI, 0.61-1.01]; log-rank p = 0.06; 5-year BCRFS, 88.7 % vs 85.0 %). Thus, the use of tailored dose-dense chemotherapy compared with standard adjuvant chemotherapy did not result in a statistically significant improvement in BCRFS. The EFS was significantly better in tailored dose-dense group than in the control group (HR 0.79 [95 % CI, 0.63-0.99]; p = 0.04; 5-year EFS, 86.7 % vs 82.1 %). The groups did not differ in OS (HR 0.77 [95 % CI, 0.57-1.05]; p = 0.09; 5-year OS, 92.1 % vs 90.2 %) or DDFS (HR, 0.83 [95 % CI, 0.64-1.08]; p = 0.17; 5-year DDFS, 89.4 % vs 86.7 %). High-grade non-hematological toxicities were more frequent in the tailored dose-dense group (52.6 %) as compared to control group (36.6 %) [1].
An exploratory analysis of tailored dosing in the PANTHER trial demonstrated that obese patients (BMI ≥ 30) treated with tailored dose-dense chemotherapy had improved BCRFS compared to non-obese ones (BMI < 30) (HR = 0.51 [95 % CI 0.30-0.89]; p=0.02). Furthermore, the tailored dose-dense chemotherapy was associated with improved BCRFS compared to standard anthracycline/taxane containing treatment only in obese patients (HR=0.49 [95 %CI 0.26-0.90]; p=0.022, test for interaction p=0.175). There were no differences in terms of toxicity between the BMI groups. Thus, the use of tailored dose-dense regimen as adjuvant chemotherapy is a feasible strategy that can potentially improve outcomes in obese patients without increasing toxicity and should be pursued in further clinical studies [2,3].

Publications

1. Foukakis T, von Minckwitz G, Bengtsson NO, et al. Effect of Tailored Dose-Dense Chemotherapy vs Standard 3-Weekly Adjuvant Chemotherapy on Recurrence-Free Survival Among Women With High-Risk Early Breast Cancer: A Randomized Clinical Trial. JAMA 2016; 316(18):1888-1896.
2. Matikas A, Foukakis T, Moebus V et al. Dose tailoring of breast cancer adjuvant chemotherapy aiming at avoiding both over and undertreatment: Results from the prospective PANTHER study. J Clin Oncol 2018; 36.15_suppl.538.
3. Matikas A, Foukakis T, Moebus V, et al. Dose tailoring of adjuvant chemotherapy for breast cancer based on hematologic toxicities: Further results from the prospective PANTHER study with focus on obese patients. Ann Oncol. 2018 Oct 24. [Epub ahead of print].

We would like to thank all participating sites for their efforts so far. Sites are highly encouraged to transfer their patients to the self-reported outcome registry so that long term relapse and survival data can be obtained in a timely manner.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

SBG

ABCSG AUSTRIAN BREAST & COLORECTAL CANCER STUDY GROUP

SPONSOR:
Karolinska University Hospital
Department of Oncology
Stockholm, Sweden

INTERNATIONAL PRINCIPAL INVESTIGATOR:
Prof. Dr. Jonas Bergh
Department of Oncology,
Karolinska University Hospital,
Stockholm, Sweden

STUDY CHAIR GERMANY:
Prof. Dr. Gunter von Minckwitz
German Breast Group,
Neu-Isenburg

GBG 67: APHINITY

A randomized multicenter, double-blind, placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo versus chemotherapy plus trastuzumab plus pertuzumab as adjuvant therapy in patients with operable HER2-positive primary breast cancer

NCT01358877

APHINITY is an adjuvant, prospective, two-arm, randomized, multicenter, international, double-blind, placebo-controlled phase III trial that has recruited 4810 patients, including 459 from Germany.

Background
Approximately 20 % of breast cancer patients have HER2-positive tumors which are associated with a poorer prognosis if untreated (Slamon et al. Science 1987). Numerous studies have shown that adjuvant use of the anti-HER2 humanized monoclonal antibody trastuzumab improves disease-free and overall survival (Joensuu et al. J Clin Oncol 2009; Slamon et al. N Engl J Med 2011; Gianni et al. Lancet Oncol 2011; Perez et al. J Clin Oncol 2011). However, not all patients treated with this agent benefit from this therapy and resistance is a challenge in the treatment of HER2-positive breast cancer (Wong et al. Int J Breast Cancer 2012). Pertuzumab is a humanized monoclonal antibody that is designed to inhibit HER2-dimerization and induce antibody-dependent cell-mediated cytotoxicity with a complementary mechanism of action to trastuzumab. In HER2-positive advanced breast cancer the combination trastuzumab and pertuzumab was shown to be active in patients who previously progressed on trastuzumab (Baselga et al. J Clin Oncol 2010; Portera et al. Clin Cancer Res 2008). In the neoadjuvant setting, trastuzumab and pertuzumab in combination with chemotherapy nearly doubled the pathological complete response rate compared to either trastuzumab or pertuzumab administered in combination with chemotherapy (45.8 % vs 29 % vs 24 %, respectively) (Gianni et al. Lancet Oncol 2012). Therefore, the potential for a more comprehensive HER2 blockade with two anti-HER2 monoclonal antibodies warrants further investigation in the adjuvant setting.
APHINITY aims to investigate 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.

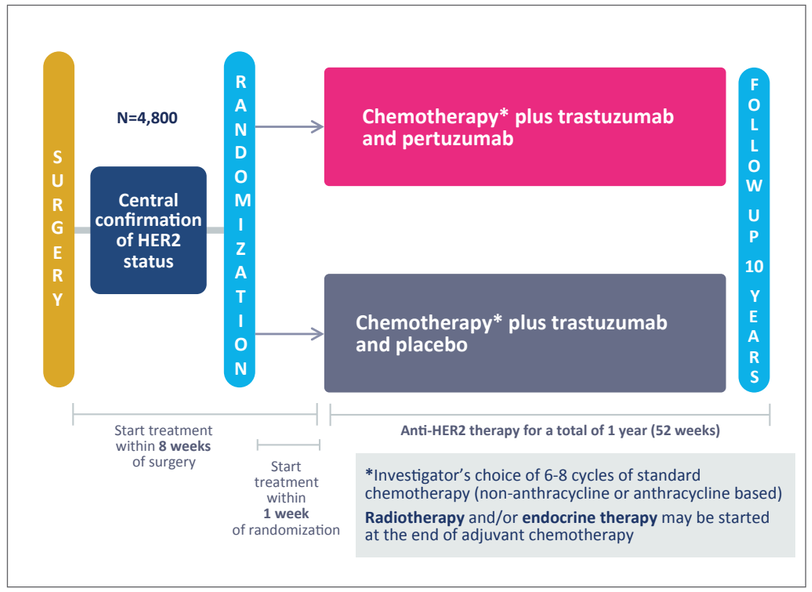


Figure 1: APHINITY study design

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

Study design and objectives
After surgery, patients were randomized to receive either pertuzumab (840 mg loading dose in cycle 1, followed by 420 mg) or placebo intravenously every 3 weeks for one year, in addition to 6-8 cycles of chemotherapy and 1 year of trastuzumab (8 mg/kg loading dose in cycle 1, followed by 6 mg/kg) intravenously every 3 weeks. Total duration of anti-HER2 treatment was 52 weeks. Patients will be followed up for 10 years. APHINITY primarily aimed to compare invasive disease-free survival, excluding second primary non-breast cancers between treatment arms. Secondary objectives of the study were invasive disease-free survival including second primary non-breast cancers, disease-free survival, overall survival, recurrence-free interval, distant recurrence-free interval, cardiac and overall safety as well as health related quality of life in the two treatment arms.

Study report
APHINITY randomized a total of 4,805 patients between November 2011 and August 2013 and the last patient completed treatment in August 2014. The study is now in follow-up with patients being followed at approximately 3-monthly intervals for 2 years, then every 6 months during years 3 to 5 and annually thereafter. The study will continue until 10 years after the randomization of the last patient (around September 2023). The first analysis of the primary endpoint has included all 4,805 patients (2,400 in the pertuzumab and 2,405 in the placebo arms, respectively) [1, 2]. The median follow-up period in the intention-to-treat population was 45.5 months (48.3 months for patients with node-negative and 44.5 months for patients with node-positive breast cancer). In total, invasive-disease-events occurred in 171 patients (7.1 %) in the pertuzumab arm and 210 patients (8.7 %) in the placebo arm. The 3-year rates of invasive disease-free survival (iDFS) were 94.1 % with pertuzumab compared to 93.2 % with placebo (HR 0.81 [95 % CI 0.66-1.00]; p=0.045). Thus, the addition of pertuzumab to trastuzumab plus chemotherapy as adjuvant treatment for patients with HER2-positive, operable breast cancer (BC) significantly improved the rates of iDFS compared to placebo. The effect of pertuzumab on iDFS was homogeneous among the different patient subgroups. However, the improvement in 3-year rates of iDFS in favor of the pertuzumab arm was more pronounced in the cohort of patients with node-positive BC (HR 0.77 [95 % CI 0.62-0.96]; p=0.02). In contrast, no treatment effect was detected in the cohort of patients with node-negative BC (HR 1.13 [95 % CI 0.68-1.86]; p=0.64). Similarly, the 3-year iDFS rates did not significantly differ in the cohorts of patients with hormone receptor-positive or with hormone-receptor-negative BC subtypes (HR, 0.86 [95 % CI 0.66-1.13]; p=0.28 and HR, 0.76 [95 % CI 0.56-1.04]; p=0.08, respectively). High grade diarrhea (grade 3-4) was more frequent with pertuzumab than with placebo (9.8 % vs. 3.7 %). Due to the long follow-up period, results will be a long time coming.

Publications

1. von Minckwitz G, Procter M, de Azambuja E, et al. APHINITY trial (BIG 4-11): A randomized comparison of chemotherapy (C) plus trastuzumab (T) plus placebo (Pla) versus chemotherapy plus trastuzumab (T) plus pertuzumab (P) as adjuvant therapy in patients (pts) with HER2-positive early breast cancer (EBC). J Clin Oncol 2017;35 (suppl; LBA500).
2. von Minckwitz G, Procter M, de Azambuja E, et al. Adjuvant Pertuzumab and Trastuzumab in Early HER2-Positive Breast Cancer. N Engl J Med. 2017;377:122-131.

We would like to thank all participating sites for their efforts so far. Sites are highly encouraged to provide follow-up documentation of their patients in order to avoid delays in the study analysis. We would like to remind all participating sites to provide a tumor sample at disease recurrence in order to increase the robustness of data.

COLLABORATING STUDY GROUPS:
GBG German Breast Group
BIG Breast International Group

SPONSOR:
F. Hoffmann-La Roche Ltd. and Genentech, Inc.

INTERNATIONAL STUDY CHAIRS:
Prof. Dr. Gunter von Minckwitz
German Breast Group, Neu-Isenburg

Jose Baselga, MD, PhD
Massachusetts General Hospital
Boston, USA

José Bines, MD
National Cancer Institute
Rio de Janeiro, Brazil

GBG 81: BRIGHTNESS

A randomized, placebo-controlled, double-blind, phase III study evaluating safety and efficacy of the addition of veliparib plus carboplatin versus the addition of carboplatin to standard neoadjuvant chemotherapy versus standard neoadjuvant chemotherapy in subjects with early stage triple negative breast cancer (TNBC)

NCT02032277

BRIGHTNESS is a multicenter, double-blind, placebo-controlled, randomized phase III trial that has globally recruited 624 patients (55 patients in Germany) from 250 sites (34 in Germany) in 18 countries within approximately 22 months.

Background
Patients with triple-negative breast cancer (TNBC) represent about 15 % of all breast cancer cases. In patients with a positive family history, up to 20 % harbor a germline mutation of the *BRCA*1/2 gene. Chemotherapy is still the most important treatment for TNBC irrespective of a germline *BRCA* mutation. Recently, it could be shown in the metastatic setting that carboplatin monotherapy is as effective as docetaxel in patients with TNBC, but it seems that in particular women harboring a germline *BRCA* mutation benefit from the platinum agent as first-line therapy (Tutt et al Cancer Res 2015). Platinum-containing chemotherapy combinations in patients with TNBC and germline *BRCA* mutation have been shown to be very effective in achieving high pathological complete response (pCR) rates (von Minckwitz et al. Lancet Oncol 2014; Sikov et al J Clin Oncol 2015). The success of the PARP inhibitors in platinum sensitive ovarian cancer (Liu et al. Lancet Oncol. 2014; Oza et al. Lancet Oncol. 2015) and the data in metastatic breast cancer using a PARP inhibitor (Kaufman et al. J Clin Oncol 2015) support the idea to test these agents in primary breast cancer.
The neoadjuvant BRIGHTNESS study compares paclitaxel plus carboplatin plus the PARP inhibitor veliparib with paclitaxel plus carboplatin and with paclitaxel alone, each followed by standard neoadjuvant chemotherapy with doxorubicin/cyclophosphamide. TNBC patients are included irrespective of their germline *BRCA* status, but this information is used to stratify patients prior to randomization.

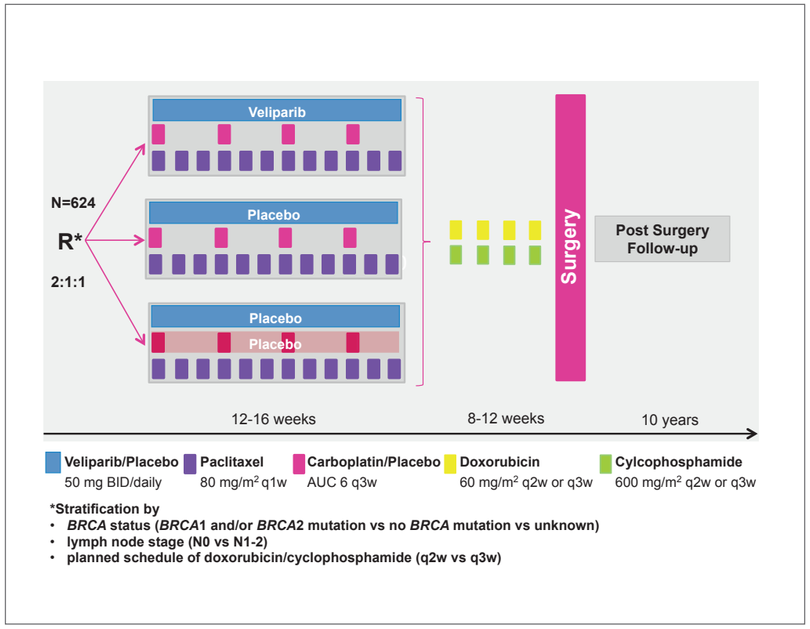


Figure 1: BRIGHTNESS study design

CONTACT:
Carmen Schmidt-Rau
Clinical Project Management
brightness@GBG.de

Study design and objectives
BRIGHTNESS primarily aimed to assess the incidence of pCR in breast and ipsilateral axillary tissue of veliparib + carboplatin + paclitaxel compared with the two placebo-containing arms. The secondary objective of the study was to assess the rate of eligibility for breast conservation after therapy. Further objectives were to assess event free survival (EFS), overall survival (OS), clinical response rate (CRR) at 12 weeks, the incidence of pCR plus minimal residual disease (defined as residual cancer burden [RCB] class I), ECOG performance status, and breast cancer related quality of life.

Study report
BRIGHTNESS has randomized globally a total number of 624 patients (with 55 patients from German centers) between February 2015 and March 2016. To ensure patient safety, an Independent Data Monitoring Committee (IDMC) has reviewed unblinded safety data. The final interim analysis was finalized in QIV/2016. The first results included 634 patients (median age 50 years; range 22-79) and showed that overall, addition of veliparib to neoadjuvant chemotherapy consisting of carboplatin + paclitaxel followed by doxorubicin + cyclophosphamide (AC) did not increase the pCR rate in the breast and lymph nodes in an unselected population of stage II-III TNBC patients. In contrast, the addition of veliparib + carboplatin or carboplatin alone to paclitaxel followed by AC 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 [1,2]. The post-surgery follow-up period of 10 years is ongoing.
An analysis evaluating the prognostic and predictive role of the homologous recombination deficiency (HRD) assay for carboplatin and PARP inhibitor response has been presented at ASCO 2018. Of the 634 patients included in the BRIGHTNESS study, 438 had available HRD status. HRD status was defined as HRD+ (HRD score ≥ 42 or a tumor *BRCA*1/2 mutation) or HRD- (HRD score < 42 and no tumor *BRCA*1/2 mutation). An exploratory HRD threshold of ≥ 33 vs < 33 was also assessed. Overall, HRD+ patients had a higher pCR rates across all treatment arms. Comparing between arms using the 42 threshold demonstrated that patients treated with carboplatin showed higher pCR rates in both HRD+ (61.7 % for patients treated with veliparib + carboplatin + paclitaxel [arm A] vs 60.7 % with carboplatin + paclitaxel [arm B] vs. 34.8 % with paclitaxel + double placebo [arm C]) and HRD- (36.1 % in arm A vs 50.0 % in arm B vs 20 % in arm C) subsets. Similar results were observed with the 33 cut-off. However, the exploratory HRD threshold of 33 appeared to provide greater sensitivity to identify responders with the addition of carboplatin + veliparib [3].

Publications

1. Geyer CE, O'Shaughnessy J, Untch M et al. Phase 3 study evaluating efficacy and safety of veliparib (V) plus carboplatin (Cb) or Cb in combination with standard neoadjuvant chemotherapy (NAC) in patients (pts) with early stage triple-negative breast cancer (TNBC). J Clin Oncol 2017; 35 (suppl.520).
2. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomized, phase 3 trial. Lancet Oncol. 2018;19:497-509.
3. Telli ML, Metzger O, Timms K et al. Evaluation of homologous recombination deficiency (HRD) status with pathological response to carboplatin +/- veliparib in BrighTNess, a randomized phase 3 study in early stage TNBC. J Clin Oncol 2018; 36.15_suppl.519.

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 BRIGHTNESS study by entering study participants in the General Follow-up or invite them to join the patient self-reported registry.

COLLABORATING STUDY GROUPS:
GBG GERMAN BREAST GROUP

SPONSOR:
abbvie

INTERNATIONAL STUDY CHAIRS:
Prof. Dr. Sibylle Loibl
German Breast Group, Neu-Isenburg
Prof. Dr. Charles Geyer
University Richmond, USA

CO-ORDINATING INVESTIGATOR:
Prof. Dr. Jens Huober
Universitätsfrauenklinik Ulm, Germany

GBG 84: GeparOcto

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 (GeparOcto)

NCT02125344

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 were 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

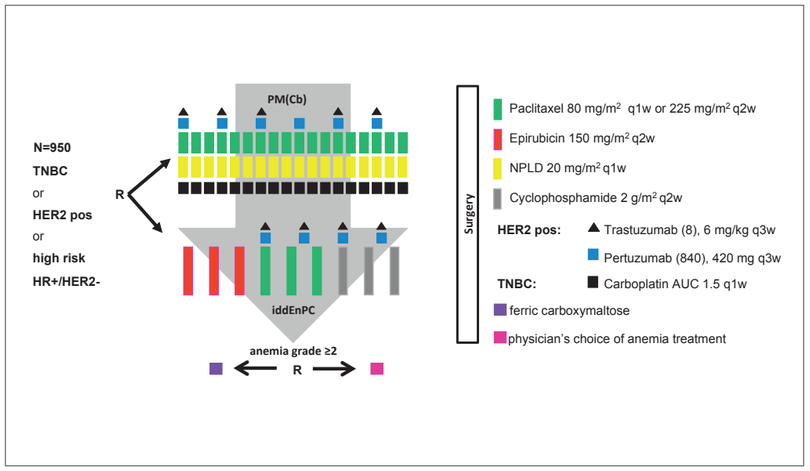


Figure 1: GeparOcto study design

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

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 ≥ 11g/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).

Substudies

Pharmacogenetic Substudy:

Aim of this study is to analyze potential associations between the germline genotype of the patient, treatment response, toxicities, long term prognosis and molecular profile of the tumors.

Ovarian function substudy:

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

Study report

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). The median age was 48 years; 7.6 % had cT3-4, 46 % cN+, 66 % G3, 40 % HER2-positive, 43 % TNBC. The pCR (ypT0/is ypN0) rate with iddEPC was 48.3 %, with PM(Cb) 48.0 %, respectively (PM(Cb) versus iddEPC odds ratio 0.99; 95 % confidence interval 0.77-1.28, P = 0.979). Non-inferiority of the PM (Cb) treatment could not be shown. The pCR rates between the biological subtypes did not significantly differ. The safety analysis showed that 16.4 % with iddEPC and 34.1 % with PM(Cb) discontinued treatment (P < 0.001), mainly due to adverse events. Two patients on PM(Cb) died. Hence, the use of PM (Cb) regimen appeared to be less feasible for treatment of patients with high-risk early stage breast cancer. iddEPC is one of the effective dose-dense regimens feasible in daily practice [1].

Publication

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 randomized phase III trial. Eur J Cancer. 2019;106:181-192.

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 GeparOcto study by transferring participants to the General Follow-up and to the self-reported outcome registry. We also encourage all participating sites to support the various substudies by providing biomaterials in a timely manner.

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

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

Completed Studies

CONTACT:
Dr. Mathias Uhlig
Clinical Project Management
trafo@GBG.de

GBG 77: Katherine

A study of trastuzumab emtansine versus trastuzumab as adjuvant therapy in patients with HER2-positive breast cancer who have residual tumor in the breast or axillary lymph nodes following preoperative therapy

NCT01772472

Katherine is a randomized, multicenter, open-label phase III study that has recruited 1487 patients from 328 international sites (57 in Germany) within 3 years.

Background

HER2-positive patients who do not achieve pathologic complete response (pCR) following neoadjuvant therapy have a worse prognosis compared to patients who achieve a pCR (Untch et al. J Clin Oncol. 2011; von Minckwitz et al. J Clin Onco. 2012). HER2-targeted neoadjuvant therapy has shown to improve pCR rates in patients with HER2-positive (Gianni et al. Lancet 2010; von Minckwitz et al. Breast Cancer Res Treat 2011) and a double HER2 blockade can lead to an even further increase (Gianni et al. Lancet Oncol. 2012).

Patients with residual disease after neoadjuvant chemotherapy and anti-HER2 treatment are at an increased risk of recurrence and mortality and it is unknown whether the application of additional agents following surgery may provide further benefit.

The antibody–drug conjugate trastuzumab emtansine (T-DM1) combines the antitumor activities of trastuzumab with intracellular delivery of the cytotoxic agent DM1 via a stable linker (Lewis Phillips et al. Cancer Res 2008). T-DM1 prolonged progression free survival with a more favorable toxicity profile compared with trastuzumab and docetaxel in a phase II study in patients with previously untreated HER2-positive metastatic breast cancer (Hurvitz et al. J Clin Oncol 2013). Moreover, the phase III EMILIA trial has shown that T-DM1 prolonged progression-free and overall survival with less toxicity in patients with previously treated HER2-positive metastatic breast cancer compared with capecitabine and lapatinib (Verma et al. N Engl J Med 2012, Diéras et al. Lancet Oncol 2017).

Given the results with T-DM1 in the metastatic setting, the Katherine trial aimed to explore the efficacy and safety of single-agent T-DM1 compared with trastuzumab in patients with HER2-positive primary breast cancer.

Study design and objectives

Katherine aimed to investigate whether adjuvant T- DM1 was more effective than trastuzumab in patients with HER2-positive primary breast cancer who have received neoadjuvant chemo-therapy including trastuzumab and have residual invasive disease after surgery.

The study primarily aimed to compare invasive disease-free survival between the two treatment arms. Secondary endpoints included disease-free survival, overall survival, distant recurrence-free interval, quality of life, and pharmacokinetics. Safety objectives included all adverse events, abnormal laboratory values, cardiac events, and LVEF (left ventricular ejection fraction). Patient reported outcomes using different quality of life questionnaires were also assessed.

Moreover, Katherine assessed the pharma-cokinetics of T-DM1 in T-DM1–treated patients and trastuzumab in trastuzumab-treated patients, which permits an intra-study comparison of trastuzumab exposure in the 2 treatment arms. Exposure–effect (efficacy and safety) relation-ships can also be explored in this patient population.

A range of translational research questions were also addressed within the Katherine study, such as correlations between biomarker status and efficacy and/or safety or the incidence of anti-therapeutic antibodies and their effect on pharmacokinetics, safety, and efficacy.

Study report

Katherine randomized a total of 1,486 patients (292 patients in Germany) between April 2013 and December 2015. The interim analysis showed that among all randomly assigned patients (743 in the T-DM1 group and 743 in the trastuzumab group), invasive disease or death had occurred in 91 (12.2 %) patients in the T-DM1 and 165 (22.2 %) patients in the trastuzumab group. The estimated percentage of patients who were free of invasive disease at 3 years was 88.3 % in the T-DM1 group and 77.0 % in the trastuzumab group. Invasive disease-free survival was significantly higher in the T-DM1 group than in the trastuzumab group (hazard ratio for invasive disease or death, 0.50; 95 % confidence interval, 0.39 to 0.64; $P < 0.001$). Distant recurrence as the first invasive-disease event occurred in 10.5 % of patients in the T-DM1 group and 15.9 % of those in the trastuzumab group. The safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone. In conclusion, T-DM1 was found to significantly reduce the risk of invasive disease recurrence or death compared to trastuzumab as adjuvant treatment in patients with HER2-positive early breast cancer and residual disease after neoadjuvant therapy [1].

Publication

1. von Minckwitz G, Huang CS, Mano MS, et al. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. N Engl J Med. 2019; 380:617-628.

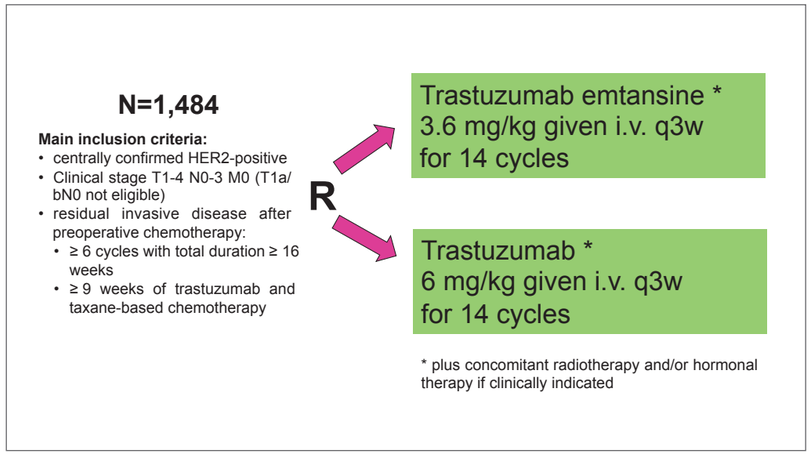


Figure 1: Katherine study design

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

COLLABORATING STUDY GROUPS:
GBG GERMAN BREAST GROUP
NSABP National Surgical Adjuvant Breast and Bowel Project PARTNERS IN CANCER RESEARCH

SPONSOR:
F. Hoffmann-La Roche Ltd

INTERNATIONAL STUDY CHAIR:
Prof. Dr. Charles Geyer
NSABP

STUDY CHAIR GERMANY:
Prof. Dr. Gunter von Minckwitz
German Breast Group,
Neu-Isenburg

GBG 89: GeparNuevo

A randomized phase II study to investigate the addition of PD-L1 antibody MEDI4736 to a taxane-anthracycline containing chemotherapy in triple negative breast cancer

NCT02685059

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

GeparNuevo is a multicenter, prospective, randomized, double-blinded, placebo controlled phase II study that has recruited 174 patients from 28 sites in Germany.

Background
Triple negative breast cancer (TNBC) is a highly aggressive disease. Patients who have received neoadjuvant therapy with chemotherapy alone and achieved a pathological complete response (pCR), have an excellent survival, however, women who did not achieve a pCR did significantly worse.
TNBC and especially the basal like subtype can have a high mutational load with up to 200 mutations per cancer (Shah S et al. Nature. 2012). Moreover, patients with TNBC and a higher score of stromal tumor-infiltrating lymphocytes (sTILs) have a significantly better disease-free survival (DFS) than patients whose TNBC tumor lack sTILs (Adams S et al. J Clin Oncol. 2014). Therefore, immunotherapy might be an option to increase the pCR rate in patients with TNBC.
So far, two studies have shown activity of check point inhibitors in breast cancer. The KEYNOTE-012 study investigated the PD-1 inhibitor pembrolizumab in metastatic TNBC, demonstrating a response rate of 20 % and about 50 % having stable disease or a response (Nanda R et al. J Clin Oncol. 2016). In another phase I study of 12 patients with TNBC treated with the PD-L1 inhibitor MPDL3280A, 33 % had a response. The tolerability was good.
Durvalumab (MEDI4736) is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) that blocks PD-L1 binding to PD-1 and CD80, preventing PD-L1-mediated inhibition of T-cell activation.
These data supported an early investigation of these drugs for treatment of TNBC, when otherwise only chemotherapy is indicated.

Study design and objectives:
GeparNuevo primarily aimed to compare the 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 TNBC.
Secondary objectives were to assess the pCR rates per arm separately for the stratified subpopulations, rates of ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypT(any) ypN0, response rates of the breast tumor and axillary nodes based on physical examination and imaging tests after treatment in both arms, clinical response rate after taxane in both groups, breast conservation, toxicity and compliance, loco-regional invasive recurrence free survival (LRRFS), distant-disease-free survival (DDFS), invasive disease-free survival (IDFS), event free survival (EFS) and overall survival (OS) in both arms and according to stratified subpopulations, to examine quality of life using FACT-Taxane and to examine and compare pre-specified molecular markers as well as gene expression signatures such as tumor infiltrating lymphocytes, PD-1, PD-L1, Ki-67, etc. on core biopsies before chemotherapy, after the window phase and on surgical tissue after end of chemotherapy.
Furthermore, the GeparNuevo study also incorporated translational research questions such as an investigation of the relationship between PD-L1, TILs, immunopredict and other immune markers with response.

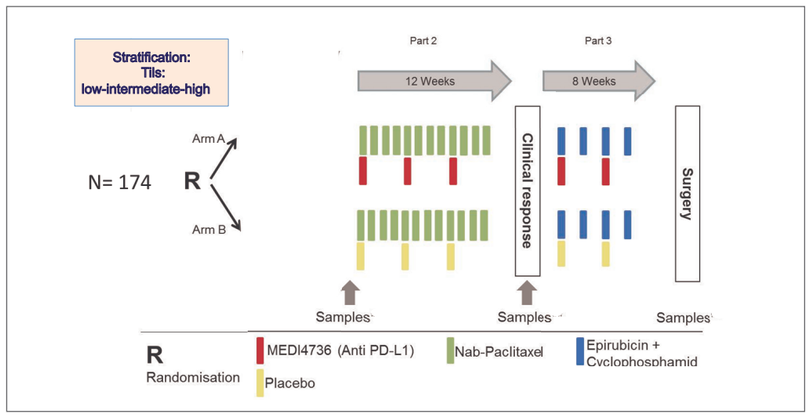


Figure 1: GeparNuevo study design (after approval of amendment 2)

Study report:
GeparNuevo randomized a total of 174 patients between June 2016 and September 2017 from 28 sites in Germany. A total of 117 patients participated in the monotherapeutic window phase which was terminated based on the IDMC (Independent Data Monitoring Committee) consideration indicating an average of 49 days from diagnosis to the start of the 1st chemotherapy as a delay to start of definitive treatment. All randomized patients completed treatment. Median age at study entry was 49.5 years (range 23-76); 47 patients (27 %) were younger than 40 years. 113 patients (65 %) had stage IIa disease and higher, 25 (14 %) had high sTILs, and 144 of 158 (91 %) were PD-L1 positive. Overall, 85 patients (48.9 %) had a pCR, 47 with durvalumab (53.4 %, 95 %CI 42.5-61.4 %) and 38 with placebo (44.2 %, 95 % CI 33.5-55.3 %; unadjusted continuity corrected χ^2 p=0.287), corresponding to an OR of 1.45 (95 % CI 0.80-2.63, unadjusted Wald p=0.224). The durvalumab effect on pCR was seen only in the window cohort (61.0 % vs 41.4 %, OR 2.22, 95 %CI 1.06-4.64) p=0.035; interaction p=0.048). Adverse events were not more frequently reported in the durvalumab arm then in the placebo arm, with the exception of thyroid dysfunction. Overall, 59 patients had at least one SAE, 30 in the durvalumab arm and 29 in the placebo arm. No patient died during treatment.
In conclusion, 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 [1-4].

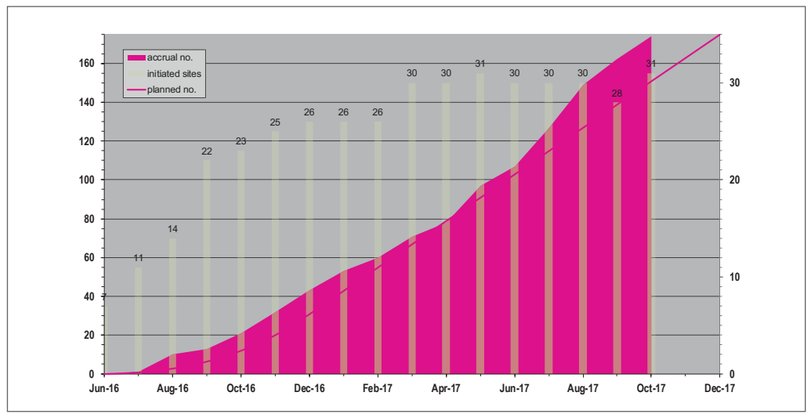


Figure 2: GeparNuevo final recruitment

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

Publications:
1. Loibl S, Untch M, Burchardi N et al. Randomized phase II neoadjuvant study (GeparNuevo) to investigate the addition of durvalumab to a taxane-anthracycline containing chemotherapy in triple negative breast cancer (TNBC). J Clin Oncol 36, 2018 (suppl; abstr 104).
2. Loibl S, Sinn BV, Karn T et al. mRNA signatures predict response to durvalumab therapy in triple negative breast cancer (TNBC)- Results of the translational biomarker programme of the neoadjuvant double-blind placebo controlled GeparNuevo trial. Poster discussion #PD2-07, SABCS 2018 (4-8 Dec 2018).
3. Sinn BV, Loibl S, Karn T et al. Pre-therapeutic PD-L1 expression and dynamics of Ki-67 and gene expression during neoadjuvant immune-checkpoint blockade and chemotherapy to predict response within the GeparNuevo trial. Poster discussion #PD5-05, SABCS 2018 (4-8 Dec 2018).
4. Massa C, Schneeweiss A, Karn T et al. Immunomonitoring of triple negative breast cancer patients undergoing neoadjuvant therapy with durvalumab - Results from the prospectively randomized GeparNuevo trial. Poster presentation #P4-06-01, SABCS 2018 (4-8 Dec 2018).

COLLABORATING STUDY GROUPS:
GBG GERMAN BREAST GROUP
AGO-B BREAST STUDY GROUP

SPONSOR:
GBG Forschungs GmbH

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

Prof. Dr. Andreas Schneeweiß
Nationales Centrum für Tumorerkrankungen,
Universitäts-Klinikum,
Heidelberg

Prof. Dr. Michael Untch
Helios Klinikum Berlin-Buch,
Berlin

GBG 90: GeparOla

A randomized phase II trial to assess the efficacy of paclitaxel and olaparib in comparison to paclitaxel/carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and Homologous Recombination Deficiency (HRD patients with deleterious *BRCA*1/2 tumor or germline mutation and/or HRD score high)

NCT02789332

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

GeparOla is a multicenter, prospective, randomized open-label phase II study that has recruited 107 patients from 28 sites in Germany within 23 months.

Background

Molecular characterizations have demonstrated a strong association between triple-negative breast cancer (TNBC) and *BRCA*1 and to a lesser degree with *BRCA*2 mutations. Tumor cells with a defect in *BRCA* genes have impaired homologous recombination (HR), the only pathway responsible for the reparation of interstrand crosslinks. Tumors with decreased DNA repair capacity are expected to show high sensitivity to DNA damaging agents (Ciccia A et al. Mol Cell. 2010; Deans AJ et al. Nat Rev Cancer. 2011). The addition of carboplatin to a neoadjuvant chemotherapy regime of anthracycline, cyclophosphamide and paclitaxel significantly increased the pathological complete response (pCR) rate in patients with TNBC in two randomized phase II neoadjuvant studies, the GeparSixto (von Minckwitz et al. Lancet Oncol 2014) and the CALBG 40603 (Silkov et al. J Clin Oncol. 2015) trials.

Olaparib is a potent polyadenosine 5'diphosphoribose [poly (ADP ribose)] polymerisation (PARP) inhibitor that is being developed as an oral therapy, both as a monotherapy (including maintenance) and for combination with anti-cancer agents. The efficacy and safety of olaparib included in a standard of care regimen like paclitaxel weekly followed by epirubicin and cyclophosphamide is unknown.

In the GeparSixto trial it has been demonstrated that among patients with measured homologous recombination deficiency (HRD), 67 % had an HRD score high whereas 28 % had *BRCA* mutant tumor (t*BRCA*). Moreover, among t*BRCA* mutated/HRD score high patients, 20 % harbored also a germline *BRCA* mutation (g*BRCA*). When using a strict pCR definition (ypT0 ypN0), patients with HRD score high/t*BRCA* intact or t*BRCA* mutant experienced the greatest benefit with the addition of carboplatin. When allowing the presence of DCIS in the pCR definition (ypT0/is ypN0), only patients with HRD score high/t*BRCA* intact derived benefit by the addition of carboplatin (Loibl et al. Ann Oncol 2018).

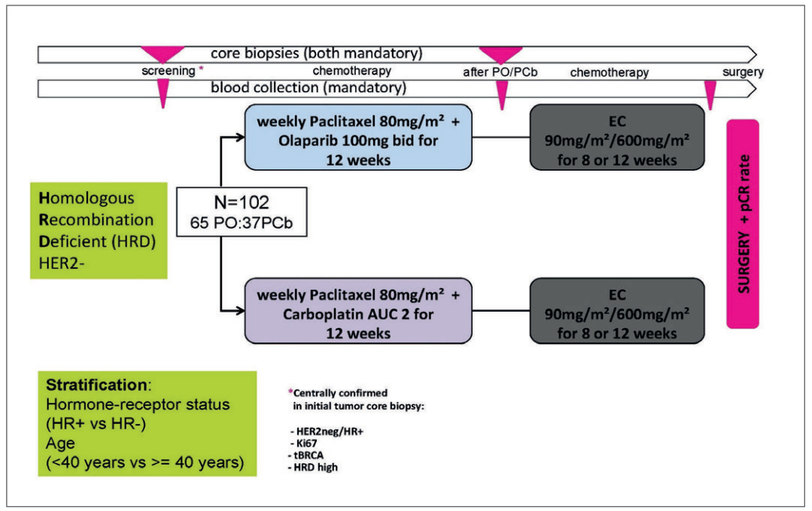


Figure 1: GeparOLA study design

Considering the inconsistency of these results and the absence of a formal interaction between HRD and carboplatin further studies are needed. The GeparOLA study aimed to support the decision for a phase III study exploring the addition of olaparib (O) to a paclitaxel (P) followed by epirubicin (E) and cyclophosphamide (C) schedule (PO→EC) by providing an estimate on the pCR rates in the targeted population, but also by providing estimate comparison to paclitaxel (P) and carboplatin (Cb) followed by EC (PCb→EC).

Study design and objectives

GeparOla primary aimed to assess the pCR (ypT0/is ypN0) rate of neoadjuvant treatment of olaparib and paclitaxel followed by epirubicin and cyclophosphamide (PO→EC) in neoadjuvant patients with early breast cancer and HRD tumors defined as either t*BRCA*1/2 mutation or HRD score high or known g*BRCA* mutation.

Secondary objectives were to assess the pCR rates of patients in both arms, overall and in stratified subgroups, to investigate the pCR rate according to other pCR definitions and to compare them between the two arms, to assess the pCR rate in HRD high with or without t*BRCA* mutation, to determine the response rates of the breast tumor and axillary nodes based on physical examination and imaging tests and to compare them between the two treatment arms, to determine the breast conservation rate, toxicity and compliance with PO→EC and to compare it with PCb→EC. Further objectives were to correlate co-occurring mutations detected by next generation sequencing in lymphocytes or in tumors cells with pCR (exploratory) and potential biomarkers predicting safety and compliance, like SNPs, TILs, PARP, 53BP1, REV7 and other biomarkers considered for breast cancer.

Pharmacogenetic substudy

A pharmacogenetic substudy on genetic markers from peripheral blood to predict tumor biology, treatment response and prognosis will be performed. All patients eligible for the GeparOla study having collected a whole blood sample will be included. The primary objective is to associate the germline genotype of the patient with the treatment response in both randomization arms. Secondary objectives are to associate the germline genotype of the patient with the long term prognosis in both randomization arms and with the molecular profile of the tumors.

Study report

GeparOla randomized a total of 107 patients between September 2016 and August 2018 from 28 sites in Germany. The analysis of the primary endpoint is planned for QI/2019.

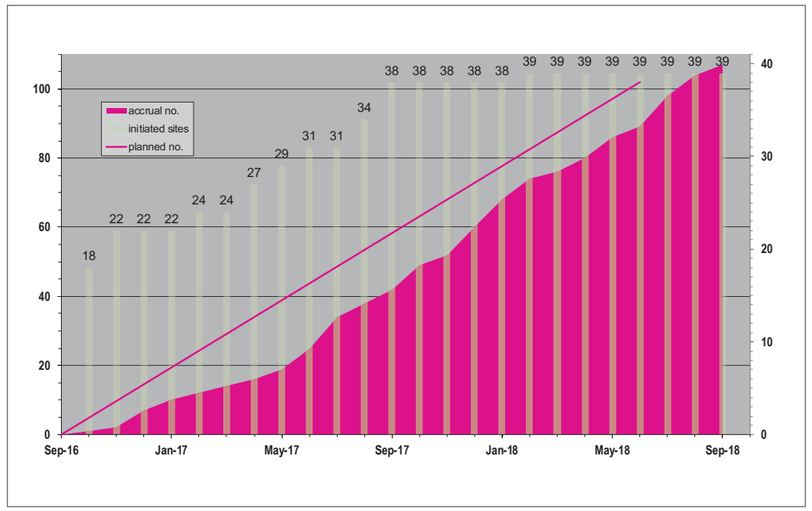


Figure 2: GeparOla final recruitment

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

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

SPONSOR:
GBG Forschungs GmbH

STUDY CHAIR:
Prof. Dr. Peter Fasching
Universitätsklinikum Erlangen

STUDY CO-CHAIRS:
Prof. Dr. Christian Jackisch
Sana Klinikum Offenbach

Prof. Dr. Jens Blohmer
Charité Berlin

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

Follow-up Activities

Follow-up Activities

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 pseudonymised medical data. 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.

Currently over 10,000 participants from 24 trials and 263 sites are included in this registry.

General Follow-Up Database and eCRF

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

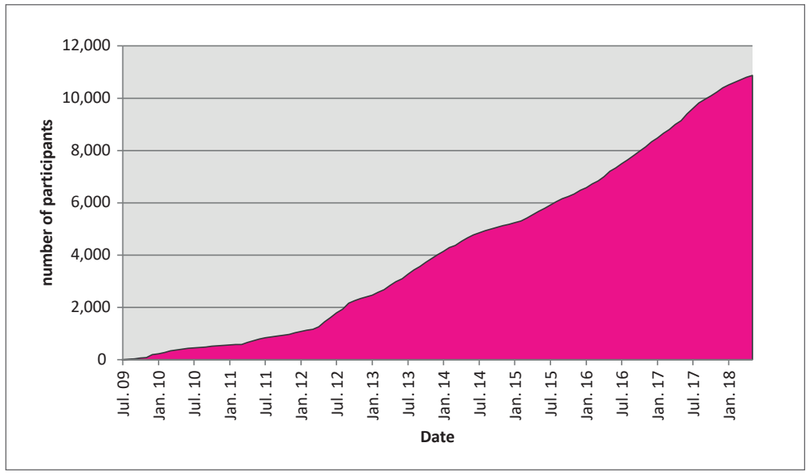


Figure 1: PSRO participants

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

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-018	GeparDuo	907	16	41,4 %
GBG-024	GeparTrio	2,357	230	46,3 %
GBG-027	REACT	814	515	62,8 %
GBG-028	IBIS-2-Prev	142	32	15,5 %
GBG-032	ICE	1,358	190	50,1 %
GBG-033	GAIN	2,995	986	68,4 %
GBG-034	IBIS-2-DCIS	780	258	20,2 %
GBG-036	NATAN	693	63	54,0 %
GBG-040	GeparQuattro	1,507	272	53,7 %
GBG-044	GeparQuinto	2,572	647	60,5 %
GBG-049	PREPARE	733	0	56,5 %
GBG-050	TECHNO	217	0	56,2 %
GBG-052	ICE-2	391	144	63,1 %
GBG-053	PANTHER	772	176	21,9 %
GBG-054	MALE	56	19	11,1 %
GBG-066	GeparSixto	588	335	68,3 %
GBG-068	GAIN-2	2,864	2,204	55,0 %
GBG-069	GeparSepto	1,203	784	76,5 %
GBG-070	DAFNE	65	51	59,1 %
GBG-074	GENEVIEVE	333	204	53,0 %
GBG-075	INSEMA	4,672	1,941	58,8 %
GBG-084	GeparOcto	945	710	47,8 %
GBG-088	GeparX	595	155	2,7 %
GBG-089	GeparNuevo	174	117	8,5 %
GBG-090	GeparOla	107	41	15,0 %

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

Translational Research

Translational Research

Translational Research Activities

Translational research is the link between clinical and experimental science. It implements scientific knowledge from basic research into clinical practice but also transfers clinical issues back to the laboratory. Translational research projects are aimed at increasing scientific knowledge for the understanding of the origin and development of a disease. The identification and validation of biological markers is accomplished to improve the treatment decision for our breast cancer patients. We therefore contribute to the development of innovative diagnostics and new, purposive cancer therapies for a more personalized medicine.

GBG Biobanking

An important pre-requisite for performing translational research projects is the availability of high-quality biomaterial collection (Figure 1). Together with the clinical data, the tissue and blood-derived samples are the key aspects for testing scientific hypotheses in a well-defined patient cohort. The wide area of biospecimens including blood, plasma and purified DNA maintained in biobanks can be described as libraries of the human organism. The Declaration of Helsinki states that all biobanks must take donated materials via a process of informed consent.

The collected biomaterials include:

- FFPE (formalin-fixed paraffin-embedded) tissue
- Fresh frozen tissue
- RNAlater® conserved tissue
- Whole blood (DNA extraction, Single Nucleotide Polymorphism (SNP) analyses, RNA analysis)
- Serum
- Plasma (also for ctDNA preparation)
- Urine

During a trial, collection of certain biomaterials is mandatory and defined in the individual study protocols. Even if the respective clinical trials are already closed for recruitment, the coordinating centers can still collect biomaterials, mostly FFPE tissues. In order to obtain meaningful results from statistical analyses, the investigated samples should represent the majority of patients included in the trial. Therefore, the sample collection rate should be at least 60 %. This goal is usually reached and also exceeded for most samples collected in GBG trials (e. g. FFPE tissue, SNP, serum samples).

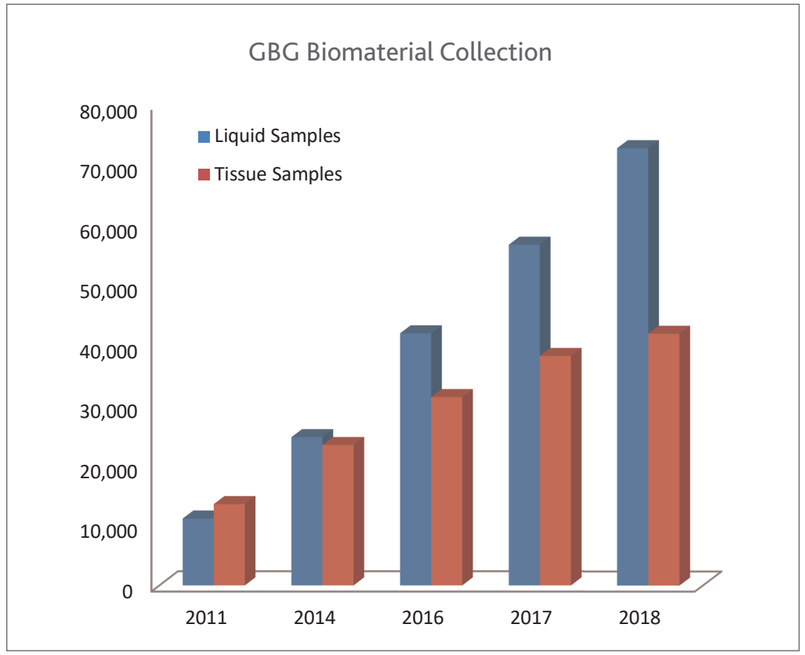


Figure: 1 Samples at GBG Biobank

Central Pathology and Biomarker Analysis

An independent central pathological assessment of standard breast cancer biomarkers such as estrogen receptor (ER), progesterone receptor (PR), HER2, Ki-67 as well as tumor infiltrating lymphocytes (TILs) is implemented in the GBG clinical trials. This allows a standardized definition of the respective patient cohorts as well as comparison of treatment outcome within and across GBG clinical trials. All these central testing methodologies are performed according to the latest standards and guidelines.

Collaborative Translational Research Projects and Substudies

Based on our standardized pathological evaluation of tumor specimens, the biomaterials combined with the clinical data from our studies become more and more interesting for further translational research approaches. The investigation of the biomaterials within the framework of our scientific projects is carried out in cooperation with our national and international partners.

BRCA in GeparOcto

Germline mutations in *BRCA*1/2 induce a predisposition for breast cancer by impairing homologous recombination (HR) and causing genomic instability. HR is also the mechanism responsible for repair of DNA lesions caused by platinum agents and PARP inhibitors. Therefore, patients with triple-negative breast cancer (TNBC) who are also carriers of *BRCA*1/2 mutations are hypothesized to respond better to platinum therapy. In the GeparOcto trial, patients with high-risk early stage breast cancer were randomized to receive treatment with intensified dose-dense epirubicin (E), paclitaxel (P), and cyclophosphamide (C; iddEPC) or weekly paclitaxel/liposomal doxorubicin (PM), plus carboplatin (Cb).
Patients with TNBC participating in the GeparOcto study were analyzed for *BRCA*1/2 mutations. The analysis was performed on germline DNA using next generation sequencing (NGS). Although the results revealed a higher pCR rate in TNBC patients with *BRCA*1/2 mutations compared with non-carriers, there was no evidence for a benefit of carboplatin treatment in this setting [1].

G9 Biomarker Substudies

The GeparNuevo trial included a broad biomaterial collection to address translational research questions such as an investigation of the association between PD-L1, tumor-infiltrating lymphocytes (TILs) and other immune markers with response.
Targeted RNA sequencing was performed on 162 pre-therapeutic FFPE core biopsies using the HTG EdgeSeq® system (HTG oncology biomarker panel). Predefined gene signatures for 1) TILs (CXCL9, CCL5, ICO1, CXCL13); 2) response to immune-checkpoint inhibition (IFNG, CD274, LAG3, CXCL9) and 3) a metagene for cytotoxic response (PRF1, GZMA) were evaluated for their predictive values to treatment response. The results revealed that the predefined signatures reflecting TILs and response to immune-checkpoint inhibition predict response to neoadjuvant chemotherapy, but not to durvalumab. However, a set of differentially expressed genes might be predictive for durvalumab effect [2]. In addition, protein expression levels of Ki-67 and PD-L1 were measured by immunohistochemical staining in tumor biopsies from pre-treatment, window and after nab-paclitaxel treatment. PD-L1 expression defined as ≥ 1 % on tumor cells was predictive for response to durvalumab. Furthermore, an increased percentage of intratumoral lymphocytes (iTILs) was observed in patients treated with a single dose of durvalumab compared to placebo (window cohort). This effect was associated with higher pCR, which might reflect an activated immune response and serve as a surrogate marker for pCR achievement [3]. To determine possible predictive and/or prognostic biomarkers of immune reaction before and during therapy, a monitoring of immune cells isolated from sequentially collected blood samples were evaluated using flow cytometry. The analysis revealed substantial differences in immune cell counts among the two treatment arms (durvalumab vs placebo). Patients treatment with durvalumab in the window phase have significant better pCR among the entire cohort, but not among the immunomonitored patients [4].

Cooperation Project with Cepheid®

Fluorescence in situ hybridization (FISH) and immunohistochemistry (IHC) are the most commonly used methods for ER, PgR, HER2 and Ki-67 assessment in breast tumor samples and are currently considered as gold standard. However, the IHC and FISH methods require well-appointed facilities with extensive lab equipment as well as expert knowledge to interpret results. Even small deviations in processing conditions may lead to variation of results within one lab and also between different labs. To overcome these limitations, Cepheid® has developed a cartridge-based assay using mRNA expression to assess ER, PgR, HER2 and Ki-67 in breast cancer tissue (Xpert® Breast Cancer STRAT4). Only one 5 µm slice of FFPE tumor tissue is required for running the real-time RT-PCR analysis with the GeneXpert® IV system. Therefore, the comparability of results generated with IHC/FISH or Xpert® Breast Cancer STRAT4 cartridge and central pathology assessment will be evaluated on tumor samples from the GeparX trial.

New 3rd party projects

- Oncobiome project, Prof. Laurence Zitvogel (Gustave Roussy Cancer Center, Villejuif)
- DDR Targeting, Prof. Andrew Tutt (Institute of Cancer Research, London)
- Role of CDH1 mutations in breast cancer, Prof. Per Eystein Lønning (University of Bergen)

Proposals may also be submitted by groups that are currently not represented in any board.
http://www.gbg.de/de/forschung/translationale-forschung.php

Publications

1. Pohl E, Schneeweiss A, Hauke J et al. Germline mutation status and therapy response in patients with triple-negative breast cancer (TNBC): Results of the GeparOcto study. Ann Oncol 2018; Volume 29, Issue suppl_8, mdy270.238.

2. Loibl S, Sinn BV, Karn T et al. mRNA signatures predict response to durvalumab therapy in triple negative breast cancer (TNBC)- Results of the translational biomarker programme of the neoadjuvant double-blind placebo controlled GeparNuevo trial. SABCS 2018, PD5-13 Poster discussion.

3. Sinn BV, Loibl S, Karn T et al. Pre-therapeutic PD-L1 expression and dynamics of Ki-67 and gene expression during neoadjuvant immune-checkpoint blockade and chemotherapy to predict response within the GeparNuevo trial. SABCS 2018, PD5-05, Poster discussion.

4. Massa C, Schneeweiss A, Karn T et al. Immunomonitoring of triple negative breast cancer patients undergoing neoadjuvant therapy with durvalumab - Results from the prospectively randomized GeparNuevo trial. SABCS 2018, P4-06-01, Poster.

FURTHER INFORMATION:

Dr. Bärbel Felder
Translational Research

Phone: +49 6102 7480-217
Fax: +49 6102 7480-440
trafo@GBG.de

GBG Study Finder 2019*

Early Breast Cancer

Operative Studies (M0)	
Untreated breast cancer: • Planned breast-conserving surgery • ≥ 18 years • T1 or T2 (imaging), N0 before surgery	**INSEMA** Axillary sentinel lymph node biopsy (SLNB) versus no axillary surgery followed by a 2nd randomisation in case of SLNB positive: SLNB alone versus axillary dissection of the lymph nodes
(Neo)adjuvant Studies (M0)	
Untreated breast cancer: • cT2-cT4a-d • cT1c if TNBC, HER2-positive and/or N+ and/or Ki67 > 20 %	**GeparX** Neoadjuvant chemotherapy with **nab-paclitaxel (weekly or 1,8 q22**) followed by EC q2/q3 **+/- denosumab** (TNBC: carboplatin; HER2-positiv: ABP980+pertuzumab)
Untreated triple-negative breast cancer: • cT2-cT3 • cT1c only if N+	**GeparDouze** Neoadjuvant chemotherapy with 12x paclitaxel weekly + carboplatin q3 followed by EC/AC q2 or q3 **+ atezolizumab or placebo q3** followed by **adjuvant therapy with atezolizumab or placebo q3** (total duration of atezolizumab/placebo will be one year)
Untreated triple-negative breast cancer: • Stage II-III	**GeparTreize** Arm A: **1x durvalumab monotherapy q2** followed by neoadjuvant chemotherapy with 12x paclitaxel weekly +/- carboplatin q1 or q3 followed by EC/AC q2 or q3 **+ durvalumab q4** followed by **12 months adjuvant therapy with durvalumab q4** Arm B: Chemotherapy alone
Untreated 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 13 cyles + standard adjuvant endocrine treatment ≥ 5 years Arm B: Adjuvant chemotherapy followed by standard adjuvant endocrine treatment ≥ 5 years
Untreated HR-positive/HER2-negative breast cancer: • cT2-cT4, N0-3 • postmenopausal women	**ULTIMATE** Neoadjuvant therapy with exemestane and **durvalumab in patients** with CD8+ T-cell-infiltration after stimulation of the immune system
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**
***gBRCA*1/2 positive and HER2-negative breast cancer:** • High risk after (neo)adjuvant chemotherapy	**OLYMPIA** **Olaparib versus placebo** as adjuvant treatment

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-positive Breast Cancer	
HER2-positive and HR-positive metastatic breast cancer: • 1st line chemotherapy (for metastatic breast cancer) with a taxane or vinorelbine in combination with trastuzumab +/- pertuzumab	**PATINA** Maintenance therapy with anti-HER2 and endocrine therapy **+/- palbociclib**
HER2-negative Breast Cancer	
HER2-negative und HR-positive metastatic breast cancer: • at least 4 cycles of a 1st line mono- or poly-chemotherapy • Previous therapy with maximum one line of anti-hormonal treatment 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 metastatic disease	**PADMA** Endocrine therapy **+ palbociclib versus mono-chemotherapy +/-** endocrine maintenance therapy Possible mono-chemotherapies (Physician's choice): • Capecitabine p.o. • Epirubicine i.v. • Paclitaxel i.v. • Vinorelbine i.v.
HER2-negative and HR-positive metastatic breast cancer: • Postmenopausal women • Recurrence or progression after therapy with a non steroidale aromatase inhibitor	**DESIREE** Exemestane in combination with **induction dose escalation of everolimus** versus exemestane in combination with **standard therapy with everolimus**

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

Notes

GBG

GERMAN
BREAST
GROUP

Impressum:

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

www.GBG.de