GBG

GERMAN
BREAST
GROUP

Heilung durch Innovation, Kompetenz und Partnerschaft

Annual Scientific Report

2022

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Annual Scientific Report 2022

Index

Introduction

Introduction

Headquarters:

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1. About the German Breast Group

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

The main focus of the GBG is on the investigator initiated trials (IIT). These are independent, academically driven studies focused on important clinical and research questions to optimize treatment strategies. This is in contrast to industry sponsored studies which are often focused on regulatory authorities to obtain approval or a label extension for a drug. All services provided by GBG are to the highest standard of the International Conference on Harmonisation of Good Clinical Practice (ICH-GCP1998) and if necessary regulatory requirements. We offer a comprehensive range of services, including:

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

2. Infrastructure of the German Breast Group

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

Recruitment of patients
Patients are recruited through the participating sites which provide detailed information on the GBG studies to the patient. Patients are treated according to the latest scientific findings and are carefully controlled and monitored. Thanks to the clinical trials, breast cancer treatment strategies and clinical guidelines have significantly improved over time and the mortality has decreased over time. 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 a therapeutic strategy 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 virtually.
Our subboards have been active discussing current studies, research results and further innovative study designs.

The members of our subboards in 2022 are shown below:

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

Adjuvant
Prof. Dr. C. Denkert, Marburg
Prof. Dr. W. Janni, Ulm
Prof. Dr. S. Loibl, Neu-Isenburg
Prof. Dr. F. Marmé, Mannheim
Dr. L. Michel, Heidelberg
Prof. Dr. T. Reimer, Rostock
PD Dr. M. Reinisch, Essen
Dr. S. Schmatloch, Kassel
Prof. Dr. M. Schmidt, Mainz
PD Dr. B. Sinn, Berlin
Prof. Dr. E. Stickeler, Aachen
Prof. Dr. M. Untch, Berlin

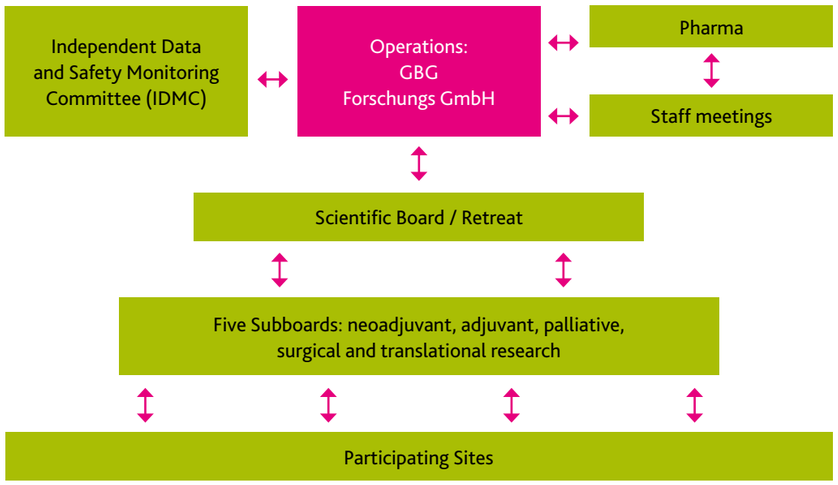

Figure 1: Structure of the German Breast Group

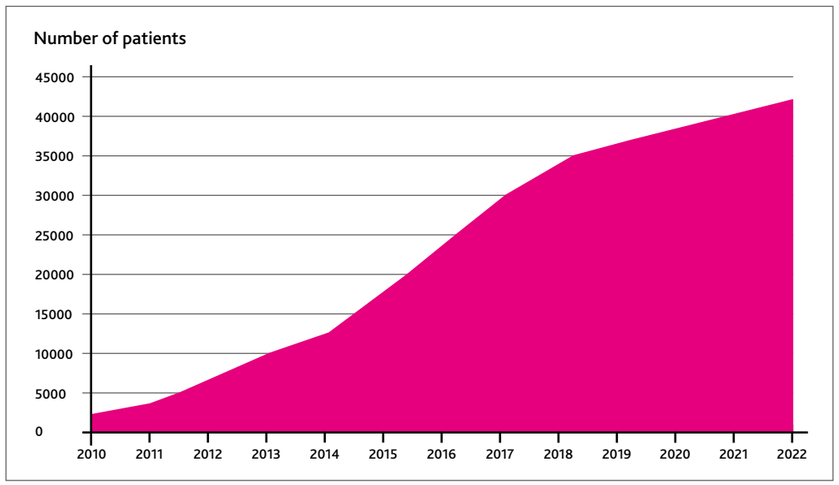

Figure 2: Annual recruitment of patients 2022

Palliative
Prof. Dr. T. Decker, Ravensburg
Prof. Dr. C. Denkert, Marburg
Prof. Dr. S. Loibl, Neu-Isenburg
Dr. K. Lübbe, Hannover
Prof. Dr. C. Mundhenke, Bayreuth
Prof. Dr. V. Müller, Hamburg
Prof. Dr. M. Schmidt, Mainz
Prof. Dr. M. Thill, Frankfurt am Main

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

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

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

The IDMC reviews all GBG sponsored trials regarding:

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

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

3. Cooperations with other study groups

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

International Research Group

ABCSG:
Austrian Breast & Colorectal Cancer Study Group

AFT:
Alliance Foundation for Clinical Trials in Oncology

AGO:
Arbeitsgemeinschaft Gynäkologische Onkologie

AGO-B:
Breast Study Group

ASAN Medical Center

BREAST CANCER TRIALS GROUP

BIG:
Breast International Group

BOOG:
Borstkanker Onderzoeksgroep Nederland

CCTG:
Canadian Cancer Trials Group

CIRG:
Cancer International Research Group

CRUK:
Cancer Research UK

CTI:
Cancer Trials Ireland

CTRU:
Clinical Trials Research Unit

DKG:
Deutsche Krebsgesellschaft

EBCTCG:
Early Breast Cancer Trialists' Collaborative Group

EORTC:
European Organisation for Research and Treatment of Cancer

Fondazione Michelangelo:
Scientific organization based in Italy

Frontier Science foundation

GEICAM:
Grupo Español de Investigación del Cáncer de Mama

IBCSG:
International Breast Cancer Study Group

ICCG:
International Collaborative Cancer Group

ICR CTSU:
The Institute of Cancer Research

IDDI
International Drug Development Institute, Inc.

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

JBCRG:
Japan Breast Cancer Research Group

LACOG:
Latin American Cooperative Oncology Group

NOGGO:
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie

NRG:
Oncology

NSABP:
National Surgical Adjuvant Breast and Bowel Project

SAKK:
Swiss Group for Clinical Cancer Research

SBG:
Scandinavian Breast Cancer Group

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

UCBG:
French breast cancer intergroup UNICANCER
UNICANCER:
UNICANCER Group, France

Uniklinik Köln

Universität Rostock

Universitätsklinikum Hamburg-Eppendorf

Universitätsspital Basel, Brustzentrum

UZL:
University Hospital of Leuven

WSG:
Westdeutsche Studiengruppe

ZKS Köln:
Zentrum für klinische Studien

4. Publications in 2022

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

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

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

Peer-review articles, reviews and congress contributions in 2022 are listed in 4.1., 4.2. and 4.3.

4.1. Peer-reviewed articles in 2022

1. Francis PA, Fleming GF, Láng I, et al.; SOFT Investigators and the International Breast Cancer Study Group (a division of ETOP IBCSG Partners Foundation). Adjuvant Endocrine Therapy in Premenopausal Breast Cancer: 12-Year Results From SOFT. J Clin Oncol. 2022 Dec 9:JCO2201065. doi: 10.1200/JCO.22.01065.

2. Maschmeyer G, Loibl S, Fehm T, Hilgendorf I, Dittrich R. Management onkologischer Erkrankungen in der Schwangerschaft. Forum (2022).

3. Curigliano G, Mueller V, Borges V, et al. Tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB): final overall survival analysis. Ann Oncol. 2022 Mar;33(3):321-329. doi: 10.1016/j.annonc.2021.12.005. Epub 2021 Dec 23. Erratum in: Ann Oncol. 2022 Dec 21;: PMID: 34954044.

4. Loibl, S., Seiler, S. Schwangerschaft nach Krebs. Forum. 2022 Dec 29.

5. Lin NU, Murthy RK, Abramson V, et al. Tucatinib vs Placebo, Both in Combination With Trastuzumab and Capecitabine, for Previously Treated ERBB2 (HER2)-Positive Metastatic Breast Cancer in Patients With Brain Metastases: Updated Exploratory Analysis of the HER2CLIMB Randomized Clinical Trial. JAMA Oncol. 2022 Dec 1:e225610. doi: 10.1001/jamaoncol.2022.5610. Epub ahead of print. PMID: 36454580; PMCID: PMC9716438.

6. Reimer T, Stachs A, Veselinovic K, et al. INSEMA investigators. Patient-reported outcomes for the Intergroup Sentinel Mamma study (INSEMA): A randomised trial with persistent impact of axillary surgery on arm and breast symptoms in patients with early breast cancer. EClinicalMedicine. 2022 Nov 25;55:101756. doi: 10.1016/j.eclinm.2022.101756. PMID: 36457648; PMCID: PMC9706517.

7. Schmidt M, Lübbe K, Decker T, et al. A multicentre, randomised, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer (DESIREE). ESMO Open. 2022 Nov 7;7(6):100601. doi: 10.1016/j.esmoop.2022.100601.

8. Loibl S, Schneeweiss A, Huober J, et al. Neoadjuvant durvalumab improves survival in early triple-negative breast cancer independent of pathological complete response. Ann Oncol. 2022 Nov;33(11):1149-1158. doi: 10.1016/j.annonc.2022.07.1940.

9. Conforti F, Pala L, Bagnardi V, et al. Surrogacy of Pathologic Complete Response in Trials of Neoadjuvant Therapy for Early Breast Cancer: Critical Analysis of Strengths, Weaknesses, and Misinterpretations. JAMA Oncol. 2022 Nov 1;8(11):1668-1675. doi: 10.1001/jamaoncol. 2022.3755.

10. Loibl S, Loirat D, Tolaney SM, et al. Health-related quality of life in the phase III ASCENT trial of sacituzumab govitecan versus standard chemotherapy in metastatic triple-negative breast cancer. Eur J Cancer. 2022 Oct 18;178:23-33. doi: 10.1016/j.ejca.2022.10.003.

11. Geyer CE Jr, Garber JE, Gelber RD, et al. Overall survival in the OlympiA phase III trial of adjuvant olaparib in patients with germline pathogenic variants in *BRCA1/2* and high-risk, early breast cancer. Ann Oncol. 2022 Oct 10:S0923-7534(22)04165-5. doi: 10.1016/j.annonc.2022.09.159.

12. Swain SM, Tan AR, Gianni L, et al. Incidence and severity of anaphylaxis and hypersensitivity in trials of intravenous pertuzumab plus trastuzumab or the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection for HER2-positive breast cancer. Eur J Cancer. 2022 Oct 7;178:70-81. doi: 10.1016/j.ejca.2022.09.024.

13. Leichsenring J, Vladimirova V, Solbach C, et al. EVI1 expression in early-stage breast cancer patients treated with neoadjuvant chemotherapy. BMC Cancer. 2022 Oct 5;22(1):1040. doi: 10.1186/s12885-022-10109-1.

14. Reinisch M, Untch M, Mahlberg R, et al. Subcutaneous injection of trastuzumab into the thigh versus abdominal wall in patients with HER2-positive early breast cancer: Pharmacokinetic, safety and patients' preference - Substudy of the randomised phase III GAIN-2 study. Breast. 2022 Oct 5;66:110-117. doi: 10.1016/j.breast.2022.10.002.

15. Dixon-Suen SC, Lewis SJ, Martin RM, et al. Physical activity, sedentary time and breast cancer risk: a Mendelian randomisation study. Br J Sports Med. 2022 Oct;56(20):1157-1170. doi: 10.1136/bjsports-2021-105132.

16. Loibl S, Huang CS, Mano MS, et al. Adjuvant trastuzumab emtansine in HER2-positive breast cancer patients with HER2-negative residual invasive disease in KATHERINE. NPJ Breast Cancer. 2022 Sep 19;8(1):106. doi: 10.1038/s41523-022-00477-z.

17. Prat A, Bardia A, Curigliano G, et al. An Overview of Clinical Development of Agents for Metastatic or Advanced Breast Cancer Without ERBB2 Amplification (HER2-Low). JAMA Oncol. 2022 Sep 15. doi: 10.1001/jamaoncol. 2022.4175.

18. Hartmann S, Kühn T, Hauptmann M, et al. Axillary Staging after Neoadjuvant Chemotherapy for Initially Node-Positive Breast Carcinoma in Germany: Initial Data from the AXSANA study. Geburtshilfe Frauenheilkd. 2022 Sep 13;82(9):932-940. doi: 10.1055/a-1889-7883.

19. Galactionova K, Loibl S, Salari P, et al. Cost-effectiveness of palbociclib in early breast cancer patients with a high risk of relapse: Results from the Penelope[B] trial. Front Oncol. 2022 Sep 5;12:886831. doi: 10.3389/fonc.2022.886831.

20. Cui W, Phillips KA, Francis PA, et al. Understanding the barriers to, and facilitators of, ovarian toxicity assessment in breast cancer clinical trials. Breast. 2022 Aug;64:56-62. doi: 10.1016/j.breast.2022.05.002.

21. Rugo HS, Tolaney SM, Loirat D, et al. Safety analyses from the phase 3 ASCENT trial of sacituzumab govitecan in metastatic triple-negative breast cancer. NPJ Breast Cancer. 2022 Aug 29;8(1):98. doi: 10.1038/s41523-022-00467-1.

22. Zhu Z, Turner NC, Loi S, et al. Comparative biomarker analysis of PALOMA-2/3 trials for palbociclib. NPJ Precis Oncol. 2022 Aug 16;6(1):56. doi: 10.1038/s41698-022-00297-1.

23. Cristofanilli M, Rugo HS, Im SA, et al. Overall Survival with Palbociclib and Fulvestrant in Women with HR+/HER2- ABC: Updated Exploratory Analyses of PALOMA-3, a Double-blind, Phase III Randomized Study. Clin Cancer Res. 2022 Aug 15;28(16):3433-3442. doi: 10.1158/1078-0432.CCR-22-0305.

24. Lambertini M, Fielding S, Loibl S, et al. Impact of Age on Clinical Outcomes and Efficacy of Adjuvant Dual Anti-HER2 Targeted Therapy. J Natl Cancer Inst. 2022 Aug 8;114(8):1117-1126. doi: 10.1093/jnci/djac096.

25. Cortes J, Rugo HS, Cescon DW, et al. Pembrolizumab plus Chemotherapy in Advanced Triple-Negative Breast Cancer. N Engl J Med. 2022 Jul 21;387(3):217-226. doi: 10.1056/NEJMoa2202809. PMID: 35857659
.

26. Amant F, Nekljudova V, Maggen C, et al. Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. Eur J Cancer. 2022 Jul;170:54-63. doi: 10.1016/j.ejca. 2022.04.014.

27. Blohmer JU, Link T, Reinisch M, et al. Effect of Denosumab Added to 2 Different nab-Paclitaxel Regimens as Neoadjuvant Therapy in Patients With Primary Breast Cancer: The GeparX 2×2 Randomized Clinical Trial. JAMA Oncol. 2022 Jul 1;8(7):1010-1018. doi: 10.1001/jamaoncol.2022.1059.

28. Laakmann E, Witzel I, Neunhöffer T, et al. Characteristics of patients with brain metastases from human epidermal growth factor receptor 2-positive breast cancer: subanalysis of Brain Metastases in Breast Cancer Registry. ESMO Open. 2022 Jun;7(3):100495. doi: 10.1016/j.esmoop.2022.100495.

29. Blenman KRM, Marczyk M, Karn T, et al. Predictive Markers of Response to Neoadjuvant Durvalumab with Nab-Paclitaxel and Dose-Dense Doxorubicin/Cyclophosphamide in Basal-Like Triple-Negative Breast Cancer. Clin Cancer Res. 2022 Jun 13;28(12):2587-2597. doi: 10.1158/1078-0432.CCR-21-3215.

30. Denkert C, Loibl S. Response-based molecular subtyping-emergence of the third generation of breast cancer subtypes. Cancer Cell. 2022 Jun 13;40(6):592-594. doi: 10.1016/j.ccell.2022.05.012.

31. Carey LA, Loirat D, Punie K, et al. Sacituzumab govitecan as second-line treatment for metastatic triple-negative breast cancer-phase 3 ASCENT study subanalysis. NPJ Breast Cancer. 2022 Jun 9;8(1):72. doi: 10.1038/s41523-022-00439-5.

32. Gelber RD, Wang XV, Cole BF, et al. Six-year absolute invasive disease-free survival benefit of adding adjuvant pertuzumab to trastuzumab and chemotherapy for patients with early HER2-positive breast cancer: A Subpopulation Treatment Effect Pattern Plot (STEPP) analysis of the APHINITY (BIG 4-11) trial. Eur J Cancer. 2022 May;166:219-228. doi: 10.1016/j.ejca.2022.01.031.

33. Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022 Apr;33(4):384-394. doi: 10.1016/j.annonc.2022.01.009.

34. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Aromatase inhibitors versus tamoxifen in premenopausal women with oestrogen receptor-positive early-stage breast cancer treated with ovarian suppression: a patient-level meta-analysis of 7030 women from four randomised trials. Lancet Oncol. 2022 Mar;23(3):382-392. doi: 10.1016/S1470-2045(21)00758-0. Epub 2022 Feb 3. Erratum in: Lancet Oncol. 2022 Apr;23(4):e161.

35. van Mackelenbergh MT, Seither F, Möbus V, et al. Effects of capecitabine as part of neo-/adjuvant chemotherapy - A meta-analysis of individual breast cancer patient data from 13 randomised trials including 15,993 patients. Eur J Cancer. 2022 May;166:185-201. doi: 10.1016/j.ejca.2022.02.003.

36. Gerber B, Schneeweiss A, Möbus V, et al. Pathological Response in the Breast and Axillary Lymph Nodes after Neoadjuvant Systemic Treatment in Patients with Initially Node-Positive Breast Cancer Correlates with Disease Free Survival: An Exploratory Analysis of the GeparOcto Trial. Cancers (Basel). 2022 Jan 20;14(3):521. doi: 10.3390/cancers14030521.

4.2. Peer-reviewed reviews in 2022

1. Dixon-Douglas J, Loibl S, Denkert C, et al. Integrating Immunotherapy Into the Treatment Landscape for Patients With Triple-Negative Breast Cancer. Am Soc Clin Oncol Educ Book. 2022 Apr;42:1-13. doi: 10.1200/EDBK_351186. PMID: 35649211. Furlanetto J, Marmé F, Loibl S. Sacituzumab govitecan: past, present and future of a new antibody-drug conjugate and future horizon. Future Oncol. 2022 Sep;18(28):3199-3215. doi: 10.2217/fon-2022-0407.

2. Furlanetto J, Marmé F, Loibl S. Sacituzumab govitecan: past, present and future of a new antibody-drug conjugate and future horizon. Future Oncol. 2022 Sep;18(28):3199-3215. doi: 10.2217/fon-2022-0407.

4.3. Congress contribution in 2022

SABCS:
San Antonio Breast Cancer Symposium, December 6-10, 2022

Decker T, Lüdtke-Heckenkamp K, Melnichuk L, et al. Maintenance therapy with ET and Ribociclib after 1st line chemotherapy (CT) in hormone receptor (HR)-positive/HER2-negative metastatic breast cancer (BC): a phase II trial (AMICA). SABCS 2022; abstract P3-01-09, poster.

Denkert C, Schneeweiss A, Rey J, et al. Spatial and temporal heterogeneity of predictive and prognostic signatures in triple-negative breast cancer treated with neoadjuvant combination immune-chemotherapy. SABCS 2022; abstract PD4-02, spotlight poster discussion.

Denkert C, Martin M, Untch M, et al. Outcome analysis of HER2-zero or HER2-low hormone receptor-positive (HR+) breast cancer patients - characterization of the molecular phenotype in combination with molecular subtyping. SABCS 2022; abstract HER2-06, spotlight poster discussion at special session.

Fasching P, Schmatloch S, Hauke J, et al. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency – long-term survival of the GeparOLA study. SABCS 2022; abstract GS5-02, oral presentation.

Knudsen E, Rachakonda K, Marmé F, et al. Immunohistochemical markers and determinants of clinical response in the Penelope^{B} trial. SABCS 2022; abstract PD17-06, spotlight poster discussion.

Krug D, Vladimirova V, Untch M, et al. Pathologic complete response and breast-conserving surgery are associated with improved prognosis in patients with early-stage triple-negative breast cancer treated with neoadjuvant chemotherapy. SABCS 2022; abstract PD15-06, spotlight poster discussion.

Loibl S, Denkert C, Liu Y, et al. Development and validation of a composite biomarker predictive of Palbociclib + endocrine treatment benefit in early breast cancer: Penelope^{B} and PALLAS Trials. SABCS 2022; abstract PD17-05, spotlight poster discussion.

Massa C, Karn T, Weber K, et al. Immunological and clinical consequences of durvalumab treatment in combination to neoadjuvant chemotherapy in triple-negative breast cancer patients. SABCS 2022; abstract PD9-04, spotlight poster discussion.

Turner NC, Oliveira M, Howell S, et al. Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant hormone receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer: results from the Phase III CAPItello-291 trial. SABCS 2022; abstract GS3-04, oral presentation.

DKK:
Deutscher Krebs-Kongress, November 13-16, 2022

Loibl S, Lin NU, Murthy RK, et al. Impact of tucatinib on progression-free survival in patients with HER2+ metastatic breast cancer and stable or active brain metastases. DKK #309, poster
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Loibl S, Reinisch M, Denkert, C, et al. GeparPiPa- A randomized, open-label, phase II trial comparing neoadjuvant trastuzumab, pertuzumab and endocrine therapy +/- the PI3K inhibitor inavolisib in patients (pts) with HER2+/HR+, *PIK3CA* mutant early breast cancer (BC). DKK #1027, poster.

Marmé F, Hanusch C, Furlanetto J, et al. Safety interim analysis (SIA) of the phase III postneoadjuvant SASCIA study evaluating sacituzumab govitecan (SG) in patients (pts) with primary HER2-negative breast cancer (BC) at high relapse risk after neoadjuvant chemotherapy (NACT). DKK #504, poster.

ESMO:
European Society for Medical Oncology, September 9-13, 2022

Galas K, Gleitsmann M, Rey J, et al. Tumor biology and immunology in patients (pts) with breast cancer occurring during pregnancy (BCP) compared to non-pregnant breast cancer pts. ESMO 2022; 151P, poster.

Hägele M, Müller KR, Denkert C, et al. Generalization of a deep learning model for HER2 status predictions on H&E-stained whole slide images derived from 3 neoadjuvant clinical studies. ESMO 2022; 68MO, mini oral presentation.

Huober J, Janni W, Untch M, et al. Long-term survival of a randomised, open-label, phase II study comparing the efficacy and safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer (GENEVIEVE). ESMO 2022; 168P, poster.

Laakmann E, Riecke K, Neunhöffer T, et al. Long-term survival of HER2-positive breast cancer patients with brain metastases: Subanalysis of the BMBC Registry. ESMO 2022; 269P, poster.

Loibl S, Reinisch M, Denkert C, at al. A randomized, open-label, phase II trial comparing neoadjuvant trastuzumab, pertuzumab and endocrine therapy +/- the PI3K inhibitor inavolisib in patients (pts) with HER2+/HR+, *PIK3CA* mutant early breast cancer (BC)- GeparPiPPa. ESMO 2022; 200TiP, poster.

ECP:
European Congress of Pathology, September 3-7, 2022
Krämer MJ, Sinn BV, Jank P, et al. Evaluation of Ki67 by image-analysis-enhanced quantitative digital pathology. Poster session #PS-03-010, poster.

DGP: Deutsche Gesellschaft für Pathologie, June 9-11, 2022
Westhoff CC, Rüschoff J, Jank P, et al. Impact of TROP-2 and its cellular localization on prognosis of breast cancer-an analysis of 1164 tumors from a prospective clinical trial. Abstract AG06.12, oral presentation.

ASCO: American Society of Clinical Oncology, Annual Meeting June 3-7, 2022
Bardia A, et al. Sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) in patients (pts) with previously treated metastatic triple-negative breast cancer (mTNBC): Final results from the phase 3 ASCENT study. Poster Session #1071, poster.

Denkert C, Schneeweiss A, Rey J, et al. Biomarkers for response to immunotherapy in triple-negative breast cancer – differences between survival and pCR biomarkers. Poster Session #583, poster.

Juric D, et al. Alpelisib (ALP) + fulvestrant (FUL) in patients (pts) with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2–) advanced breast cancer (ABC): Biomarker (BM) analyses by next-generation sequencing (NGS) from the SOLAR-1 study. Oral Abstract Session #1006, oral presentation.

Karn T, Denkert C, Rey J, et al. Low TMB as predictor for additional benefit from neoadjuvant immune checkpoint inhibition in triple-negative breast cancer. Poster Session #581, poster.

Pfeiler G, et al. Impact of Body Mass Index on treatment and outcomes in early hormone receptor-positive breast cancer patients receiving endocrine therapy with or without palbociclib in the PALLAS trial. Poster Discussion Session #518, poster discussion.

ESMO-Breast Cancer
May 3-5, 2022
Furlanetto J, Marmé F, Thode C, et al. Ovarian function in young patients (pts) treated with postneoadjuvant palbociclib (PAL) and endocrine therapy (ET) for hormone receptor (HR)-positive, HER2-negative early breast cancer (BC): explorative analysis in Penelope[B]. ESMO Breast 2022; 60MO, mini oral presentation.

Marmé F, Hanusch C, Furlanetto J, et al. Safety interim analysis (SIA) of the phase III postneoadjuvant SASCIA study evaluating sacituzumab govitecan (SG) in patients with primary HER2-negative breast cancer (BC) at high relapse risk after neoadjuvant treatment. ESMO Breast 2022; 58O, proffered paper presentation.

Reinisch M, Blohmer JU, Link T, et al. Patient quality of life (QoL) from the GeparX trial on the addition of denosumab (Dmab) added to two different nab-paclitaxel (nP) regimens as neoadjuvant chemotherapy (NACT) in primary breast cancer (BC). ESMO Breast 2022; 94P, poster presentation.

Riecke K, Laakmann E, Neunhöffer T, et al. Long-term survival of breast cancer patients with brain metastases: Subanalysis of the BMBC Registry. ESMO Breast 2022; 170P, poster presentation.

Sinn BV, Untch M, Karn T, et al. Intermediate biopsies during neoadjuvant chemotherapy for breast cancer to predict patient outcome. ESMO Breast 2022; 24P, poster presentation.

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.

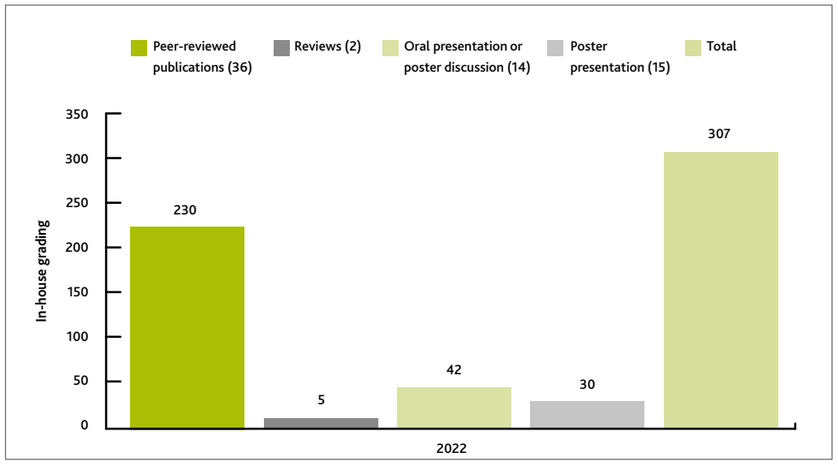


Figure 3: Overview of GBG's in-house grading for publications in 2022

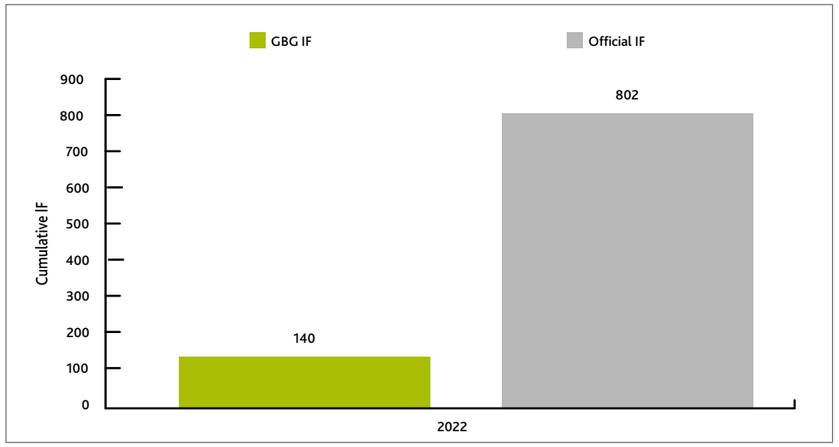


Figure 4: GBG and official Impact Factor (IF) in 2022

4.5. Guideline for Authorship

In order to guarantee a maximum of transparency when assigning the co-authorship we have established an 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

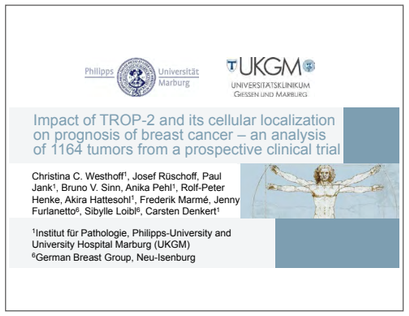
GBG Publications on translational research project

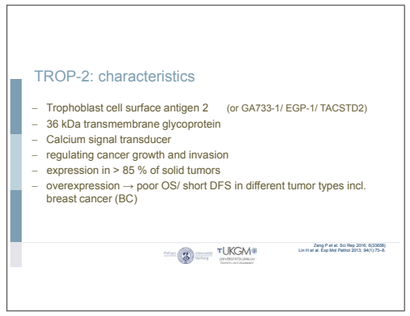
- Project leader (should prepare manuscript)
- Involved team member of this TRAFO project
- TRAFO board / protocol board members*
- Biomaterial provider
- 1-2 local pathologists providing most tumor tissue
- Biometrician
- PI (if involved in TRAFO project)

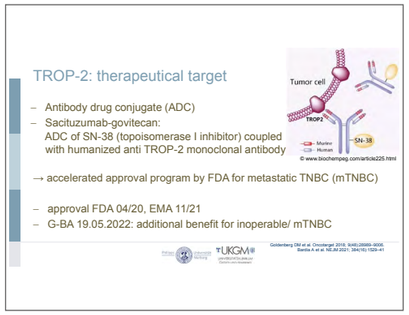
* Subboard and protocol board members will share in general authorships with best biomaterial providers on a 2:1 basis

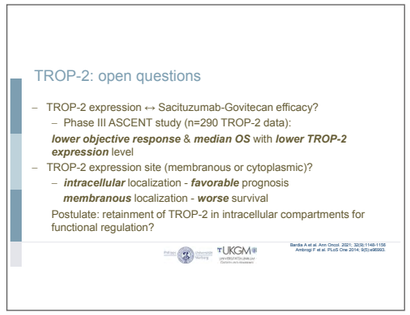
4.6. Oral and poster presentations

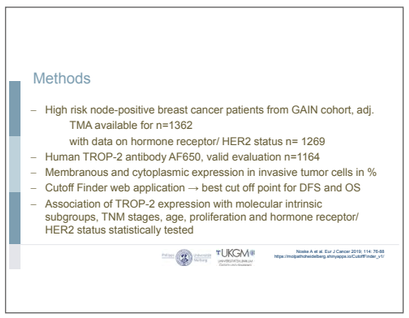
GAIN
(DGP Jahrestagung 2022)

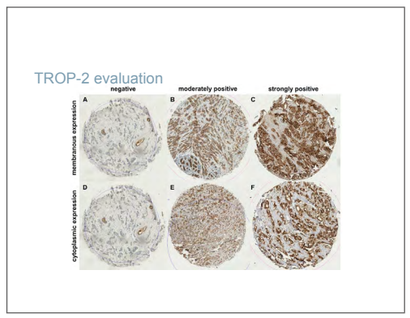


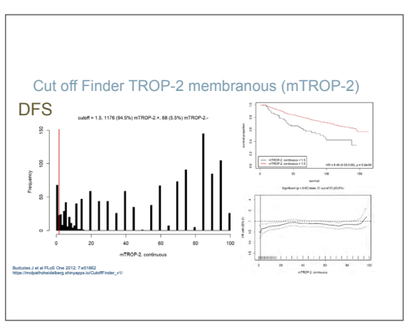


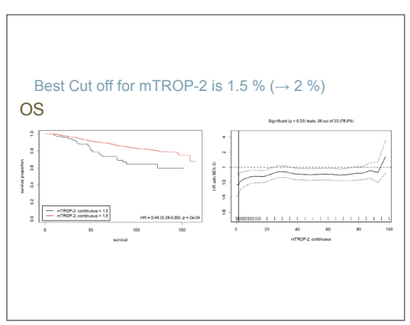












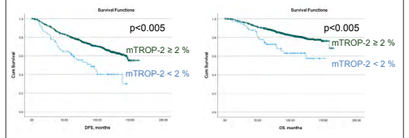
PENELOPE[B]
(ESMO 2022)

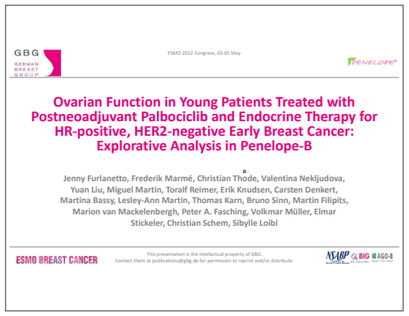
Parameter	All (n=1164)	mTROP-2 < 2%	mTROP-2 ≥ 2%	p-value
Histological tumor type				0.290[1]
NST	895 (76.9)	46 (69.7)	849 (77.3)	
ILC	131 (11.3)	11 (16.7)	120 (10.9)	
Other	138 (11.9)	9 (13.6)	129 (11.7)	
Molecular subgroup				0.017[1]
Lum/Her2-	724 (62.2)	38 (57.6)	686 (62.5)	
HER2+	269 (22.3)	10 (15.2)	259 (22.6)	
TNBC	180 (15.5)	18 (27.3)	162 (14.8)	
Ki67				0.490
≤ 20 %	759 (75.6)	34 (70.8)	725 (75.8)	
>20 %	245 (24.4)	14 (29.2)	231 (24.2)	
missing	160 (13.7)			
Grading				0.007
G1-2	606 (52.1)	23 (35.4)	583 (53.1)	
G3	557 (47.9)	42 (64.6)	515 (46.9)	
missing	1 (0.1)			
pT				0.166
T1-2	1025 (88.4)	54 (83.1)	971 (88.7)	
T3-4	135 (11.6)	11 (16.9)	124 (11.3)	
missing	4 (0.3)			
pN				0.898
N1	470 (40.4)	26 (39.4)	444 (40.4)	
N2-3	694 (59.6)	40 (60.6)	654 (59.6)	
missing	470 (40.4)			
Age (in years)				0.091
<60	970 (83.3)	50 (75.8)	920 (83.8)	
≥ 60	194 (16.7)	16 (24.2)	178 (16.2)	

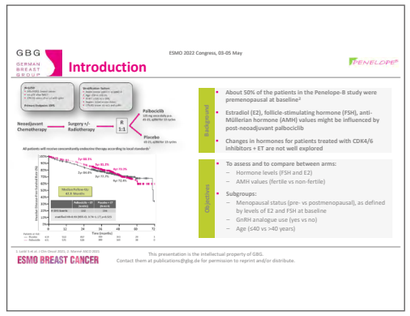
n (%)
[1] p-values calculated from Pearson-Chi-Square test

mTROP-2 is significantly associated with molecular subgroup and grading.

Better DFS/ OS with higher mTROP-2 (all patients)

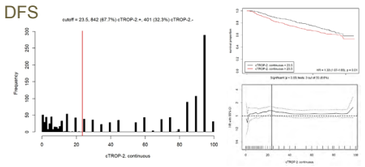






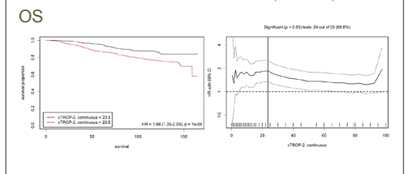
Cut off Finder TROP-2 cytoplasmic (cTROP-2)

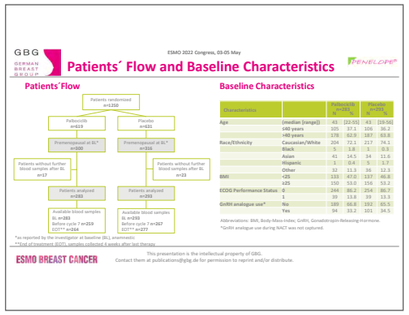
DFS

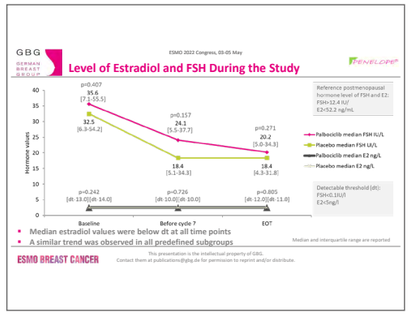


Best Cut off for cTROP-2 is 23.5 % (→ 23 %)

OS





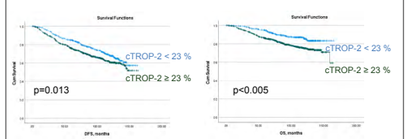


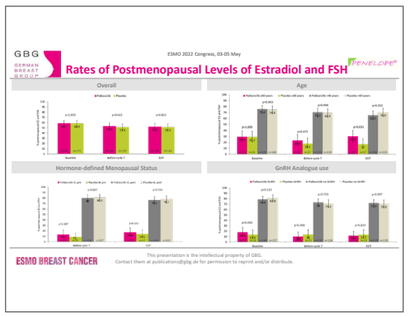
Parameter	All (n=1164)	cTROP-2 < 23%	cTROP-2 ≥ 23%	p-value
Histological tumor type				0.710[1]
NST	895 (76.9)	289 (78.3)	606 (76.2)	
ILC	131 (11.3)	38 (10.3)	93 (11.7)	
Other	138 (11.9)	42 (11.4)	96 (12.1)	
Molecular subgroup				<0.0001[1]
Lum/Her2-	724 (62.2)	268 (72.6)	456 (57.3)	
HER2+	260 (22.3)	79 (21.4)	181 (22.8)	
TNBC	180 (15.5)	22 (6.0)	158 (19.9)	
Ki67				0.533
≤ 20 %	759 (75.6)	247 (74.4)	512 (76.2)	
>20 %	245 (24.4)	85 (25.6)	160 (23.8)	
missing	160 (13.7)			
Grading				0.801
G1-2	606 (52.1)	190 (51.5)	416 (52.4)	
G3	557 (47.9)	179 (48.5)	378 (47.6)	
missing	1 (0.1)			
pT				0.140
T1-2	1025 (88.4)	332 (90.5)	693 (87.4)	
T3-4	135 (11.6)	35 (9.5)	100 (12.6)	
missing	4 (0.3)			
pN				0.124
N1	470 (40.4)	161 (43.6)	309 (38.9)	
N2-3	694 (59.6)	208 (56.4)	486 (61.1)	
missing	470 (40.4)			
Age (in years)				0.448
<60	970 (83.3)	303 (82.1)	667 (83.9)	
≥ 60	194 (16.7)	66 (17.9)	128 (16.1)	

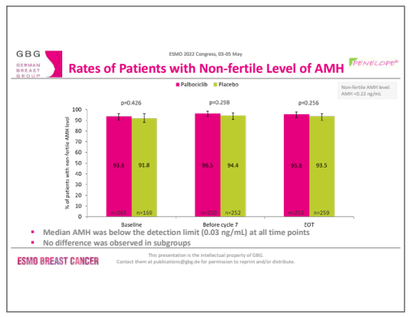
n (%)
[1] p-values calculated from Pearson-Chi-Square test

cTROP-2 is significantly associated with molecular subgroup.

Better DFS/ OS with lower cTROP-2 (all patients)

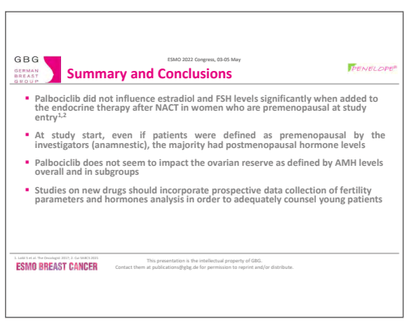






Summary

- Large TMA-based study on differential expression of TROP-2 in BC
- mTROP-2 ≥ 2% & cTROP-2 < 23%
  → better OS/ DFS for all patients and some subgroups, independent variable in multivariate analysis
  ↔ **partial discordance with previous studies**
- Closer look at differential TROP-2 expression promising
  → ongoing SASCIA study by GBG



SASCIA
(ESMO Breast Cancer 2022)

ESMO Breast Cancer 2022, 3-5 May 2022

Safety interim analysis of the phase III postneoadjuvant SASCIA study evaluating sacituzumab govitecan in patients with primary HER2-negative breast cancer at high relapse risk after neoadjuvant treatment

Frederik Marmé, Claus Hanusch, Jenny Furlanetto, Patrick Morris, Theresa Link, Carsten Denkert, Peter A. Fasching, Christian Jackisch, Silvia Antolin, Christine Solbach, Philippe Aftimos, Jens Huober, Michael Untch, Marija Balic, Mattea Reinisch, Jens-Uwe Blohmer, Anthony Goncalves, Julia Rey, Thomas Buechele, Sibylle Loibl

EudraCT 2019-004100-35

Presented by F. Marmé, MD

ESMO Breast Cancer 2022, 3-5 May 2022

Rationale

- Neoadjuvant chemotherapy (NACT) is the standard option for patients with triple-negative breast cancer (TNBC) but also for high-risk hormone-receptor (HR)-positive/HER2-negative breast cancer (BC).
- TNBC patients without pCR have a high-risk of recurrence.[1]
- Patients with HR-positive/HER2-negative BC and a CPS+EG-Score ≥3 or =2 with ypN+ have a high-risk of recurrence.[2]
- Post-neoadjuvant therapy can significantly improve survival in TNBC and in HR-positive/HER2-negative BC as demonstrated.[3,4,5,6]
- Sacituzumab govitecan (SG) improves overall survival (OS) in heavily pretreated, widely chemotherapy refractory TNBC and has activity in HR-positive/HER-negative metastatic BC.[7, 8]

1. Mamtani R et al. Ann Oncol 2016; 2. Masuda N et al. Ann Oncol 2016; 3. Liedtke C et al. J Clin Oncol 2009; 4. Gianni L et al. Lancet Oncol 2012; 5. Untch M et al. J Clin Oncol 2018; 6. Loibl S et al. Ann Oncol 2018; 7. Rugo HS et al. Ann Oncol 2021; 8. Hurvitz S et al. Ann Oncol 2021

ESMO Breast Cancer 2022, 3-5 May 2022

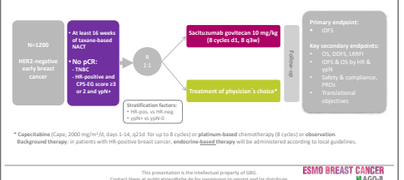
Significant different AEs: SG vs TPC

ESMO Breast Cancer 2022, 3-5 May 2022

AEs: SG vs Capecitabine

ESMO Breast Cancer 2022, 3-5 May 2022

Study Design



* **Capecitabine** (Cape, 2000 mg/m²/d, days 1-14, q21d for up to 8 cycles) or **platinum-based** chemotherapy (8 cycles) or **observation**.
Background therapy: in patients with HR-positive breast cancer, **endocrine-based therapy** will be administered according to local guidelines.

ESMO Breast Cancer 2022, 3-5 May 2022

Safety Interim Analysis

- A prespecified **safety interim analysis (SIA)** was to take place **after the first 50 randomised patients completed 4 cycles** of treatment (Cape, SG) **or three months of observation**.
- **Objectives:**
  - Safety: assessment of any grade (1-5) and high grade (3-5) adverse events coded according to NCI-CTCAE version 5.
  - Compliance: assessment of dose reductions, dose delays, treatment interruptions, and treatment discontinuation rates.
- **SIA set** includes all patients who **completed at least 2 cycles** of treatment (or discontinued earlier) respectively all patients who have been **observed for 6 weeks** as part of TPC at the cut-off time point (October 14, 2021).

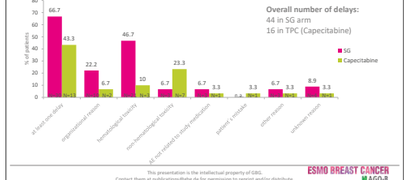
ESMO Breast Cancer 2022, 3-5 May 2022

AEs High Grade:

AEs, N (%)	SG N=45 N (%)		TPC N=43 N (%)		Capecitabine N=32 N(%)	
	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4
Any AE	19 (42.2)	11 (24.4)	4 (9.3)	5 (11.6)	4 (12.5)	5 (15.6)
Any hematological AE	17 (37.8)	8 (17.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Any non-hematological AE	12 (26.7)	3 (6.7)	4 (9.3)	5 (11.6)	4 (12.5)	5 (15.6)
Anaemia	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Leukopenia	12 (26.7)	1 (2.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutropenia	14 (31.1)	5 (11.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	2 (4.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Diarrhoea	2 (4.4)	0 (0.0)	1 (2.5)	0 (0.0)	1 (3.1)	0 (0.0)
Palmar plantar erythrodysaesthesia	0 (0.0)	0 (0.0)	3 (7.5)	0 (0.0)	3 (9.4)	0 (0.0)

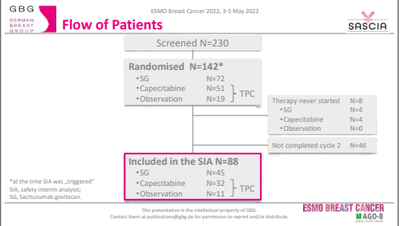
ESMO Breast Cancer 2022, 3-5 May 2022

Dose Delays



ESMO Breast Cancer 2022, 3-5 May 2022

Flow of Patients



ESMO Breast Cancer 2022, 3-5 May 2022

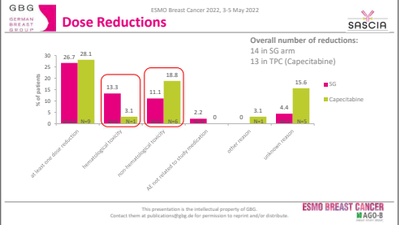
Selected Baseline Characteristics

Clinical parameters	Category	SG N=45 N(%)	TPC N=43 N(%)
Age	Median (range)	46.0 (24.0-71.0)	51.0 (32.0-74.0)
BMI	Median (range)	25.8 (20.0-42.6)	23.8 (18.2-35.4)
ECOG	ECOG 0	41 (91.1)	33 (76.7)
	ECOG 1	4 (8.9)	10 (23.3)
ypN	ypN0	22 (48.9)	24 (55.8)
	ypN+	23 (51.1)	19 (44.2)
Grading	G2	7 (15.6)	8 (18.6)
	G3	38 (84.4)	35 (81.4)
ER/PgR (central)*	both negative (TNBC)	30 (66.7)	29 (67.4)
	at least one positive	15 (33.3)	14 (32.6)
CPS-EG (HR+ pts only)	CPS-EG score ≥3	10 (66.6)	9 (64.3)
	CPS-EG score 2, ypN+	5 (33.3)	5 (35.7)

*cut-off: ≥1% positive stained cells; assessed on residual cancer at surgery or if not possible from lymph nodes, otherwise from core biopsy

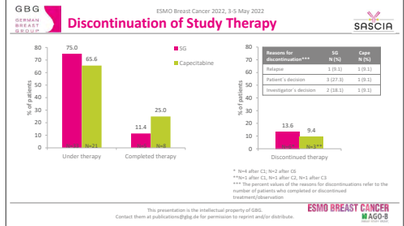
ESMO Breast Cancer 2022, 3-5 May 2022

Dose Reductions



ESMO Breast Cancer 2022, 3-5 May 2022

Discontinuation of Study Therapy



* N=4 after C1; N=2 after C2
**N=1 after C1, N=1 after C2, N=1 after C3
*** The percent values of the reasons for discontinuations refer to the number of patients who completed or discontinued treatment/observation

ESMO Breast Cancer 2022, 3-5 May 2022

Prior NACT & Endocrine Background Therapy

	Therapy	SG N=45 N (%)	TPC All N=43 (%)	TPC Cape N=32 (%)
prior neoadjuvant chemotherapy (all pts)	EC/AC, Taxane, Carboplatin	23 (51.1)	29 (67.4)	29 (90.6)
	EC/AC, Taxane	20 (44.4)	9 (20.9)	2 (6.3)
	Taxane + Cyclophosphamide	0 (0.0)	2 (4.6)	1 (3.1)
	ddETC	1 (2.2)	3 (7.0)	0 (0.0)
	TAC	1 (2.2)	0 (0.0)	0 (0.0)
	Immune-checkpoint inhibitor	1 (2.2)*	0 (0.0)	0 (0.0)

	Therapy	SG N=15 N (%)	TPC All N=14 (%)	TPC Cape N=3 (%)
Endocrine background Treatment* (ER + pts only)	Endocrine therapy	10 (66.7)	8 (57.1)	0 (0.0)
	Tamoxifen	6 (40.0)	6 (42.9)	0 (0.0)
	Letrozole	4 (26.7)	2 (14.3)	0 (0.0)
	Ovarian ablation	3 (20.0)	2 (14.3)	0 (0.0)

*before start of study

ESMO Breast Cancer 2022, 3-5 May 2022

SAEs According to SOC

Absolute numbers, N=88 (N=45 in SG arm and N=43 in TPC arm)

SOC	SG absolute numbers	TPC* absolute numbers
Total	6	1
Patients with at least 1 SAE	5	1
– Infections and infestations	1	1
– Blood and lymphatic system disorders	2	0
– Cardiac disorders	1	0
– Gastrointestinal disorders	1	0
– Investigations	1	0

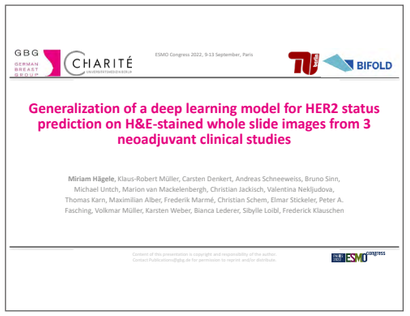
*TPC = capecitabine or observation

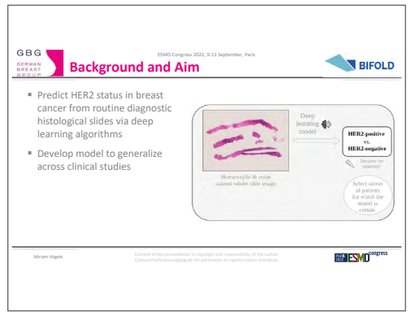
ESMO Breast Cancer 2022, 3-5 May 2022

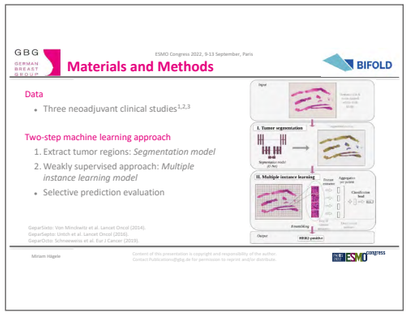
Summary and Conclusion

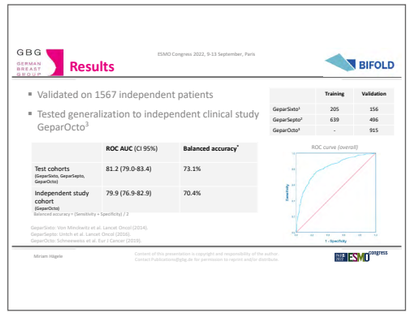
- Patients in the SG arm reported more haematologic and non-haematologic toxicities.
- More dose delays were observed in the SG vs TPC (Cape) arm.
- Dose reductions occured equally in both arms, mostly due to haematologic toxicities in the SG and non-haematologic toxicities in the TPC (Cape) arm.
- Overall, in this pretreated and high-risk eBC population no unexpected toxicities occured and the safety profile of SG is in line with available data.
- Guidelines for SG supportive therapy should be strictly followed.
- The IDMC recommended to continue the study without any modifications.

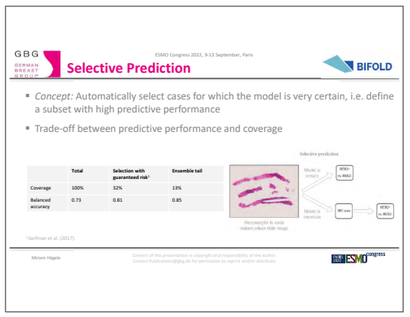
G6-G8

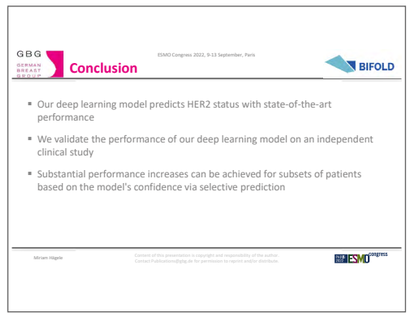


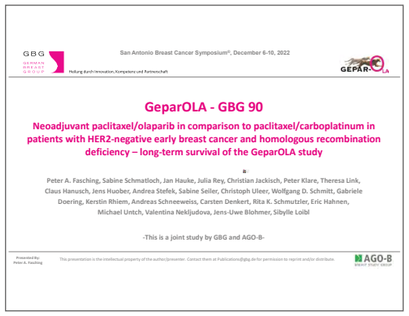


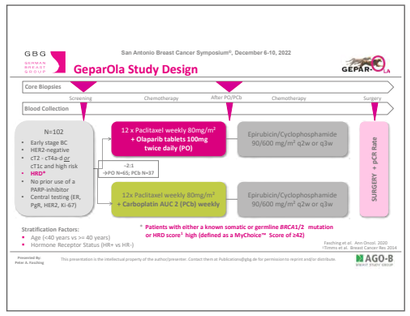


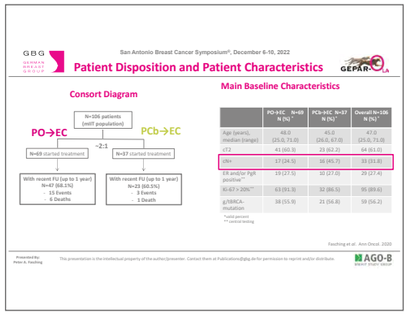


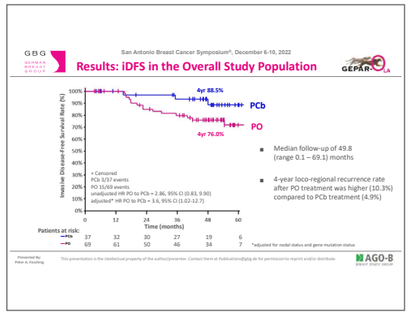


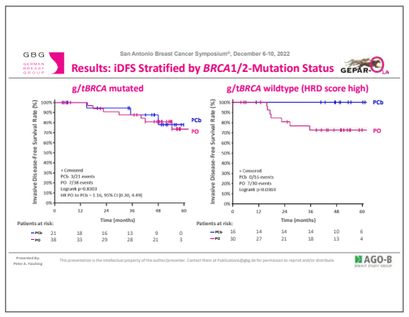


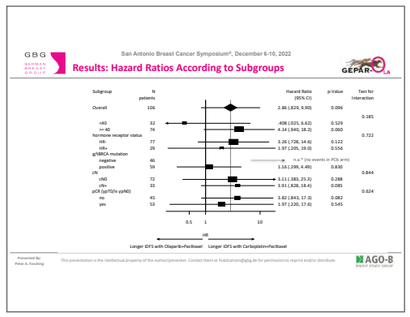


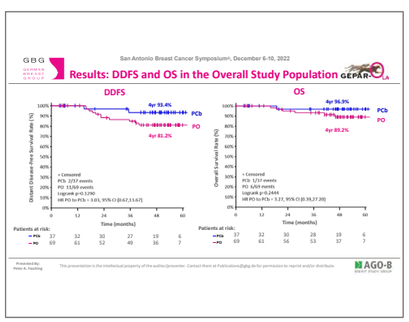


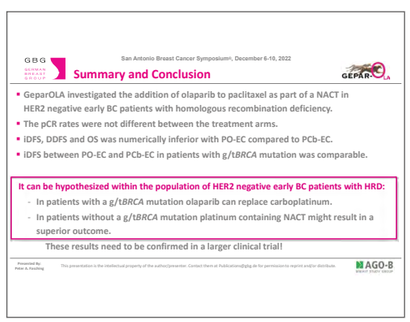












GeparOla
(San Antonio Breast Cancer Symposium® 2022)

Biomarkers for response to immunotherapy in triple-negative breast cancer – differences between survival and pCR biomarkers

Abstract #583

Carsten Denkert[1], Andreas Schneeweiss[2], Julia Rey[3], Thomas Karn[4], Michael Braun[5], Jens Huober[6], Hans-Peter Sinn[7], Dirk-Michael Zahm[8], Claus Hanusch[5], Frederik Marmé[9], Jenny Furlanetto[3], Jörg Thomalla[10], Jens-Uwe Blohmer[11], Marion van Mackelenbergh[12], Peter Staib[13], Christian Jackisch[14], Peter A. Fasching[15], Bruno Sinn[16], Michael Untch[17], Sibylle Loibl[3]

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Background

Immunotherapy is entering clinical practice as a promising new neoadjuvant therapeutic approach in triple-negative breast cancer, and it is important to identify biomarkers to focus this therapy on those patients that have the highest benefit. Interestingly, an improved survival outcome is observed in pCR and non-pCR patients, which raises the hypothesis that biomarkers might also be different for pCR prediction as well as prognosis. In this study, we investigated this hypothesis in the neoadjuvant GeparNuevo trial.

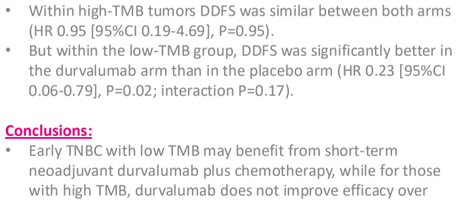
Patients and Methods

A total of 174 patients were randomized to receive neoadjuvant chemotherapy with durvalumab vs. placebo. HTG EdgeSeq mRNA analysis was performed retrospectively for a total of 2549 genes in 162 pretherapeutic core biopsies collected before randomization. In addition, tumor-infiltrating lymphocytes (stromal and intratumoral) as well as PD-L1 protein expression by IHC was evaluated. We systematically compared the distant disease-free survival (DDFS) of 6 predefined gene signatures (including the GeparSixto immune signature) as well as 12 single mRNA markers identified in previous projects between treatment arms using univariate Cox proportional-hazard regression analyses.

Table 1: Description of signatures

Signature name	Genes in signature	Reference
11-gene-prolif-sig	BIRC5, CCNB1, CDC20, NUF2, CEP55, NDC80, MKI67, PTTG1, RRM2, TYMS, UBE2C	Metzger Filho O, et al J Clin Oncol 2019
10-gene-G6-sig	CXCL9, CCL5, CD8A, CD80, CXCL13, IDO1, PDCD1, CD274, CTLA4 , FOXP3	Denkert et al, JCO 2015, modified in Sinn et al, 2021
2-gene-CYT-sig	PRF1, GZMA	Rooney et al, Cell 2015
4-gene-IFN-sig	IFNG, CD274 , LAG3 , CXCL9	Higgs et al, CCR 2018
4-gene-G6-sig	CXCL9, CCL5, IDO1, CXCL13	based on Denkert et al, JCO 2015, modified
12-gene_G9-sig	ITGA2, TAP1, HLA-A, HLA-B, GBP1, STAT1, CXCL10, CD38, CD274, PSIP1, TNFRSF8, HEY2	based on Sinn et al, 2021; additional genes added

Figure 1: GeparNuevo clinical trial design



Main results

- In the GeparNuevo cohort, immune biomarkers are predictive for increased pCR and improved survival with neoadjuvant durvalumab therapy.
- Significant signatures for survival (DDFS) were observed only in the durvalumab arm, but not in the placebo arm.

Figure 2: Clinical results of GeparNuevo

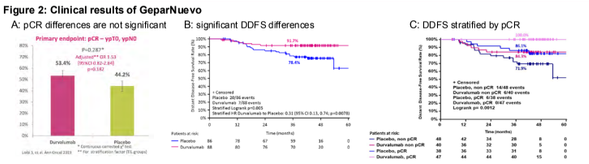


Table 2: Gene signatures associated with pCR and DDFS in the complete cohort, the durvalumab arm and the placebo arm

	complete cohort – both therapy arms (n=162)				Durvalumab therapy arm (n=83)				Placebo therapy arm (n=79)			
Signature	**OR for pCR**	**p-value**	**HR for DDFS**	**p-value**	**OR for pCR**	**p-value**	**HR for DDFS**	**p-value**	**OR for pCR**	**p-value**	**HR for DDFS**	**p-value**
11-gene-prolif-sig	2.22 (1.25-3.92)	0.0063	1.20 (0.60-2.39)	0.5992	1.88 (0.84-4.21)	0.1252	1.28 (0.33-4.96)	0.7193	2.64 (1.16-6.02)	0.0204	1.14 (0.52-2.50)	0.7433
10-gene-G6-sig	1.69 (1.23-2.31)	0.0011	0.75 (0.53-1.06)	0.0983	1.87 (1.21-2.88)	0.0049	0.51 (0.27-0.97)	0.0411	1.54 (0.97-2.46)	0.0677	0.87 (0.57-1.34)	0.5299
2-gene-CYT-sig	1.37 (1.04-1.82)	0.0274	0.75 (0.55-1.03)	0.0730	1.56 (1.06-2.30)	0.0252	0.62 (0.36-1.08)	0.0918	1.21 (0.80-1.84)	0.3724	0.80 (0.54-1.18)	0.2654
4-gene-IFN-sig	1.78 (1.30-2.44)	0.0003	0.77 (0.55-1.09)	0.1378	1.84 (1.20-2.80)	0.0048	0.47 (0.24-0.89)	0.0209	1.77 (1.10-2.84)	0.0182	0.97 (0.63-1.50)	0.8971
4-gene-G6-sig	1.52 (1.19-1.92)	0.0006	0.79 (0.61-1.02)	0.0730	1.66 (1.19-2.32)	0.0031	0.61 (0.37-0.99)	0.0477	1.41 (1.00-2.00)	0.0502	0.85 (0.62-1.17)	0.3198
12-gene_G9-sig	2.63 (1.53-4.53)	0.0005	0.63 (0.36-1.13)	0.1230	3.40 (1.58-7.34)	0.0018	0.38 (0.15-0.99)	0.0478	2.16 (0.97-4.80)	0.0596	0.73 (0.33-1.62)	0.4442

Results

Figure 3: A: Overview on gene signatures for pCR and DDFS in the complete GeparNuevo cohort and the two therapy arms; B, C: KM-Plots for selected signatures

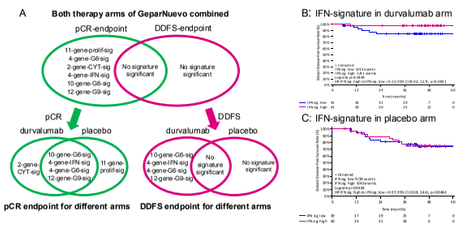
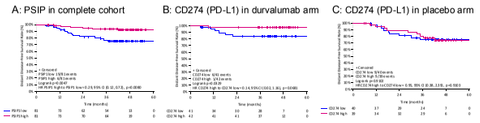


Figure 4 A-C: Selected KM-Plots for individual genes



Presented at: ASCO Meeting, 2022

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Low TMB as predictor for additional benefit from neoadjuvant immune checkpoint inhibition in triple negative breast cancer

#581

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Background:

- High TMB is anticipated to predict immune checkpoint blockade (ICB) response.
- However, high TMB also predicted pCR after chemotherapy without ICB in the neoadjuvant GeparNuevo TNBC trial (PMID 32461104).

Methods:

- We obtained TMB from WES for 149 of 174 GeparNuevo TNBC patients.
- We used the previously published cutoff of the upper tertile (2.05 mut/Mb).
- Median follow-up was 43.7 months.

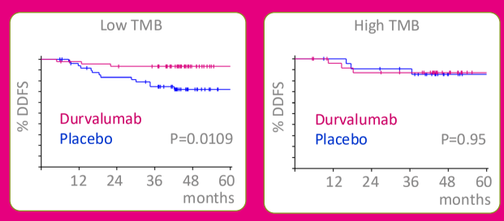
Results:

- 3yr DDFS in the durvalumab-chemo combination arm and the chemo-only arm was 91.7% (83.3-95.9%) and 78.4% (67.6%-86.0%), respectively.
- Within high-TMB tumors DDFS was similar between both arms (HR 0.95 [95%CI 0.19-4.69], P=0.95).
- But within the low-TMB group, DDFS was significantly better in the durvalumab arm than in the placebo arm (HR 0.23 [95%CI 0.06-0.79], P=0.02; interaction P=0.17).

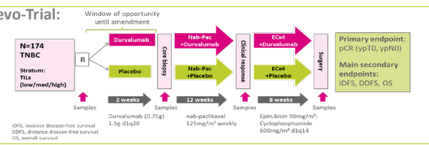
Conclusions:

- Early TNBC with low TMB may benefit from short-term neoadjuvant durvalumab plus chemotherapy, while for those with high TMB, durvalumab does not improve efficacy over chemotherapy alone.

Unexpectedly, early TNBC with ***low*** TMB may ***benefit*** from additional neoadjuvant ***ICB***, while for ***high*** TMB ***chemotherapy*** might suffice.

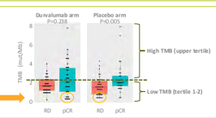


GeparNuevo-Trial:



Distribution of TMB values:

Cases with lowest TMB values experienced a pCR with Durvalumab in contrast to RD in the Placebo arm

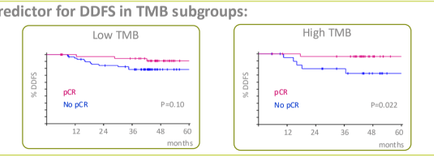


Cox regression of DDFS according to treatment arm in TMB subgroups:

TMB-Group (n=durva./placebo)	Low-TMB (47/52)	High-TMB (27/23)
HR (DDFS):	**0.23**	0.95
95% CI:	0.06-0.79	0.19-4.69
P-Value	**P=0.020**	P=0.95

Data from univariate Cox regression analysis for treatment arm are shown.

pCR as predictor for DDFS in TMB subgroups:



Limitations: Small sample size.

References:

- Loibl et al. 2019, PMID 31095287
- Karn et al. 2020, PMID 32461104
- Loibl et al. 2021, ASCO, J Clin Oncol 39, 2021 (suppl 15; abstr 506)

Presented at: ASCO Meeting, 2022

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The trial was financially supported by AstraZeneca and BMS (Celgene).

GeparPiPPa - A randomized, open-label, phase II trial comparing neoadjuvant trastuzumab, pertuzumab and endocrine therapy +/- the PI3K inhibitor inavolisib in patients (pts) with HER2+/HR+, *PIK3CA* mutant early breast cancer (BC)

Sibylle Loibl[1], Mattea Reinisch[2], Carsten Denkert[3], Andreas Schneeweiss[4], Sabine Seiler[1], Peter A. Fasching[5], Claus Hanusch[6], Theresa Link[7], Vesna Bjelic-Radisic[8], Jens Huober[9], Michael Untch[10], Christian Jackisch[11], Christine Solbach[12], Jens-Uwe Blohmer[13], Kerstin Rhiem[14], Thomas Buechele[1], Valentina Nekljudova[1], Sherene Loi[15]

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Poster # 1027

Background

Neoadjuvant treatment has become the standard of care for HER2-positive (+) breast cancer. HER2+/hormone receptor-negative and HER2+/hormone receptor-positive (HR+) breast cancers are biologically distinct, with less aggressive characteristics and less chemosensitivity of HER2+/HR+ subgroup.[1]

Several attempts have been made to use a more targeted approach in HER2+/HR+ breast cancer by investigating different anti-HER2 therapies with or without endocrine therapies in pre-and postmenopausal women.

The PI3K/AKT/mTOR pathway was found to be a key survival mechanism responsible for endocrine resistance, and crosstalk between HR and the PI3K/AKT/mTOR pathways has been described. In addition, inhibition of PI3K signaling results in activation of HER2-pathway.[2,3,4,5,6,7]

PIK3CA mutations can be found in about 20%-30% of HER2+ breast cancer patients and indicate a lower response to chemotherapy and anti-HER2 therapy, especially in HER2+/HR+ tumors.[8,9,10]

The phase III Solar-1 study demonstrated a significant improvement in progression-free survival with the addition of alpelisib to fulvestrant in *PIK3CA*-mutant metastatic breast cancer.[11]

GeparPiPPa investigates - in the neoadjuvant setting - the potential incremental efficacy and safety of inavolisib, an oral pure PI3Kα inhibitor, in addition to endocrine and anti-HER2 therapy, in patients with early HER2+/HR+ and *PIK3CA*-mutant breast cancer.

Study Overview

GeparPiPPa (GBG 105/EUDRA-CT 2021-002323-38) is a multicenter, randomized, open-label, parallel-group, phase II study. Approximately 170 patients with early-stage HER2+/HR+, *PIK3CA*-mutant breast cancer will be randomized in a 1:1 ratio to receive neoadjuvant endocrine therapy in combination with dual anti-HER2 blockade consisting of ready-to-use fixed-dose combination of pertuzumab and trastuzumab as subcutaneous (PH-FDC SC) formulation q3w for 6 cycles (18 weeks) with or without inavolisib (9mg 1x1/d orally, day 1-21 q3w). Endocrine therapy consists of either tamoxifen 20mg or an aromatase inhibitor (1x1/d orally, day 1-21 q3w). Premenopausal women and men receive a gonadotropin-releasing hormone (GnRH) analogue in addition to an aromatase inhibitor. After end of therapy, patients will undergo a core biopsy and/or surgery. In case of tumor residuals in the biopsy, additional neoadjuvant treatment may be given. In case of ycT0 and no tumor residuals in the biopsy, it is recommended to undergo surgery. Further (neo)adjuvant systemic treatment and radiotherapy will be administered at the discretion of the investigator and according to standard of care.

Primary objective:

- To compare pathological complete response (pCR=ypT0/is ypN0) rates between the two treatment arms

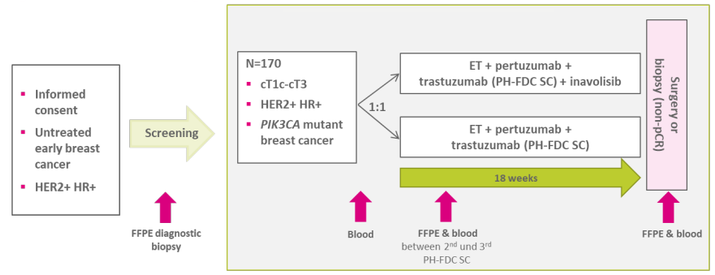
Secondary objectives (selection):

- To assess other pCR definitions
- To assess invasive disease-free survival and overall survival
- To assess breast conservation rate
- To assess safety, tolerability and compliance

Correlative objectives (selection):

- To examine molecular/pathway markers in core biopsies and residual disease
- To assess the predictive/prognostic effect of different *PIK3CA* hot spot mutations
- To explore potential novel biomarkers through the use of baseline and on-therapy specimens

Figure 1. GeparPiPPa Study Design



Study Treatment:

- Endocrine Therapy (ET): tamoxifen or an aromatase inhibitor (1x1/d orally, day 1-21 q3w) +/- GnRH analogue
- Pertuzumab/trastuzumab as subcutaneous formulation on d1, q3w:
  - Loading dose 1st cycle: 1200 mg/600 mg
  - 2nd-6th cycles: 600 mg/600 mg
- Inavolisib 9mg 1x1/d orally, day 1-21 q3w

Supportive Treatment:

- Strategies for prevention of stomatitis, hyperglycemia (including home glucose monitoring), and diarrhea are provided in the protocol

Key Inclusion Criteria

- Age ≥ 18 years
- Females or males
- Diagnosis of a unilateral primary carcinoma of the breast by core needle biopsy
- Central testing must confirm HER2 positivity and HR positivity (according to ASCO/CAP guidelines) as well as *PIK3CA* mutation(s) (tumor)
- Primary tumor must be cT1c – cT3
- Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF ≥55%)
- Complete staging work-up prior to randomization

Key Exclusion Criteria

- Excisional biopsy or lumpectomy and/or surgical axillary staging procedure prior to randomization
- Patients with definitive clinical or radiologic evidence of Stage IV BC
- Need of immediate neoadjuvant chemotherapy, e.g. inflammatory BC
- Body-Mass Index >30
- Patients with diabetes mellitus type I or uncontrolled type II
- Patients with currently documented pneumonitis/interstitial lung disease
- Patients with active uveitis or vitritis, history of uveitis, or active infectious process in the eye

Collection of Biomaterial

Study requirements	Screening	Pre-treatment	After 2nd/ before 3rd dose of PH-FDC SC	At end of treatment
FFPE tissue breast tumor	X[1]		X	X
Whole blood		X		
Plasma collection ctDNA		X	X	X

1. Central testing of *PIK3CA* mutation status

Follow-Up

Information on the health status of German patients will be collected within the GBG's patient self-reporting registry (Patientenselbstauskunft) and of patients from other countries within the GBG's long-term registry of previous study participants (Eternity[®]).

Recruitment

- The study will be conducted in approximately 50 GBG and IBCSG sites.
- First patient in Q IV/2022.

References

1. Vaz-Luis I, et al. Ann Oncol. 2013 Feb;24(2):283-291; 2. Nwabo Kamdje AH, et al. Cell Signal. 2014;26:2843–2856; 3. Miller TW, et al. J Clin Oncol. 2011; 29(33): 4452-61; 4. Bosch A, et al. Sci Transl Med. 2015; 7(283): 283ra51; 5. Hsu PY, et al. Clin Cancer Res. 2018; 24(2): 395-406; 6. Loi S et al. Proc Natl Acad Sci U S A. 2010; 107(22): 10208-13; 7. Serra V, et al. Oncogene. 2011; 30(22): 2547-57; 8. Loibl S, et al. Ann Oncol. 2016; 27: 1519-2; 9. Bianchini G, et al. Breast Cancer Res. 2017; 19: 16; 10. Loibl s, et al. J Clin Oncol. 2014; 32: 3212-20; 11. André F, et al. N Engl J Med. 2019; 380: 1929-1940.

Disclosure Statement

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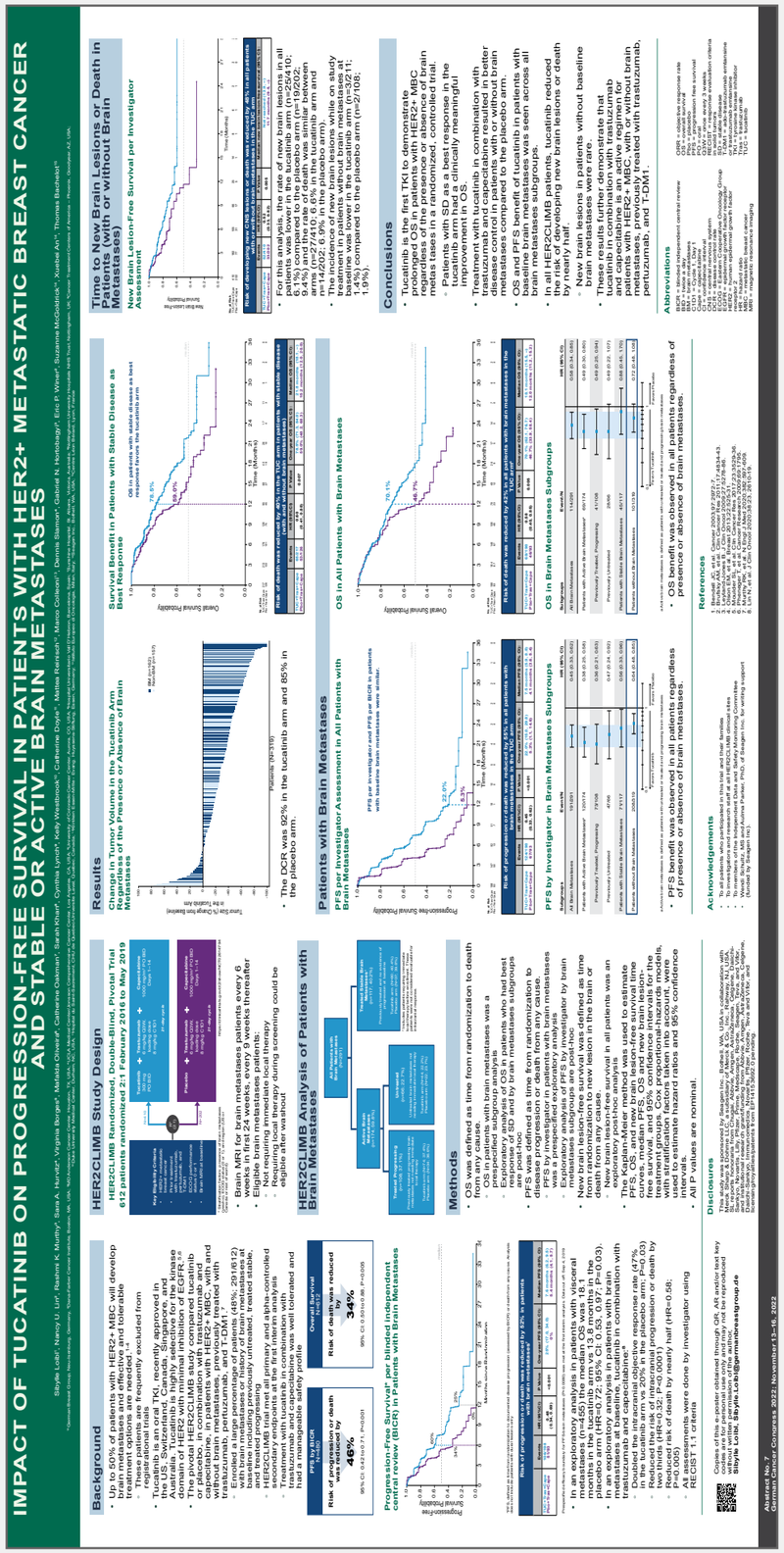

Safety interim analysis of the phase III post-neoadjuvant SASCIA study evaluating sacituzumab govitecan in patients with primary HER2-negative breast cancer at high relapse risk after neoadjuvant treatment

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Poster # 504

Background

SASCIA (NCT04595565) is an ongoing phase III study randomizing patients with HER2-breast cancer (BC) and residual disease after standard neoadjuvant chemotherapy (NACT) or hormone receptor (HR) positive (+) with a CPS+EG (clinical, pathologic stage + estrogen receptor status and grade) score ≥3 or 2 and ypN+ after NACT to sacituzumab govitecan (SG) or treatment of physician´s choice (TPC).[1,2] We present the results of the pre-planned safety interim analysis (SIA).

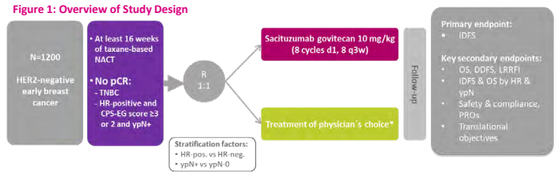
Patients and Methods

A prespecified SIA was performed after the first 50 randomized patients had completed 4 cycles of treatment (capecitabine, SG) or three months of observation. Patients were included if they received ≥2 cycles, were observed ≥6 weeks, or discontinued earlier. Objectives:

- Safety: Assessment of any grade (1-5) and high grade (3-5) adverse events (AEs) coded according to NCI-CTCAE version 5.
- Compliance: Assessment of dose reductions, dose delays, treatment interruptions, and treatment discontinuation rates in patients receiving SG vs. active treatment in TPC arm.

Study Design

Figure 1: Overview of Study Design



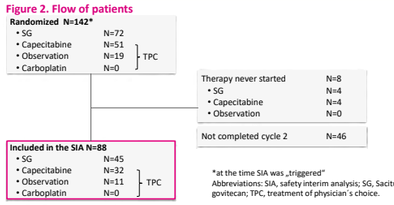
* **Capecitabine** (Cape, 2000 mg/m²/d, days 1-14, q21d for up to 8 cycles) or **platinum-based** chemotherapy (8 cycles) or **observation**.
Background therapy: in patients with HR-positive breast cancer, **endocrine-based therapy** will be administered according to local guidelines.

Amendment 1 will allow the use of **pembrolizumab** as monotherapy in the TPC arm in patients with TNBC who received pembrolizumab as neoadjuvant therapy (according to the approval). Adjuvant pembrolizumab may be given until the completion of radiotherapy. Patients with known g*BRCA1/2* mutation, if adjuvant **olaparib** is indicated or planned, are not allowed to participate in the trial.

Results

At the time of analysis, 142 patients were randomized, and 88 were included in the SIA (**Figure 2**). Baseline characteristics are shown in **Table 1**, previous neoadjuvant chemotherapy in **Table 2**. Any AEs G1-4 and G3-4 were more frequent with SG compared to Capecitabine, especially hematological AEs G3-4. No death occurred (**Figure 3**). Granulocyte colony-stimulating factor was received by 42.2% (N=19) patients in SG arm (N=16 as primary and N=3 as secondary prophylaxis), none in TPC arm. Overall, 6 (13.6%) patients in SG arm vs. 3 (9.4%) in TPC arm discontinued therapy prematurely (**Figure 4**). At least one dose delay was reported in 66.7% of the patients in SG arm compared to 43.2% in TPC arm (**Figure 5**). At least one dose reduction occurred in 26.7% of the patients in SG arm vs. 28.1% in TPC arm (**Figure 6**).

Figure 2. Flow of patients



*at the time SIA was „triggered"
Abbreviations: SIA, safety interim analysis; SG, Sacituzumab govitecan; TPC, treatment of physician´s choice.

Table 1. Selected baseline characteristics

Clinical parameters	Category	SG N=45 N (%)	Capecitabine + observation in TPC N=43 N (%)
Age	Median (range)	46.0 (24.0-71.0)	51.0 (32.0-74.0)
BMI	Median (range)	25.8 (20.0-42.6)	23.8 (18.2-35.4)
ECOG	ECOG 0	41 (91.1)	33 (76.7)
	ECOG 1	4 (8.9)	10 (23.3)
ypN	ypN0	22 (48.9)	24 (55.8)
	ypN+	23 (51.1)	19 (44.2)
Grading	G2	7 (15.6)	8 (18.6)
	G3	38 (84.4)	35 (81.4)
ER/PgR (central)*	both negative	30 (66.7)	29 (67.4)
	at least one positive	15 (33.3)	14 (32.6)
CPS-EG (HR+ patients)	CPS-EG score ≥3	10 (66.6)	9 (64.3)
	CPS-EG score 2, ypN+	5 (33.3)	5 (35.7)

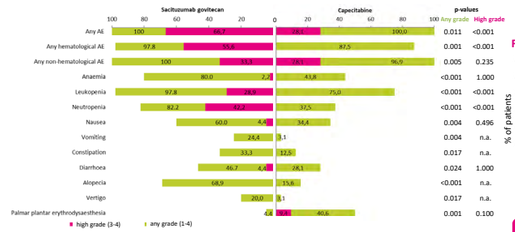
*cut-off: ≥1% positive stained cells; assessed on residual cancer at surgery or if not possible from lymph nodes, otherwise from core biopsy
Abbreviations: BMI, Body Mass Index; CPS-EG, clinical, pathological stage, estrogen receptor, grade; ER, estrogen receptor; G, grade; HR, hormone receptor; PgR, progesteron receptor; SG, Sacituzumab govitecan; TPC, treatment of physician´s choice.

Table 2. Prior neoadjuvant chemotherapy

Therapy	SG N=45 N (%)	Capecitabine + observation in TPC All N=43 (%)
EC/AC, Taxane, Carboplatin	23 (51.1)	29 (67.4)
EC/AC, Taxane	20 (44.4)	9 (20.9)
Taxane + Cyclophosphamide	0 (0.0)	2 (4.6)
ddiETC	1 (2.2)	3 (7.0)
TAC	1 (2.2)	0 (0.0)
Immune-checkpoint inhibitor	1 (2.2)	0 (0.0)

Abbreviations: A, doxorubicin; C, cyclophosphamide; ddi, dose-dense intensified; E, epirubicine; SG, Sacituzumab govitecan; T, Docetaxel; TPC, treatment of physician´s choice.

Figure 3. Significantly different AEs in SG and Capecitabine in TPC arm



Abbreviations: AE, adverse event; TPC, treatment of physician´s choice.

Figure 4. Dose discontinuation in SG and Capecitabine in TPC arm

Reasons for discontinuation	SG N (%)	Cape N (%)
Relapse	1 (9.1)	1 (9.1)
Patient´s decision	3 (27.3)	1 (9.1)
Investigator´s decision	2 (18.1)	1 (9.1)

Abbreviations: Cape, Capecitabine; SG, Sacituzumab govitecan; TPC, treatment of physician´s choice.

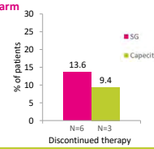


Figure 5. Dose delays in SG and Capecitabine in TPC arm

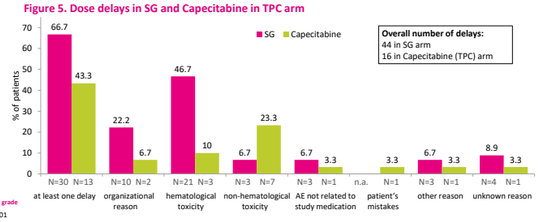
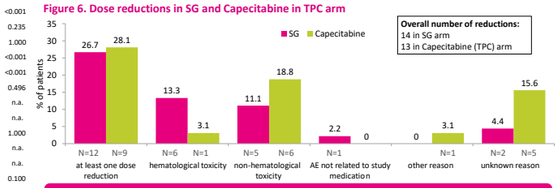


Figure 6. Dose reductions in SG and Capecitabine in TPC arm



Conclusions

Patients in the SG arm reported more hematologic and non-hematologic toxicities. Proportions of AEs, especially G3-4, were in line with the known safety profile of SG and led to more dose delays. Dose reductions occurred equally in both arms, mostly due to hematologic toxicities in the SG arm and non-hematologic toxicities in the TPC arm. AEs due to SG therapy were manageable using the recommended supportive measures. The study continues as planned.

References

1. Marmé F et al. EJC, 2016; 2. Marmé et al., EJC 2021.

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PS-03-010

Evaluation of Ki67 by image-analysis-enhanced quantitative digital pathology

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Background

Assessment of prognosis of breast cancer by Ki67 immunohistochemistry is an important element of personalized treatment strategies. A precise assessment is crucial for clinically relevant therapy decisions. We aimed to evaluate a Ki67 quantification tool using whole slide images (WSI). VMscope's Ki67-Hotspot detection was developed within the CognoScan research project and is now available together with the CE-certified "Ki-67 Quantifier clinical" module.

Patients and Methods

61 Ki67 stained, pre- (pre-NACT) and intratherapeutic core biopsies, as well as corresponding surgical residual disease tissue (post-NACT) from neoadjuvant GBG trials, were digitalized. Manual Ki67 scoring was performed by five individual pathologists on WSI (multi-observer), while semi-automated Ki67 scoring was done using VMscope's Scan Connect (multi-tumor-area). Scan Connect analyzed up to four 600x600 dpi areas on WSI, followed by pathologist supervision.

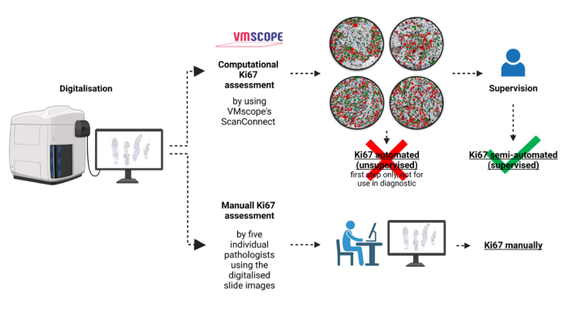

Figure 1: **Ki67 scores were obtained in three different ways. For manual scoring pathologists assessed the Ki67 staining on the digitalized WSIs. ScanConnect used the same WSIs and analyzed four different tumor-areas unsupervised. The analyzed areas then have to be looked over by a trained pathologist for quality control, leading to the final semi-automated Ki67 scores. ScanConnect is intended to be used in a semi-automated manner.**

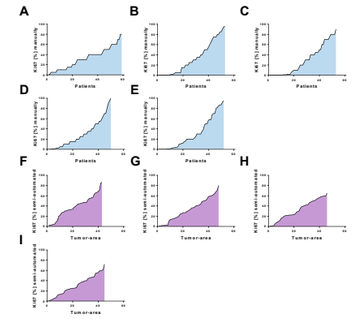

Figure 2: **Manual and semi-automated Ki67 scores sorted by size. A-E** Scores of pathologists one to five **F-I** Scores of tumor-areas one to four. Case numbers vary due to pathologist's individual case exclusion (artefacts, tumor content, necrosis).

Results

The Pearson correlation between manual (man.) and computational (semi-aut.) Ki67 assessment was r = 0.781, with no significant deviation in overall scoring (p = 0.333) or global precision (p = 0.070), indicating that ScanConnect results are comparable to manual scoring. Semi-automated multi-area analysis on pre-NACT tissues had a significantly lower variability than manual assessment (n = 29, p < 0.001), while showing no differences on intratherapeutic samples (n = 29, p = 0.885). Using German S3-Guideline cut-offs: Ki67 low >10 %, intermediate (int.) ≤25 % and high <25 %, we observed that in Ki67 low and intermediate groups standard deviations (sd) were lower, while being higher for Ki67 high group, irrespectively of the assessment method (man. & aut.: low sd = ±3.4 & ±2.0; int. sd = ±4.3 & ±3.9; high sd = ±18.2 & ±12.7). In comparison with digital unsupervised assessment, the supervised semi-automated assessment improved the precision significantly (p = 0.008).

Conclusion

We found strong correlation between manual (multi-observer) and professionally supervised semi-automated (multi-tumor-area) Ki67 assessment. In comparison to inter-observer variance in manual Ki67 assessment, improved precision was seen in semi-automated assessment considering intra-tissue variance. Supervised VMscope's ScanConnect software could be a useful tool in pathological cancer diagnostic to assess therapy relevant biomarkers, such as Ki67, in a standardized manner. As a next step, results should be validated in a larger cohort and survival data could be included.

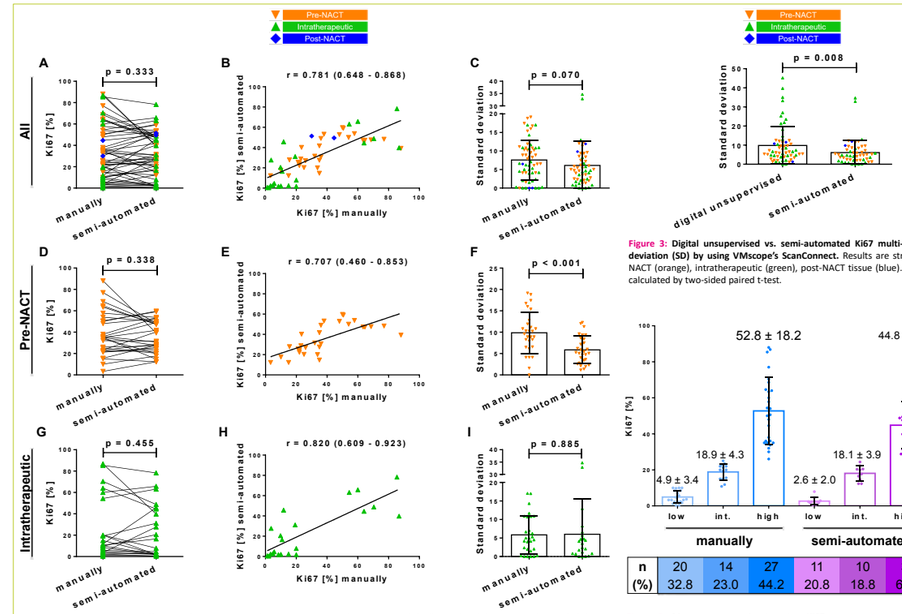

Figure 4: **A,D,G mean Ki67 differences between manual vs. semi-automated assessment.** (**A**) All samples, (**D**) pre-NACT (orange), (**G**) intra-therapeutic (green) tissue. **B,E,H Pearson correlation between manual and supervised assessment,** brackets indicate the 95% confidence interval. (**B**) All samples, (**E**) pre-NACT (orange), (**H**) intra-therapeutic (green) tissue. **C,F,I Intra-tumor and interrater standard deviation.** (**C**) All samples, (**F**) pre-NACT (orange), (**I**) Intratherapeutic (green) tissue. All p-values were calculated by two sided paired t-testing.

Figure 3: **Digital unsupervised vs. semi-automated Ki67 multi-area standard deviation (SD) by using VMscope's ScanConnect.** Results are stratified by pre-NACT (orange), intratherapeutic (green), post-NACT tissue (blue). p-values were calculated by two-sided paired t-test.

Figure 5: **Manual and semi-automated Ki67 scores, grouped according to German S3-Guideline:** Ki67 low >10 %, intermediate (int.) ≤25 % and high <25 %.

Presented at: **European Congress of Pathology 2022**

In collaboration with:

Tumor biology and immunology in patients with breast cancer occurring during pregnancy (BCP) compared to non-pregnant breast cancer patients

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151P

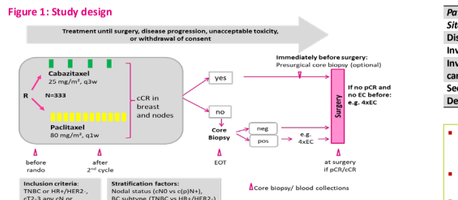
Background

Breast cancer (BC) is one of the most common malignancies during pregnancy. The incidence is likely to increase as more women tend to delay childbearing into later life and the overall lifetime cancer risk increases with age. Pregnancy presents a complex and unique immunological condition. Patients diagnosed with BC during pregnancy usually present more advanced stages than young, non-pregnant patients.[1,2] This study investigated the tumor biology and immunology of a BCP cohort compared to a non-pregnant BC cohort.

Patients and Methods

Tissue microarrays (TMA) of formalin-fixed paraffin embedded core biopsies or surgical specimens from 125 pregnant BC patients treated with (neo-) adjuvant chemotherapy were constructed. The BCP cohort was matched to an appropriate non-pregnant BC cohort with existing TMAs from the GAIN study by variables age, tumour stage, nodal status (N0 patients were not eligible in the GAIN study), grading and subtype. The nearest neighbour matching in a 1:1 ratio was performed in R, version 4.1.0, especially the R package MatchIt, version 4.1.2,[3] by using the Mahalanobis distance without replacement. TMAs were stained via immunohistochemistry (IHC) to assess estrogen and progesterone receptor (ER, PgR), human epidermal growth factor receptor 2 (HER2), Ki-67 (≤20% vs >20%), and immune response relevant markers HLA class I (EMR8-5, heavy chain), HLA-G (4H84), PD-L1 (<1% vs ≥1%), TIGIT (BLR047F), Nectin-4 (EPR15613-68, Abcam) and tumour-infiltrating lymphocytes (TILs, ≤25% vs 26-60% vs >60%). PD-L1 expression was evaluated in tumour and immune cells using the 22C3 antibody (Abcam). H-scores of HLA, HLA-G, TIGIT and Nectin-4 as continuous variables were calculated.[4-7] Comparisons between the pregnant and non-pregnant cohort were performed by using Wilcoxon test (continuous parameters), Fisher's exact test resp. Pearson's χ^2 test (categorical parameters). All statistical tests were considered to be descriptive.

Figure 1: Flow diagram for patient selection



Results

Table 1: Baseline characteristics in BC patients

Parameter	Category	Non-pregnant N=125 N(%)	Pregnant N=125 N(%)	Overall N=250 N(%)	P-value
Age at diagnosis, years	18-29	5 (4.0)	14 (11.2)	19 (7.6)	<.001
	30-34	32 (25.6)	56 (44.8)	88 (35.2)	
	35-39	51 (40.8)	44 (35.2)	95 (38.0)	
	≥40	37 (29.6)	11 (8.8)	48 (19.2)	
HR status combined**	ER and PgR negative	50 (40.0)	52 (41.6)	102 (40.8)	0.898
	ER and/or PgR positive	75 (60.0)	73 (58.4)	148 (59.2)	
HER2 status**	negative	98 (81.0)	95 (78.5)	193 (79.8)	0.749
	positive	23 (19.0)	26 (21.5)	49 (20.2)	
	missing	4	4	8	
Biological subtype**	TNBC	44 (35.2)	45 (36.0)	89 (35.6)	0.989
	HER2+/HR-	6 (4.8)	7 (5.6)	13 (5.2)	
	HER2+/HR+	19 (15.2)	19 (15.2)	38 (15.2)	
	HER2-/HR+	56 (44.8)	54 (43.2)	110 (44.0)	
Histological tumor type**	ductal or ductal-lobular invasive	101 (80.8)	111 (90.2)	212 (85.5)	0.058
	lobular invasive	9 (7.2)	7 (5.7)	16 (6.5)	
	other	15 (12.0)	5 (4.1)	20 (8.1)	
	missing	0	2	2	
Tumor grading**	G1	1 (0.8)	1 (0.8)	2 (0.8)	0.991
	G2	40 (32.0)	39 (31.2)	79 (31.6)	
	G3	84 (67.2)	85 (68.0)	169 (67.6)	
T stage*	T1	38 (30.4)	38 (30.4)	76 (30.4)	0.947
	T2	65 (52.0)	63 (50.4)	128 (51.2)	
	T3	17 (13.6)	17 (13.6)	34 (13.6)	
	T4	5 (4.0)	7 (5.6)	12 (4.8)	
N stage*	N0	0 (0.0)	58 (46.4)	58 (23.2)	<.001
	N1	89 (71.2)	47 (37.6)	136 (54.4)	
	N2	16 (12.8)	14 (11.2)	30 (12.0)	
	N3	20 (16.0)	6 (4.8)	26 (10.4)	
Ki67**, at diagnosis	≤20%	70 (61.9)	56 (46.7)	126 (54.1)	0.025
	>20%	43 (38.1)	64 (53.3)	107 (45.9)	
	missing	12	5	17	
Pregnancy trimester	1st trimester	0 (n.a.)	23 (18.5)	23 (18.5)	n.a.
	2nd trimester	0 (n.a.)	43 (34.7)	43 (34.7)	
	3rd trimester	0 (n.a.)	58 (46.8)	58 (46.8)	
	missing	125	1***	126	

*pT resp. pN, if not available cT and cN; **assessed from stained TMAs (via IHC) by the central pathology, Marburg; *** in 1 patient BC was histologically diagnosed 6 days post partum; Data are N (valid %)

Figure 2: Expression of selected immunomarkers as continuous variables

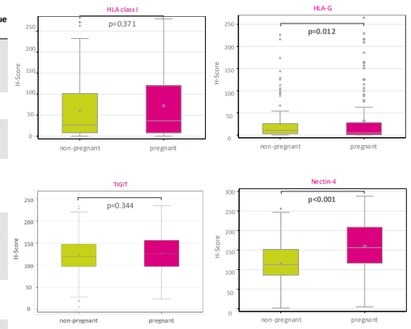


Table 2: Expression of immunomarkers PD-L1 and TILs as categorical variables

Parameter	Category	Non-pregnant N=125 N(%)	Pregnant N=125 N(%)	Overall N=250 N(%)	p-value
PD-L1 IC	negative	103 (85.1)	91 (76.5)	194 (80.8)	0.102
	positive	18 (14.9)	28 (23.5)	46 (19.2)	
	missing	4	6	10	
PD-L1 TC	negative	111 (91.7)	108 (90.8)	219 (91.3)	0.823
	positive	10 (8.3)	11 (9.2)	21 (8.8)	
	missing	4	6	10	
TILs	0-25%	112 (92.6)	53 (86.9)	165 (90.7)	0.46
	26-60%	8 (6.6)	7 (11.5)	15 (8.2)	
	>60%	1 (0.8)	1 (1.6)	2 (1.1)	
	missing	4	64	68	

- Pregnant BC patients were younger than non-pregnant (median 34 [26-47] vs 37 [27-47] years).
- Pregnant BC patients had a higher Ki-67 expression (>20%: 53.3% vs 38.1%, p=0.025).
- The H-score of HLA-G was significantly lower (median: 4.9 vs 10.6, p=0.012), in the BCP cohort compared to the non-pregnant BC cohort.
- H-scores of HLA class I showed no significant differences in both cohorts (median: 36.8 vs 26.7, p=0.371).
- There is weak correlation between the H-scores of HLA class I and HLA-G in the non-pregnant cohort and a moderate correlation for both markers in the pregnant cohort (Spearman`s ρ = 0.27 resp. 0.45).
- The H-score of Nectin-4 (median: 156 vs 113, p<0.001) was significantly higher in the BCP cohort compared to the non-pregnant BC cohort.
- No significant differences were found for TILs, PD-L1 or H-score of TIGIT.

Conclusions

- **TILs, TIGIT and PD-L1 seem to be pregnancy independent factors of BC in young women.**
- **The effect of pregnancy on the expression patterns of HLA and HLA-G is inconclusive and needs further investigation.**
- **The significantly higher Ki-67 expression in the BCP cohort suggests an increased proliferation in BC cells during pregnancy.**
- **The higher Nectin-4 expression in the BCP cohort could be a sign of an altered anti-tumour response.**
- **Together, the results suggest differences in tumor proliferation and tumor/host immunogenicity in BCP cohort vs non-pregnant BC cohort.**

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Long-term survival of a randomised, open-label, phase II study comparing the efficacy and safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer (GENEVIEVE)

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168P

Background

The GENEVIEVE study compared the pathological complete response (pCR) rate in patients with operable triple-negative (TNBC) or luminal B/human epidermal growth factor receptor 2 (HER2)-negative breast cancer (BC) treated with either cabazitaxel or weekly paclitaxel. Primary analyses showed no short-term effect of cabazitaxel in TNBC or luminal B/HER2-negative primary BC, while there seemed to be no differences in drug exposure and patient compliance between the two arms[1]. Here, we report long-term survival data.

Patients and Methods

Study design: GENEVIEVE (NCT01779479) study randomised patients with cT2-3 any cN or cT1, cN+/pN_{SLN+} and centrally confirmed TNBC or luminal B/HER2-negative BC to receive either cabazitaxel 25 mg/m² q3w for 4 cycles or paclitaxel 80 mg/m² weekly for 12 weeks. All patients had the opportunity to receive anthracycline-containing chemotherapy before (if core biopsy detected invasive tumour residuals after end of study treatment) or after surgery (Figure 1).

Endpoints: Primary endpoint was pCR (ypT0/is ypN0/+) rate. Secondary time-to-event endpoints included invasive disease-free survival (iDFS), distant disease-free survival (DDFS) and overall survival (OS). Long-term endpoints were defined as the time in months between randomization and first event.[2]

Statistical considerations: Time-to-event endpoint analyses were planned with mature follow-up of at least 5 years after a follow-up completeness of at least 70%. Differences in iDFS, DDFS and OS between treatment arms were analyzed by the log-rank-test and depicted by Kaplan-Maier curves. Cox proportional hazard model was used to estimate hazard ratio of cabazitaxel arm to paclitaxel arm with 95% CI. The significance level was set to a two-sided α=0.05.

Figure 1: Study design

Results

Figure 2: Consort flow

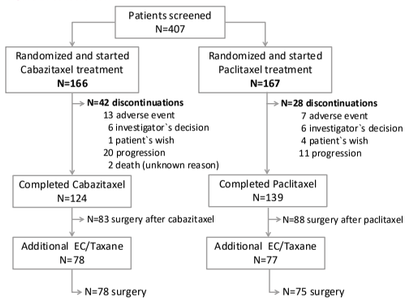
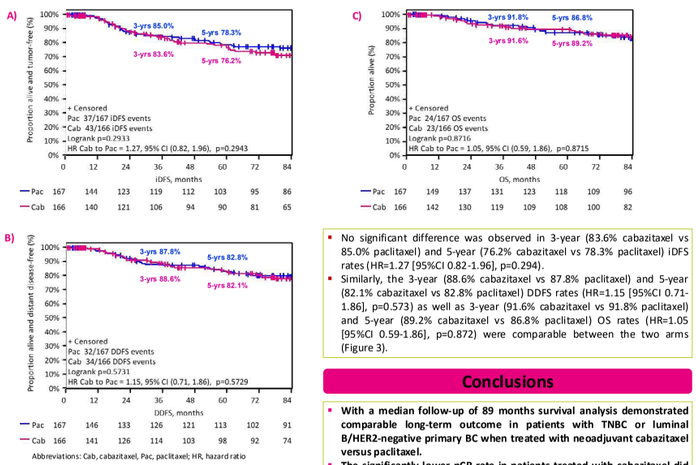


Table 1: Recurrence events

First event of the patient	Cabazitaxel N=166 N(%)	Paclitaxel N=167 N(%)	Overall N=333 N(%)
Patient with events	43 (25.9)	37 (22.2)	80 (24.0)
Site of first invasive disease event			
Distant recurrence	14 (8.4)	14 (8.4)	28 (8.4)
Invasive locoregional relapse	15 (9.0)	13 (7.8)	28 (8.4)
Invasive contralateral breast cancer	2 (1.2)	1 (0.6)	3 (0.9)
Secondary malignancy	5 (3.0)	5 (3.0)	10 (3.0)
Death without previous event	7 (4.2)	4 (2.4)	11 (3.3)

Figure 3: Kaplan-Meier estimates for iDFS (A), DDFS (B) and OS (C) according to treatment arm



Abbreviations: Cab, cabazitaxel, Pac, paclitaxel; HR, hazard ratio

- Between April 2013 and June 2015, 333 patients were randomised and started treatment with 74.7% and 83.2% of patients completing treatment in the cabazitaxel and paditaxel arms, respectively (Figure 2). Baseline characteristics were well balanced. Patients in cabazitaxel arm had a significantly lower pCR rate compared to the paclitaxel arm (1.2% vs 10.8%; p=0.001).[1]
- After a median follow-up of 89.3 months (range 87.2-90.6), overall 80 iDFS events (43 after cabazitaxel and 37 after paclitaxel) and 47 deaths (23 after cabazitaxel and 24 after paclitaxel) were reported.
- Recurrence events which occurred as first iDFS event are listed in Table 1.

- No significant difference was observed in 3-year (83.6% cabazitaxel vs 85.0% paclitaxel) and 5-year (76.2% cabazitaxel vs 78.3% paclitaxel) iDFS rates (HR=1.27 [95%CI 0.82-1.96], p=0.294).
- Similarly, the 3-year (88.6% cabazitaxel vs 87.8% paclitaxel) and 5-year (82.1% cabazitaxel vs 82.8% paclitaxel) DDFS rates (HR=1.15 [95%CI 0.71-1.86], p=0.573) as well as 3-year (91.6% cabazitaxel vs 91.8% paclitaxel) and 5-year (89.2% cabazitaxel vs 86.8% paclitaxel) OS rates (HR=1.05 [95%CI 0.59-1.86], p=0.872) were comparable between the two arms (Figure 3).

Conclusions

- **With a median follow-up of 89 months survival analysis demonstrated comparable long-term outcome in patients with TNBC or luminal B/HER2-negative primary BC when treated with neoadjuvant cabazitaxel versus paclitaxel.**
- **The significantly lower pCR rate in patients treated with cabazitaxel did not negatively impact survival rates.**

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Long-term survival of HER2-positive breast cancer patients with brain metastases: Subanalysis of the BMBC Registry

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269P

Background

- The incidence of brain metastases (BM) in breast cancer (BC) patients is rising
- The development of BM is associated with a limited prognosis and a decreased quality of life
- Survival of patients with BM of BC has not improved over the last decades[1]
- Up to 40% of patients with a human epidermal growth receptor 2 (HER2)-positive metastatic BC develop BM
- Identification of factors associated with long-term survival is important for the improvement of treatment modalities

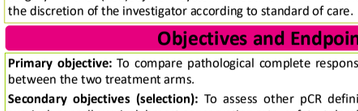
Patients and Methods

A total of 1160 HER2-positive patients out of 3234 patients of the Brain Metastases in Breast Cancer Registry (BMBC) was available for the analysis. The clinical data of patients diagnosed with BMs of BC from the year 2000 onward has been prospectively and retrospectively collected in the registry. Patients registered before 5th of December 2020, were included in this analysis

Long-term survival was defined as overall survival (OS) in the upper third of the survival curve resulting in a cut-off of 23 months. 328 patients were categorized as long-term survivors (Figure 1).

Baseline characteristics were compared by Wilcoxon test, Fisher's exact test resp. Pearson χ^2 test between short-term vs. long-term survivors. Uni- and multivariate logistic regression analyses were performed to characterize exploratively the prognostic behavior of several factors to the assignment in the group of long-term survivors. All reported p-values were two sided, and the significance level was set to 0.05. CIs symmetrically cover 95%.

Figure 1: Patient cohort including in the analysis



Results

Clinical characteristics of HER2-positive long-term survivors compared to other patients:

Long-term survivors compared to other patients:

- were younger at BC and BM diagnosis (median 48 vs 53 and 52 vs 57 years, p<0.001)
- had more often hormone receptor positive tumor biology (ER+ and/or PR+ 65 vs 56%, p=0.009)
- had lower tumor grading (G3 53% vs.62%, p=0.04)
- had better ECOG performance status at time of BM diagnosis (ECOG 0-1: 80 vs 56%, p<0.001)
- had lower BM number (n=1 BM 38 vs 25%, p<0.001)
- had lower rate of extracranial metastases at BM diagnosis (69 vs 82%, p<0.001)
- had lower rate of leptomeningeal metastases (6 vs 11%, p=0.018)
- were more often neurologically asymptomatic at BM diagnosis (28 vs 20%, p=0.005)

- Median OS in long-term survivors was 45.2 months (95%CI 40.4-47.7).
- Median time from diagnosis of BM to progress (BM, extracranial metastases or death) was 21.9 months (95%CI 18.9-23.6).
- Age, ECOG, number of BM, extracranial metastases and anti-HER2 therapy were significantly associated with a categorization of long-term survivors in multivariate analysis (Table 3).

Figure 2: Overall survival in HER2-positive long-term survivors

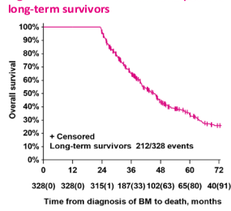


Table 1: Treatment modalities of HER2-positive long-term survivors

Local treatment	Short term survivors N(%)	Long-term survivors N(%)	P-Value
Surgery only	39 (5.6)	15 (4.9)	<.001
Radiotherapy only	505 (72.3)	174 (56.3)	
Surgery and radiotherapy*	154 (22.1)	120 (38.8)	
missing	134	19	

*no significant differences dependent on the type of the radiotherapy (data not shown)

Table 2: HER2-targeted treatment (after BM diagnosis)

HER2-targeted treatment after BM	Short-term-survivors N(%)	Long-term-survivors N(%)
Trastuzumab	90 (34.9)	76 (41.1)
Trastuzumab+Pertuzumab	28 (10.9)	24 (13.0)
Lapatinib-contaning regimes	89 (34.5)	59 (31.9)
TDM1	52 (20.2)	30 (16.2)

- Long-term survivors were significantly more often treated with a combination of brain surgery and radiotherapy (39 vs 22%, p<0.001).
- 443 patients were treated with anti-HER2-targeted therapies after the diagnosis of BM (in overall 764 therapy lines, for 1 patient in one therapy line the setting was not specified), in average 1.4 lines (range: 1-8) lines in short-term and 2.2 lines (range: 1-10) lines in long-term survivors.

Table 3: Univariate and multivariate logistic regression in long-term survivors vs. short-term survivors

Parameter at diagnosis	Category	Univariate analysis		Multivariate analysis	
		Odds Ratio* (95% CI)	p-value	Odds Ratio* 95% CI	p-value
Age, years**	≥60 vs < 60	0.45 (0.34-0.60)	<0.001	0.59 (0.38-0.91)	**0.018**
Hormone receptor	positive vs negative	1.43(1.1-1.88)	0.008	1.47 (0.96-2.25)	0.078
ECOG**	2-4 vs 0-1	0.33(0.21-0.5)	<0.001	0.51 (0.32-0.82)	**0.006**
Number of BM	2-3 vs 1	0.62(0.44-0.88)	0.006	0.66 (0.39-1.13)	0.127
	≥4 vs 1	0.49(0.36-0.67)	<0.001	0.53 (0.32-0.88)	**0.015**
Leptomeningeal metastases	Yes vs no	0.55(0.33-0.91)	0.02	0.70 (0.30-1.66)	0.421
Clinical symptoms**	Yes vs no	0.64(0.48-0.87)	0.004	0.68 (0.41-1.14)	0.147
Extracranial Metastases**	Yes vs no	0.49(0.36-0.65)	<0.001	0.58 (0.36-0.94)	**0.028**
Chemotherapy***	Yes vs no	2.36(1.82-3.07)	<0.001	1.40 (0.86, 2.28)	0.174
Anti-HER2 therapy***	Yes vs no	2.88(2.21-3.74)	<0.001	1.98 (1.23-3.19)	**0.005**

*An odds ratio ≥1 means to have a higher probability to be assigned to the group of long-term survivors; **at diagnosis of BM; ***after diagnosis of BM

Conclusions

- **Our analysis identified factors associated with long-term survival of HER2-positive BC patients with BM and characterized clinical features of this patient cohort**
- **Anti-HER2 targeted therapy after BM diagnosis is an important factor associated with long-term survival of HER2-positive patients with BM**
- **Hormone receptor status was not significantly associated with long-term survival in HER2-positive patients, although significantly better survival could be shown in triple-positive patients with BC and BM in the previous BMBC subanalysis[2]**
- **Further HER2-targeted agents are urgently needed to improve survival of HER2-positive BC patients with BM**
- **The role of a multimodal approach (an optimal combination of local brain therapy and systemic treatment options) in the treatment of BM of HER2-positive BC patients should be further evaluated in prospective trials**

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Presenting author: PD Dr. med. Elena Laakmann

Presenting author declares no conflict of interests
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A randomized, open-label, phase II trial comparing neoadjuvant trastuzumab, pertuzumab and endocrine therapy +/- the PI3K inhibitor inavolisib in patients with HER2+/HR+, PIK3CA mutant early breast cancer - GeparPiPPa

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200TiP

Background

PIK3CA mutations can be found in about 20%-30% of HER2-positive (+) breast cancer (BC) patients and indicate a lower response to chemotherapy and anti-HER2 therapy, especially in HER2+/hormone receptor-positive (HR+) tumours.[1,2,3] Crosstalk exists between key signaling pathways (HR, HER2 and PI3K) and inhibition of PI3K results in the activation of HER2-pathway.[4] The phase III Solar-1 study demonstrated a significant improvement in progression-free survival with the addition of alpelisib to fulvestrant in *PIK3CA* mutant metastatic BC.[5] GeparPiPPa investigates in the neoadjuvant setting the potential incremental efficacy and safety of inavolisib, an oral pure PI3Kα inhibitor, in addition to endocrine and anti-HER2 therapy in patients with early HER2+/HR+ and *PIK3CA* mutant BC.

Study Overview

GeparPiPPa (GBG 105/EUDRA-CT 2021-002323-38) is a multicenter, randomized, open-label, parallel-group, phase II study. Approximately 170 patients with early-stage HER2+/HR+, *PIK3CA* mutant BC will be randomized in a 1:1 ratio to receive neoadjuvant endocrine therapy in combination with dual anti-HER2 blockade consisting of ready-to-use fixed-dose combination of pertuzumab and trastuzumab as subcutaneous (PH-FDC SC) formulation q3w for 6 cycles (18 weeks) without or with inavolisib (9mg 1x1/d orally, day 1-21 q3w). Endocrine therapy consists of either tamoxifen 20mg or an aromatase inhibitor (1x1/d orally, day 1-21 q3w). Premenopausal women and men receive a GnRH analogue in addition to an aromatase inhibitor. After end of therapy, patients will undergo a core biopsy and/or surgery. In case of tumor residuals in the biopsy additional neoadjuvant treatment may be given. In case of ycT0 and no tumor residuals in the biopsy, it is recommended to undergo surgery. Further (neo)adjuvant systemic treatment and radiotherapy will be administered at the discretion of the investigator according to standard of care.

Objectives and Endpoint

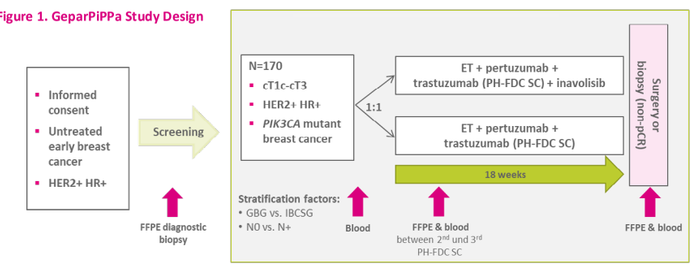
Primary objective: To compare pathological complete response (pCR=ypT0/is ypN0) rates between the two treatment arms.

Secondary objectives (selection): To assess other pCR definitions, invasive disease-free survival, overall survival, breast conservation rate, safety, tolerability and compliance.

Correlative objectives (selection, Table 1):

- To examine molecular/pathway markers on core biopsies and residual disease.
- To assess the predictive/prognostic effect of different *PIK3CA* hot spot mutations.
- Use of baseline and on-therapy specimens to explore potential new biomarkers.

Figure 1. GeparPiPPa Study Design



Study Treatment:

- Endocrine Therapy (ET): tamoxifen or an aromatase inhibitor (1x1/d orally, day 1-21 q3w) +/- gonadotropin-releasing hormone analogue
- Pertuzumab/trastuzumab as subcutaneous formulation on d1, q3w:
  - loading dose 1st cycle: 1200 mg/600 mg
  - 2nd-6th cycle: 600 mg/600 mg
- Inavolisib 9mg 1x1/d orally, day 1-21 q3w

Key Inclusion Criteria

- Age ≥ 18 years
- Females or males
- Diagnosis of a unilateral primary carcinoma of the breast by core needle biopsy
- Central testing must confirm HER2 positivity and HR positivity (according to ASCO/CAP guidelines) as well as *PIK3CA* mutation(s) (tumor)
- Primary tumor must be cT1c – cT3
- Normal cardiac function must be confirmed by ECG and cardiac ultrasound (LVEF ≥55%)
- Complete staging work-up within prior to randomization

Key Exclusion Criteria

- Excisional biopsy or lumpectomy and/or surgical axillary staging procedure prior to randomization
- Patients with definitive clinical or radiologic evidence of Stage IV BC
- Need of immediate neoadjuvant chemotherapy, e.g. inflammatory BC
- Body-Mass Index >30
- Patients with diabetes mellitus type I or uncontrolled type II
- Patients with currently documented pneumonitis/interstitial lung disease
- Patients with active uveitis or vitritis, history of uveitis, or active infectious process in the eye

Collection of Biomaterial

Study requirements	Screening	Pre-treatment	After 2nd/ before 3rd dose of PH-FDC SC	At end of treatment
FFPE tissue breast tumor (biopsy)	X		X	X
Whole Blood		X		
Plasma collection ctDNA		X	X	X

Abbreviations: ctDNA: circulating tumor DNA; FFPE: formalin-fixed, paraffin-embedded

Recruitment

- It is planned to conduct the study within approximately 50 GBG and IBCSG sites.
- First patient in Q IV/2022.

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Disclosure statement: SL reported grants and honorarium from Abbvie, AstraZeneca, BMS, Gilead, Novartis, Pfizer, Roche, Daiichi-Sankyo; honorarium from Amgen, Eirgenix, GSK, Lilly, Merk, Pierre-Fabre, Seagen, Sanofi; patents pending EP14153692.0, EP21152186.9, EP19808852.8, issued EP15702464.7, Digital Ki67 Evaluator; all paid to the institute

Patient quality of life from the GeparX trial on the addition of denosumab to two different nab-paclitaxel regimens as neoadjuvant chemotherapy in primary breast cancer

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94P

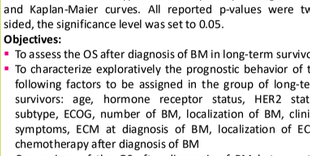
Background

The phase III prospective randomized GeparX study (NCT02682693) investigated the efficacy and safety of adding denosumab to standard neoadjuvant chemotherapy (NACT) in two different nab-paclitaxel (nP) schedules for primary breast cancer. The addition of denosumab to NACT did not improve pathological complete response (pCR) rates but nP weekly (q1w) significantly increased pCR rate compared to d1,8 3-weekly (q3w) schedule. The q1w schedule was associated with higher toxicity[1]. Here we present the results of the quality of life (QoL) analysis.

Patients and Methods

Patients were randomized to receive or not receive denosumab and to either nP q1w or nP d1,8 q3w schedule followed by epirubicin/cyclophosphamide (EC) (Fig.1)[1]. QoL was assessed at baseline (BL), after nP, at end of treatment and 90 days (90d) post surgery using the Functional Assessment of Cancer Therapy-Taxane (FACT-Taxane) questionnaire including FACT-G total and FACT-Taxane Trial Outcome Index (TOI) scales. Higher mean scores indicate better functioning and QoL. Repeated measures mixed models including BL value as a random effect and treatment, time, and treatment by time interaction as fixed effects were used to compare the QoL scores based on the safety set.

Figure 1: Study design



Results

Between 02/2017 and 03/2019, 780 patients were randomized and started treatment, of whom 766 (98.2%) were eligible for QoL analyses. 376 patients received denosumab versus 390 who did not; 394 patients received nP q1w compared to 372 with nP d1,8 q3w. BL parameters were well balanced[1].

Figure 2: FACT-Taxane total scores according to denosumab randomisation

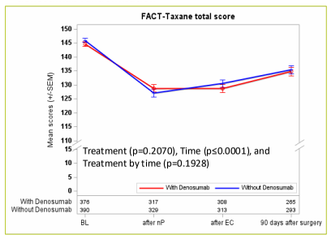


Figure 3: FACT-Taxane total scores according to nab-paclitaxel randomisation

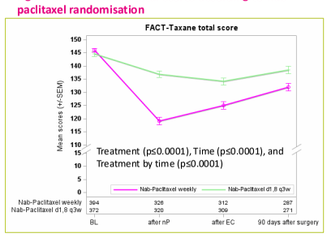


Figure 4: Physical well-being (A) and functional well-being (B) scores according to nab-paclitaxel randomisation

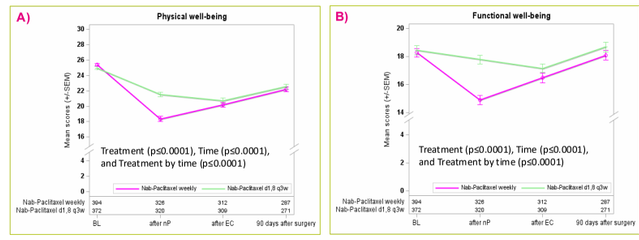
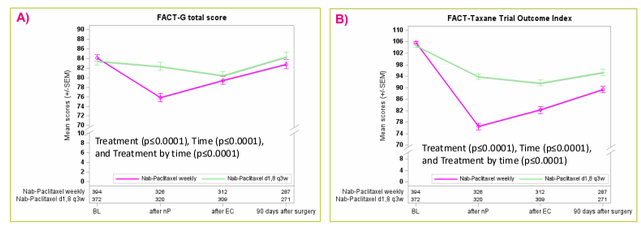


Figure 5: FACT-G total (A) and FACT-Taxane TOI (B) scores according to nab-paclitaxel randomisation



Questionnaire completion response remained >70% throughout the trial. The addition of denosumab did not change any aspect of QoL scores at any evaluated time point (Fig. 2).

Patients receiving nP q1w reported significantly lower mean FACT-Taxane total scores (at BL: 146.0 with nP q1w vs 144.6 with nP d1,8 q3w and after nP: 119.2 with nP q1w vs 136.9 with nP d1,8 q3w, Fig. 3).

The mean scores of physical and functional well-being (Fig. 4), FACT-G total and FACT-Taxane TOI scores (Fig. 6) significantly differed, favouring nP d1,8 q3w in all post-BL assessments (p<0.001). The decreased well-being with nP q1w partly persists 90d post surgery (Fig.4).

Social/family and emotional aspects were not affected by any of the applied nP schedules (data not shown).

Conclusions

nP q1w led to a significantly higher pCR rate but is associated with impaired QoL compared to nP d1,8 q3w, which is consistent with the higher toxicity reported for nP q1w[1]. The correlation between QoL and dose intensity of nP[2] or other taxans versus taxane-free schedules[3] have been described in literature in patients with early[3] and metastatic breast cancer[2]. Benefit and risks need to be discussed with the patients considering the curative setting in early breast cancer.

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Long-term survival of breast cancer patients with brain metastases: Subanalysis of the BMBC registry

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170P

Background

Up to 30% of metastatic breast cancer (BC) patients develop brain metastases (BM). Prognosis of patients with BM is poor and long-term survival is rare. Despite commonly known short median survival times of brain metastatic breast cancer patients differing between 7 and 8 months, long-term survivors with survival rates longer than 2 years make almost 25% of the whole cohort.[1] Identification of factors associated with long-term survival is important for improving treatment modalities.

The aim of this retrospective analysis from the BMBC registry was to identify long-term survivors and characterize prognostic factors being associated with long-term survival.

Patients and Methods

Clinical data for this analysis derived from the **brain metastases in breast cancer (BMBC) registry**. A total of **2889** out of 3234 patients of the BMBC registry were available for this analysis. Long-term survival was defined as overall survival (OS) after diagnosis of BM in the upper third of the survival curve resulting in a cut-off of 15 months. **887 patients were categorized as long-term survivors.** Baseline characteristics were assessed by Wilcoxon test, Fisher's exact test resp. Pearson χ^2-test between short-term vs long-term survivors. Associations with the assignment into the group of long-term survivors were analyzed by logistic regression models with 95% Wald confidence interval (CI). Differences in OS of long-term survivors between subtypes were analyzed by the log-rank-test and Kaplan-Maier curves. All reported p-values were two-sided, the significance level was set to 0.05.

Objectives:

- To assess the OS after diagnosis of BM in long-term survivors
- To characterize exploratively the prognostic behavior of the following factors to be assigned in the group of long-term survivors: age, hormone receptor status, HER2 status, subtype, ECOG, number of BM, localization of BM, clinical symptoms, ECM at diagnosis of BM, localization of ECM, chemotherapy after diagnosis of BM
- Comparison of the OS after diagnosis of BM between the groups of BC subtypes (HER2-positive, Luminal-like, TNBC).

Figure 1: Patient cohort including in the analysis

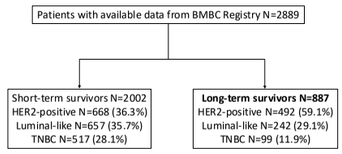

Table 1: Baseline characteristics

Parameter at diagnosis	Category	Short-term survivors N (valid %)	Long-term survivors N (valid %)	p-value
Age at first BC diagnosis, years	Median (range)	54.0 (10.0-98.0)	48.0 (20.0-92.0)	<0.001
Age at first BM diagnosis, years	Median (range)	59.0 (13.0-99.0)	53.0 (25.0-93.0)	<0.001
ECOG	0-1	457 (51.0)	306 (76.9)	<0.001
	2-4	440 (49.1)	92 (23.2)	
Hormone receptor	negative	826 (42.8)	279 (33.1)	<0.001
	positive	1104 (57.2)	563 (66.9)	
HER2	negative	1180 (65.1)	342 (42.8)	<0.001
	positive	633 (34.9)	458 (57.3)	
Number of BM	1	453 (25.4)	337 (40.9)	<0.001
	2-3	476 (26.7)	218 (26.5)	
	≥4	853 (47.9)	269 (32.6)	
Leptomeningeal metastases	no	1652 (82.5)	795 (89.6)	<0.001
	yes	350 (17.5)	92 (10.4)	
Clinical symptoms*	no	402 (20.1)	235 (26.5)	<0.001
	yes	1600 (79.9)	652 (73.5)	
ECM*	yes	351 (17.5)	234 (26.4)	<0.001
	no	1651 (82.5)	653 (73.6)	
ypT after NACT	ypT0	83 (13.7)	60 (21.6)	<0.001
	ypTis	33 (5.4)	22 (7.9)	
	ypT1	174 (28.7)	95 (34.2)	
	ypT2	180 (29.7)	58 (20.9)	
	ypT3	71 (11.7)	22 (7.9)	
	ypT4a-d	65 (10.7)	21 (7.5)	

*at diagnosis of BM; ECM, extracranial metastases; NACT, neoadjuvant chemotherapy

Results

- Long-term survivors compared to short-term survivors were significantly **younger** at BC and BM diagnosis, showed **better ECOG** at time of BM diagnosis and **lower number of BM**. Furthermore, long-term survivors had significantly higher **pathological complete remission rate** (21.6% vs 13.7%, p<0.001), **less leptomeningeal** metastases (10.4% vs 17.5%, p<0.001) and **less extracranial** metastases (ECM, 73.6% vs 82.5%, p<0.001) (Table 1).
- The distribution of biological subtypes in long-term vs short-term survivors was 59.1% vs 36.3% for HER2-positive tumors, 29.1% vs 35.7% for luminal-like and 11.9% vs 28.1% for TNBC (p<0.001) (Fig. 1).
- Overall, median OS in long-term survivors was **30.9 months** (95% CI 28.8-32.6). Median OS according to different subtypes was 33.9 months (95% CI 31.5-37.9) in HER2 positive, 26.9 (95% CI 25.0-30.9) in luminal-like and 26.5 months (95% CI 22.7-31.2) in TNBC patients.
- **Age, hormone receptor status, HER2 status, number of BM , ECM and chemotherapy were significantly associated with a categorization of long-term survivors in uni- and multivariate analyses (Table 2).**

Figure 2. Kaplan-Meier OS in long-term survivors by different subtypes

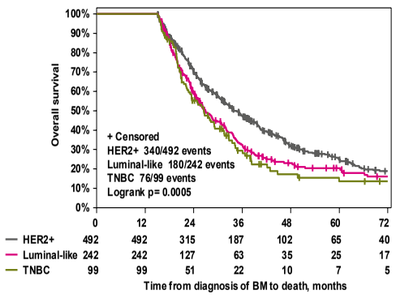

Table 2: Prognostic factors in long-term survivors

Parameter at diagnosis	Category	Univariate analysis Odds Ratio* (95% CI)	Univariate analysis p-value	Miltivariate analysis Odds Ratio* (95% CI)	Miltivariate analysis p-value
Age**, years	≥60 vs <60	0.49 (0.42-0.58)	<0.001	0.59 (0.44-0.79)	<0.001
ECOG**	2-4 vs 0-1	0.31 (0.24-0.41)	<0.001	0.45 (0.33-0.61)	<0.001
Hormone receptor	positive vs negative	1.51 (1.27-1.79)	<0.001	1.87 (1.39-2.50)	<0.001
HER2 status	positive vs negative	2.50 (2.11-2.96)	<0.001	2.74 (2.06-3.64)	<0.001
Number of BM	2-3 vs 1	0.62 (0.50-0.76)	<0.001	0.79 (0.55-1.13)	0.191
	≥4 vs 1	0.42 (0.35-0.52)	<0.001	0.46 (0.33-0.65)	<0.001
Leptomeningeal metastases	yes vs no	0.55 (0.43-0.70)	<0.001	0.99 (0.64-1.53)	0.949
Clinical symptoms**	yes vs no	0.70 (0.58-0.84)	<0.001	0.94 (0.66-1.34)	0.726
ECM**	yes vs no	0.59 (0.49, 0.72)	<0.001	0.65 (0.46-0.93)	0.017
Chemotherapy***	yes vs no	2.80 (2.38-3.30)	<0.001	2.19 (1.64-2.92)	<0.001

*An odds ratio ≥1 means to have a higher probability to be assigned to the group of long-term survivors; ** at diagnosis of BM; ***after diagnosis of BM; ECM, extracranial metastases

Conclusions

Our analysis identified factors associated with long-term survival of breast cancer patients with brain metastases and characterized clinical features of this patient cohort. Patients with better ECOG status, younger age, lower number of BM, less extended visceral metastases were more likely to show a long-term survival. Those patients might be more eligible for extended local and systemic treatment.

Further research is needed to understand the factors leading to long-term survival of patients with brain metastases.

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Intermediate biopsies during neoadjuvant chemotherapy for breast cancer to predict patient outcome

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24P

Background

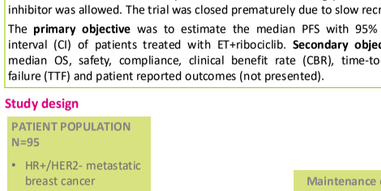
Patients with pathologic complete response (pCR) to neoadjuvant chemotherapy for invasive breast cancer have a better prognosis and are susceptible to a more limited surgical therapy. The prediction of pCR before treatment is challenging and it is unclear if biopsy procedures during neoadjuvant treatment might predict treatment outcome. This could offer opportunities for de-escalation of medical and surgical treatment beside serving as a platform for biomarker discovery.

Patients and Methods

We evaluated the use of intermediate biopsies that were taken during neoadjuvant treatment from 297 patients with invasive breast cancer treated within three prospective randomized neoadjuvant trials (GeparQuattro[1], GeparQuinto[2] and GeparSixto[3]). We evaluated the presence and quantity of invasive breast cancer as well as the quantity of tumor-infiltrating lymphocytes (TILs) and the proliferation marker Ki-67 by immunohistochemistry (IHC) and compared the results to the matched pre-treatment samples. We explored the association of residual cancer in the intermediate biopsies (tu- vs tu+) and dynamics (Δ) in TILs and Ki-67 with pCR rates and disease-free survival (DFS) using logistic and Cox regression models with 95% confidence interval (CI), respectively. The proportion of intermediate biopsies overall, and by BC subtype and tumor stage were assessed using Fisher's exact- or Pearson χ^2-test. Differences in DFS between subgroups of intermediate biopsies were analyzed by Kaplan-Maier curves and Cox proportional hazard models.

Primary objective of the study: to evaluate if intermediate biopsies taken during neoadjuvant therapy are useful for the prediction of therapy response and survival after completion of treatment.

Figure 1: Study design



Evaluation of tumor cells, TILs and Ki-67 immunohistochemistry

EC-T, epirubicin plus cyclophosphamide followed by docetaxel

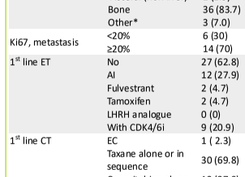
Results

Table 1: Baseline characteristics

Parameter	Category	N (valid %)
BC subtype	HR-/HER2-	87 (29.3%)
	HR+/HER2-	138 (46.5%)
	HER2+	72 (24.2%)
T stage	T1	25 (8.4%)
	T2	181 (60.9%)
	T3	42 (14.1%)
	T4	49 (16.5%)
N stage	N0	125 (42.1%)
	N1-3	171 (57.6%)
	Missing	1 (0.3%)
Grading	G1-2	156 (52.5%)
	G3	136 (45.8%)
	Missing	5 (1.7%)
Histology	NST	268 (90.2%)
	Lobular/other	29 (9.7%)
TILs	TILs < 60 %	79 (26.6%)
	TILs ≥60 %	25 (8.4%)
	Missing	193 (65.0%)
Response	No pCR	235 (79.1%)
	pCR	62 (20.9%)

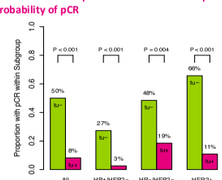
NST, no special type

Figure 2: Intermediate biopsies and tumor characteristics



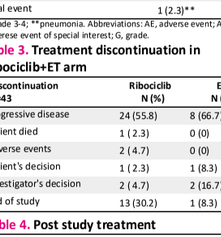
90 (30%) intermediate biopsies were negative for residual cancer (tu-). This was more frequently observed in HER2+, HR-/HER2- and low-stage tumors. There was no significant association with nuclear grade, nodal status or TILs.

Figure 3: Patients with positive intermediate biopsies had a low probability of pCR



Overall, pCR rate was 50% in patients without residual cancer (tu-) and 8% in patients with residual cancer (tu+) in the intermediate biopsy after completion of treatment.

Figure 4: Intermediate biopsies are not independently predictive for survival

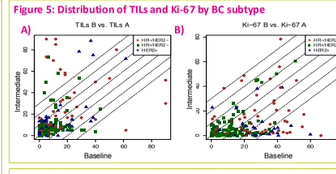


Parameter	HR (95% CI)	P
tu- vs. tu+	0.54 (0.22-1.37)	0.19
pCR vs. no pCR	0.28 (0.08-0.96)	0.04

tu+, residual cancer; tu-,without residual cancer

In univariate analysis the presence of tumor cells in intermediate biopsies was predictive for DFS in HR-/HER2- but not in the other subtypes. It was not predictive in HR-/HER2- in a bivariate Cox regression analysis adjusted for pCR (table).

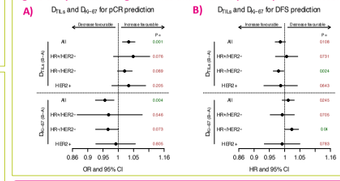
Figure 5: Distribution of TILs and Ki-67 by BC subtype



TILs increased in a subset of patients after onset of treatment (Fig. 5A).
We observed a decrease in proliferation in most patients (Ki-67 IHC) (Fig. 5B).

Abbreviation: A, baseline; B, intermediate

Figure 6: Dynamic changes of TILs and Ki-67 to predict patient outcome



An increase in TILs or a decrease in Ki-67 was associated with a higher probability of pCR in the overall study cohort (Fig. 6A; univariate logistic regression).
An increase in TILs or a decrease in Ki-67 was associated with a longer DFS in HR-/HER2- breast cancer. but not within the other subtypes (Fig. 6B).

Conclusions

- **Intermediate biopsies can identify patients that are unlikely to respond to treatment.** However, it is not suitable for pCR prediction as the probability in patients with negative biopsies is 50%.
- **Intermediate biopsies might be useful for translational biomarker discovery** to study mechanisms of therapy resistance.
- **Intermediate biopsies might be used to tailor therapy concepts** for patients at high risk for non-pCR within clinical trials.
- **Further studies are needed** to evaluate if a standardized biopsy procedure during neoadjuvant treatment can improve diagnostic sensitivity and can be used to adapt the planned treatment strategy.

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Disclosure statement: BVS has no conflicts of interest to declare.

Anti-hormonal maintenance treatment with the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in hormone receptor positive/HER-2 negative metastatic breast cancer: a phase II trial (AMICA) GBG 97

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P3-01-09

Background

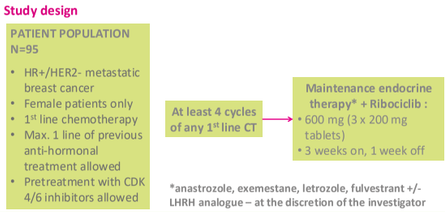
Albeit guidelines recommend to use endocrine-based therapy (ET) as 1st line therapy in HR-positive/HER2-negative metastatic breast cancer (MBC) patients, about 30% of them will receive chemotherapy (CT). Longer duration of therapy is associated with longer progression-free survival (PFS) and overall survival (OS).[1] However, chemotherapy duration is usually determined by toxicities and patients' and physicians' preferences, resulting in treatment periods of less than 6 months. Maintenance ET after achievement of maximal tumor response with CT is an accepted treatment strategy in everyday clinical practice, but prospective data are lacking. Well tolerated maintenance treatments with the potential to prolong progression-free survival (PFS) and even overall survival (OS) are urgently needed.

Patients and Methods

The AMICA trial (NCT03555877) is a multicenter, prospective, open-label phase II study to test the addition of the CDK4/6 inhibitor ribociclib to ET as maintenance therapy in patients with disease control after at least 4 cycles of 1st line mono- or poly-CT at investigator´s discretion. Initially patients were randomized to receive ET with or without ribociclib. Due to slow accrual the study was amended after inclusion of 37 patients and all subsequent patients received ET together with ribociclib. Treatment was given until disease progression, unacceptable toxicity, or withdrawal of consent. Maintenance ET could have already been started up to 6 weeks before enrolment. One previous line of ET including prior use of CDK4/6 inhibitor was allowed. The trial was closed prematurely due to slow recruitment.

The **primary objective** was to estimate the median PFS with 95% confidence interval (CI) of patients treated with ET+ribociclib. **Secondary objectives** were median OS, safety, compliance, clinical benefit rate (CBR), time-to-treatment-failure (TTF) and patient reported outcomes (not presented).

Study design



*anastrozole, exemestane, letrozole, fulvestrant +/- LHRH analogue – at the discretion of the investigator

Results

Between March 2018 and December 2021, 56 patients were enrolled and 53 started treatment (n=43 received ET+ribociclib (=mITT set), 10 ET alone before Amendment). Baseline characteristics were well balanced between arms (**Table 1**). Overall, 46.5% of the patients received letrozole, 14.0% anastrozole, 7.0% exemestane, 32.6% fulvestrant. Adverse events are presented in **Table 2**. The median extent of ribociclib exposure was 42 (6.9-198) weeks (**Table 3**). Median follow-up was 32.7 (3.3-49.7) months. Time to event endpoints are presented in **Figure 1**. CBR with ET+ribociclib was 65.1% (**Table 5**).

Table 1. Baseline and pretreatment

Parameter	Category	Ribociclib+ET, N= 43 N (valid %)
Age, years	Median	61.0
	Min, Max	36.0, 87.0
BMI, kg/m^2	Median	25.7
	Min, Max	16.8, 40.6
Menopausal status	premenopausal	5 (11.6)
	postmenopausal	38 (88.4)
cT at diagnosis	cT1/cT2	17 (70.8)
	cT3	2 (8.3)
	cT4	5 (20.8)
cN at diagnosis	cN0	4 (18.2)
	cN+	18 (81.8)
M at diagnosis	M0	25 (58.1)
	M1	17 (39.5)
Location of M	Loco-regional	1 (2.3)
	Lymph node	8 (18.6)
	Lung	9 (20.9)
	Pleura	7 (16.3)
	Liver	32 (74.4)
	Visceral (non liver)	1 (2.3)
	Bone	36 (83.7)
	Other*	3 (7.0)
Ki67, metastasis	<20%	6 (30)
	≥20%	14 (70)
1st line ET	No	27 (62.8)
	AI	12 (27.9)
	Fulvestrant	2 (4.7)
	Tamoxifen	2 (4.7)
	LHRH analogue	0 (0)
	With CDK4/6i	9 (20.9)
1st line CT	EC	1 (2.3)
	Taxane alone or in sequence	30 (69.8)
	Capecitabine alone	12 (27.9)
	Bevacizumab	34 (79.1)
	Other**	4 (9.3)
CR after 1st line CT	CR	2 (4.7)
	PR	18 (41.9)
	SD	23 (53.5)

*gastric, brain, pleural effusion; **Denosumab, Bevacizumab/Capecitabine, Bisphosphonate, Carboplatin/Gemcitabine. Abbreviations: AI, aromatase inhibitor; BMI, body mass index; EC, epirubicine, cyclophosphamide; CR, complete response; CT, chemotherapy; ET, endocrine therapy; PR, partial response; SD, stable disease.

Table 2. Adverse Events

Adverse Events	Ribociclib+ET, N=43 N (%)
Any AEs G1-4	43 (100)
G3-4	29 (67.4)
Hematological AEs G1-4	41 (95.3)
G3-4	25 (58.1)
Non-hematological AEs G1-4	43 (100)
G3-4	17 (39.5)
AESI	2 (4.7)
Hepatotoxicity*	1 (2.3)
Overdose	1 (2.3)
Serious AEs	11 (25.6)
Fatal event	1 (2.3)**

*Grade 3-4; **pneumonia. Abbreviations: AE, adverse event; AESI, adverse event of special interest; G, grade.

Table 3. Treatment discontinuation in Ribociclib+ET arm

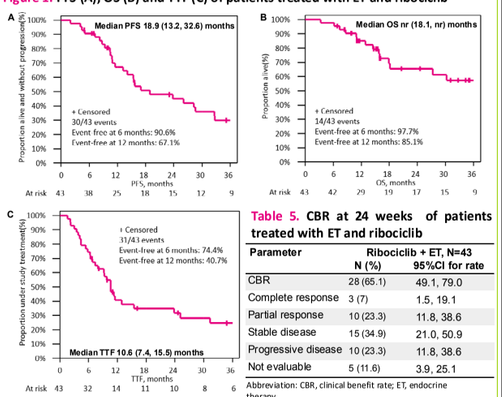
Discontinuation N=43	Ribociclib N (%)	ET N (%)
Progressive disease	24 (55.8)	8 (66.7)
Patient died	1 (2.3)	0 (0)
Adverse events	2 (4.7)	0 (0)
Patient's decision	1 (2.3)	1 (8.3)
Investigator's decision	2 (4.7)	2 (16.7)
End of study	13 (30.2)	1 (8.3)

Table 4. Post study treatment

Treatment	Ribociclib + ET, N=43 N (%)
Fulvestrant alone	1 (2.7)
Chemotherapy	22 (59.5)
CDK 4/6 inhibitor+ ET	14 (29.7)
Other*	2 (5.4)
No further treatment	2 (13.5)**

*surgery, radiation; **no further treatment between relapse and death (in both cases only few weeks). Abbreviation: ET, endocrine therapy.

Figure 1. PFS (A), OS (B) and TTF (C) of patients treated with ET and ribociclib



Abbreviation: OS, overall survival; PFS, progression-free survival; TTF, Time-to-treatment-failure.

Table 5. CBR at 24 weeks of patients treated with ET and ribociclib

Parameter	Ribociclib + ET, N=43 N (%)	95%CI for rate
CBR	28 (65.1)	49.1, 79.0
Complete response	3 (7)	1.5, 19.1
Partial response	10 (23.3)	11.8, 38.6
Stable disease	15 (34.9)	21.0, 50.9
Progressive disease	10 (23.3)	11.8, 38.6
Not evaluable	5 (11.6)	3.9, 25.1

Abbreviation: CBR, clinical benefit rate; ET, endocrine therapy

Conclusion

The AMICA study shows promising efficacy of ribociclib as part of endocrine-based maintenance therapy in delaying tumor progression after chemotherapy with an acceptable safety profile.

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Spatial and temporal heterogeneity of predictive and prognostic signatures in triple-negative breast cancer treated with neoadjuvant combination immune-chemotherapy

PD4-02

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Background

Immunological pathways are relevant for response to classical neoadjuvant chemotherapy as well as combined chemo-immunotherapy. In addition, it has been shown that combined chemo-immunotherapy significantly improves survival, even in the context of only moderate effects on pCR. Due to the window therapy with durvalumab-alone, the administration of durvalumab only in the neo-adjuvant phase and the option to analyze multiple consecutive biopsies, the GeparNuevo trial[1,2] offers the opportunity to

- determine gene expression patterns for pCR and DDFS endpoints in two different neoadjuvant therapy arms
- identify pathways most relevant for pCR and DDFS in the different therapy arms
- analyze the temporal heterogeneity at different time points, with a focus on genes regulated by durvalumab vs placebo
- evaluate the tumor microenvironment by spatial sequencing of tumor cell and stroma areas.

Patients and Methods

264 tumor samples were evaluated by gene expression analysis: 148 pretherapeutic core biopsies, 72 post-window biopsies, 27 biopsies during chemotherapy and 17 biopsies of the residual tumor after therapy. These samples were analyzed by HTG OBP panel targeting 2549 genes which are assigned to 25 different biological mechanisms or cellular pathways. In addition, spatial profiling was compared in a subset of pre-and post-window samples using the Nanostring GeoMx spatial RNA profiling system guided by cytokeratine immunofluorescence. We compared areas with high tumor cell content with stromal areas with or without TILs. Endpoints were pCR and DDFS.

Table 1: Consort table

Patient set	N
G9 mITT analysis set	174
… QC cleaned HTG data available	148
- durvalumab arm	77
- non pCR	35
- pCR	42
- placebo arm	71
- non pCR	35
- pCR	36

Table 2. Baseline characteristics

Parameter	Category	Durvalumab N=77 N (%)	Placebo N=71 N (%)	Overall N=148 N (%)	p-value
Age, years	<40	24 (31.2)	16 (22.5)	40 (27.0)	0.237
	>=40	53 (68.8)	55 (77.5)	108 (73.0)	
Breast Cancer Stage	Stage 0 or I	27 (35.1)	26 (36.6)	53 (35.8)	0.865
	Stage IIA and higher	50 (64.9)	45 (63.4)	95 (64.2)	
Grading	G2	13 (16.9)	13 (18.3)	26 (17.6)	0.820
	G3	64 (83.1)	58 (81.7)	122 (82.4)	
Tumor type	Duct. or duct.lob.	60 (77.9)	58 (81.7)	118 (79.7)	0.437
	lobular	0 (0.0)	1 (1.4)	1 (0.7)	
	other	17 (22.1)	12 (16.9)	29 (19.6)	
sTILs	low (0-10%)	27 (35.1)	26 (36.6)	53 (35.8)	0.852
	Interm. (11-59%)	39 (50.6)	33 (46.5)	72 (48.6)	
	high (60-100%)	11 (14.3)	12 (16.9)	23 (15.5)	
PD-L1	negative	8 (11.3)	10 (14.9)	18 (13.0)	0.616
	positive	63 (88.7)	57 (85.1)	120 (87.0)	
	missing	6	4	10	
pCR(ypT0 ypN0)	no	35 (45.5)	35 (49.3)	70 (47.3)	0.742
	yes	42 (54.5)	36 (50.7)	78 (52.7)	

Results

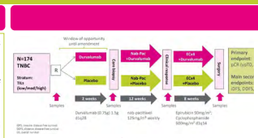

Figure 1: Study design of the GeparNuevo trial

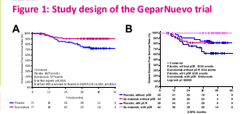

Figure 2: DDFS by treatment arm (A) and pCR (B)
(ypT0 ypN0, landmark-analysis, biomarker cohort, n=148)

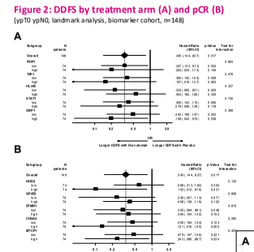

Figure 5. Survival analysis for selected genes: **A** Cox-regression (DDFS) for the most significant pCR genes in the durvalumab arm; **B** Cox-regression (DDFS) for the most significant pCR genes in the placebo arm

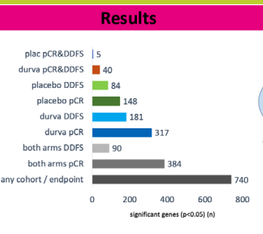

Figure 3. Number of significant genes for different endpoints and cohorts

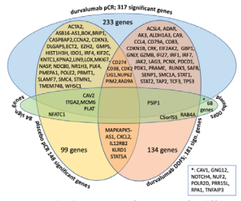

Figure 4. Overlap between significant genes for different endpoints and study arms

Figure 6. Gene set enrichment analysis for pathways included in the HTG oncology biomarker panel (2549 genes, 24 pathways)

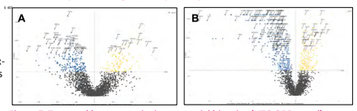

Figure 7. Temporal heterogeneity in sequential biopsies (HTG OBP panel):
A: durvalumab-induced changes (comparison of core biopsy before therapy and after one dose of durvalumab) B: chemotherapy-induced changes: comparions of core biopsy before therapy and after 4 cycles of chemotherapy)

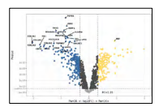

Figure 8. Spatial heterogeneity in different tumor regions: Tumor cell areas vs. stromal areas (GeoMx platform)

Results and Conclusions

1. The survival results of the biomarker cohort were similar to the complete GeparNuevo trial cohort, with an improved survival in the durvalumab arm (**Figure 2**). The pCR rate was not significantly different between both arms (not shown).
2. A total of 740 genes were significantly associated with either pCR or DDFS in either the complete GeparNuevo cohort or one of the two therapy arms.
3. There was a large number of predictive or prognostic genes (n=317 for pCR and n=181 for DDFS) in the durvalumab arm, while the number of genes in the placebo arm was considerably lower (n=148 for pCR and n=84 for DDFS) (**Figure 3**).
4. Overall, the overlap between the significant genes for pCR and DDFS in the two trial arms was limited. There was no single gene significant for all endpoints/cohorts, and only a limited set of genes for three of four scenarios (**Figure 4**). A considerable overlap of genes was observed for pCR and DDFS in the durvalumab arm (40 genes) and for pCR in the placebo and durvalumab arms (43 genes). Only 5 genes were significant in the placebo arm for both, pCR and DDFS.
5. Genes with high significance for pCR did typically not have a significant test for interaction with therapy in the survival analysis (**Figure 5**).
6. Gene set enrichment analyses identified immuno-oncology, NF-kappa B as well as cell cycle as the most common pathways for DDFS and pCR, with a considerable heterogeneity between the different trial arms and endpoints (**Figure 6**). Interestingly, immuno-oncology genes were relevant for pCR in the placebo arm, but not in the durvalumab arm. This is in line with the observation that a pre-activated immune system is relevant for response to conventional chemotherapy. In our cohort, this immune pre-activation is less relevant for pCR to durvalumab, but might play a role for DDFS after durvalumab.
7. Temporal as well as spatial heterogeneity of gene expression was observed, this might contribute to the differences observed in the different trial arms (**Figure 7-8**).

In our analysis, we show that immune gene signatures, NF-kappa B signaling as well as proliferation contribute to therapy response and prognosis after neoadjuvant durvalumab combined with chemotherapy, with considerable heterogeneity of the different genes and gene sets in the different clinical situations. The parallel targeting of immune- and proliferation pathways as well as the additional effect on survival might explain why a combined immunotherapy-chemotherapy approach is more successful than each single therapy strategy alone.

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Presented at: San Antonio Breast Cancer Symposium, December 6-10, 2022

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Outcome analysis of HER2-zero or HER2-low hormone receptor-positive (HR+) breast cancer patients - characterization of the molecular phenotype in combination with molecular subtyping

HER2-06

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Background

Breast cancer with low HER2 expression (HER2-low) is of high clinical relevance because of new therapeutic options with antibody-drug conjugates. We have recently shown in a large cohort from neoadjuvant clinical trials that HER2-low breast cancer has different molecular characteristics as well as different clinical outcomes compared to HER2-zero.[1] Considering the positive correlation between HER2-low expression and hormone receptor positivity observed consistently in many investigations, we have extended our analysis to HR+ tumors from the post-neoadjuvant PenelopeB trial[2]. In PenelopeB, patients with HR+ breast cancer (BC) and residual disease after neoadjuvant chemotherapy (NACT) were randomized to post-neoadjuvant palbociclib versus placebo in addition to endocrine therapy. We evaluated the molecular phenotype and clinical outcomes of HER2-low compared to HER2-zero patients.

Patients and Methods

A total of 1250 patients were randomized, tRR2 status was available for 1152 tumors from pre-NACT core biopsies, determined by local pathology, and 1213 post-NACT tumors, determined as part of central pathology. For 1119 patients, a paired HER2-status was available. HER2-zero was defined as IHC0, and HER2-low was defined as IHC1+ or IHC2+/ISH-. Gene expression analysis of 2549 genes using the HTG oncology biomarker panel was performed in 629 pretherapeutic biopsies and 780 post-NACT residual tumor samples, with paired gene expression in 540 tumors. Breast cancer subtypes were determined using the AIMS approach.

Consort statement:

PenelopeB mITT cohort n=1250
↓
Core biopsies with (local) HER2 score n=1152 (n=629 with HTG mRNA data)
↓
Surgical resections with (central) HER2 score; n=1213 (n=780 with HTG mRNA data)
↓
Paired biopsies and surgical resections (n=1119) (n=540 with HTG mRNA data)

Table 1: Baseline data from pretherapeutic cohort

parameter	value	HER2-zero (n=457)	HER2-low (n=695)	Overall (n=1152)	P value
Age	≤50y	274 (60.0)	374 (53.8)	648 (56.3)	0.04
	>50y	183 (40.0)	321 (46.2)	504 (43.8)	
Region	Non-Asian	411 (89.9)	647 (93.1)	1058 (91.8)	0.06
	Asian	46 (10.1)	48 (6.9)	94 (8.2)	
Ki67	≤15	336 (73.5)	521 (75.0)	857 (74.4)	0.58
	>15	121 (26.5)	174 (25.0)	295 (25.6)	
Therapy arm	Placebo	226 (49.5)	346 (49.8)	572 (49.7)	0.91
	Palbociclib	231 (50.5)	349 (50.2)	580 (50.3)	
cT	cT1/2	250 (54.7)	380 (54.9)	630 (54.8)	0.95
	cT3/4	207 (45.3)	312 (45.1)	519 (45.2)	
	missing	0	3	3	
Tumor grade	G1-2	262 (58.2)	419 (61.1)	681 (59.9)	0.34
	G3	188 (41.8)	267 (38.9)	455 (40.1)	
	missing	7	9	16	
Histology	Ductal invasive	393 (87.3)	628 (91.7)	1021 (90.0)	0.03
	Lobular invasive	51 (11.3)	47 (6.9)	98 (8.6)	
	Others	6 (1.3)	10 (1.5)	16 (1.4)	
	missing	7	10	17	

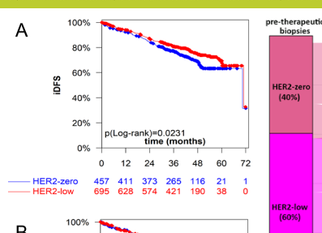

Figure 1: Prognostic impact of HER2-low status:
A: Improved prognosis of HER2-low tumors in pre-NACT biopsies (n=1152) **B:** No difference in prognosis in post-NACT samples (n=1213)

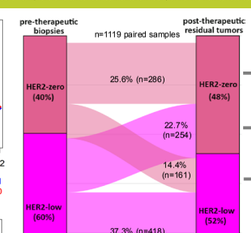

Figure 2: Changes in HER2-low status from core biopsy to residual tumor (n=1119)

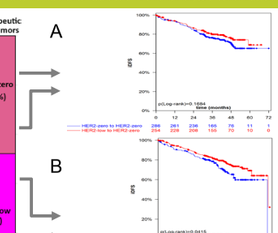

Figure 3: Survival analysis of alterations in HER2-low status:
A: No prognostic difference for tumors with new HER2-zero status after NACT (compared to persistently HER2-zero)
B: Reduced prognosis with new HER2-low status after NACT

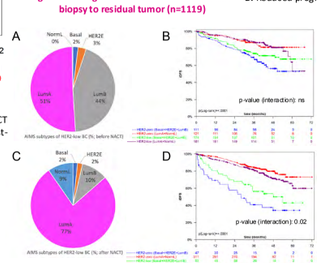

Figure 4: AIMS subtypes of HER2-low positive breast cancer before **(A,B)** and after **(C,D)** NACT: prevalence **(A,C)** and survival **(B, D)**

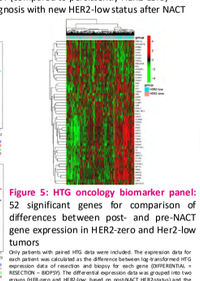

Figure 5: HTG oncology biomarker panel: 52 significant genes for comparison of differences between post- and pre-NACT gene expression in HER2-zero and Her2-low tumors

Only patients with paired HTG data were included. The expression data for each patient was calculated as the difference between log-transformed HTG expression data of resection and biopsy for each gene (DIFFERENTIAL = RESECTION – BIOPSY). The differential expression data was grouped into two groups (HER-zero and HER-low: based on post-NACT HER2-status) and the Kolmogorov-Smirnov test was used to identify differences between both groups (p<0.05). 52 genes were identified, the hierarchical clustering of those genes did not result in a clear separation of HER2-low and HER2-zero tumors.

Results

In pre-NACT biopsies, 695 tumors (60%) were HER2-low and 457 (40%) were HER2-zero. A HER2-low status pre-NACT was significantly linked to improved iDFS (HR 0.76 [95%CI 0.60-0.96], p=0.02, **Figure 1A**). In residual tumors, 632 tumors (60%) were HER2-low and 581 (40%) were HER2-zero, without any prognostic impact of HER2 low status (**Figure 1B**). A shift of HER2-status from core biopsy to residual tumor was observed in 415 (37%) of 1119 tumors (**Figure 2**). 161 (14%) had a shift from HER2-zero to HER2-low and 254 (23%) shifted from HER2-low to HER2-zero. A shift from HER2-low to HER2-zero was not associated with a significant survival difference (**Figure 3A**). In contrast, shifts from pre-NACT HER2-zero to post-NACT HER2-low were significantly linked to reduced iDFS (HR 1.43 [95%CI 1.01-2.01], p=0.04, **Figure 3B**), compared to the persistently HER2-low group. We did not observe a significant correlation of HER2-low status and AIMS subtypes. Only 3.1% of HER2-low tumors (pre-NACT) and 1.9% (post-NACT) had an HER2-enriched AIMS subtype; the majority were luminal A or B tumors (**Figure 4 A,C**). Significant iDFS differences were observed for HER2-low-status in combination with AIMS subtypes (lumB/basal/HER2E vs. lumA/normL; overall p-value <0.0001) for both pretherapeutic biopsies and residual tumor. Patients with post-NACT HER2-low tumors had an improved survival in aggressive AIMS subtypes (lumB/basal/HER2E), but not in the less aggressive AIMS subtypes (lumA/normL), with a positive test for interaction (p=0.02, **Figure 4D**). For the pre-NACT samples a similar, but non-significant trend was observed (**Figure 4B**). We used the HTG oncology biomarker panel to identify differentially expressed genes pre- and post-NACT. A total of 52 genes were significantly correlated with post-NACT HER2 status (**Figure 5**). Further evaluations are necessary to analyze the alterations of gene expression in the different HER2-low groups.

Conclusions

1. This is the first evaluation of neoadjuvant treated HER2-low patients in a prospective clinical trial cohort of high-risk HR+ BC. In this cohort, a HER2-low status in pre-NACT biopsies is related to improved disease-free survival.
2. A shift in HER2-low status was observed during chemotherapy, indicating an adaptation of pathway activity to therapy-induced stress, which might become relevant for future diagnostic and therapeutic approaches. In particular, a shift from HER2-zero to HER2-low was significantly linked to reduced survival.
3. A combination of AIMS subtypes and HER2-low status was relevant for prognosis, in particular in post-NACT samples.

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Immunohistochemical markers and determinants of clinical response in the PenelopeB trial

PD17-06

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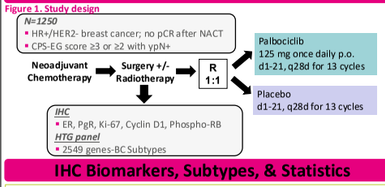
Background

The PENELOPE-B trial did not show improvement in invasive disease-free survival (iDFS) with the addition of palbociclib to endocrine therapy (ET) in patients with high-risk early breast cancer (BC) after neoadjuvant chemotherapy (NACT)[1]. Biomarkers may be able to identify subgroups of patients deriving benefit from palbociclib and guide future studies. Estrogen-receptor (ER), progesterone-receptor (PgR) and Ki-67 might be helpful in identifying patients benefiting from palbociclib. Furthermore, tumors with elevated expression of Cyclin D1 and phosphorylated retinoblastoma protein (phospho-RB) may harbor more dependency on CDK4/6 and thus higher sensitivity to palbociclib.

Figure 1. Study design



IHC Biomarkers, Subtypes, & Statistics

- Data for ER, PgR, Ki-67, HER2, Cyclin D1 and phospho-RB (Ser 807/811) immunohistochemistry were available from surgical resections after NACT from 1250 patients enrolled in PenelopeB.
- The percentage of positive ER and PgR cells and Ki-67 assessed in surgical specimens after NACT were combined to obtain the immunohistochemical score 3 (IHC3)[2]. Low vs high was based on the median IHC3 value.
- Cyclin D1 and phospho-RB Ser 807/811 immunoreactive (phospho-RB) scores were analysed in residual tumors after NACT (range 0-12 each).
- BC subtypes were determined using absolute intrinsic molecule subtyping-AIMS[3] on tumors for which HTG analyses had been performed on the biopsies (n=629) and residual tumors (n=782).

Proportional hazard regression model was used to assess the predictive and prognostic value of IHC3 and treatment on iDFS. Subgroup analysis was performed according to BC intrinsic subtypes (luminal-A/normal-like, luminal-B/HER2-enriched/basal) and HER2-status (HER2 0, HER2 low). Cox/Fine-Gray regression was used to define the predictive and prognostic value of CyclinD1 (≤1, >1), phospho-RB (≤2, >2) as dichotomized and continuous variables on iDFS, distant DFS (DDFS), locoregional invasive recurrence-free interval (LRRFI) and overall survival (OS). Multivariate analyses (MVA) were adjusted for age (≤50 vs >50), Ki-67 (≤15 vs >15), region (non-Asian vs Asian), ypN (ypN0-1 vs ypN2-3), risk status (CPS-EG=2 ypN+ vs ≥3), cT (cT1-2 vs cT3-4), ypT (ypT0-2 vs ypT3-4), and grade (G1-2 vs G3). The MVA for IHC3 include all the covariates above except Ki-67. p<0.05 was defined as statistically significant.

Results

Table 1. Baseline characteristics

Parameter	Value	Overall (%)
Age	<=50y	701 (56.1)
	>50y	549 (43.9)
Arm	Placebo	619 (49.5)
	Palbociclib	631 (50.5)
Her2 status	Her2-zero	598 (47.8)
	Her2-low	652 (52.2)
Ki-67	≤15	931 (74.5)
	>15	319 (25.5)
ER status	ER+	1236 (98.9)
	ER-	14 (1.1)
PgR status	PgR+	938 (75.0)
	PgR-	312 (25.0)

Parameter	Value	Overall (%)
T-stage (biopsy)	T1	89 (7.1)
	T2	583 (46.8)
	T3	373 (29.9)
	T4	201 (16.1)
Grade (biopsy)	G1/2	752 (60.9)
	G3	482 (39.1)
ypT	ypT0/2	986 (78.9)
	ypT3/4	263 (21.1)
ypN	ypN0/1	620 (49.6)
	ypN2/3	630 (50.4)

Overall, 98.9% of the patients had ER+ tumors, 75.0% PgR+, 52.2% had HER2 low, 25.5% Ki-67>15, median of the IHC3 score was high, 93.9% had Cyclin D1 >1, 57.8% had phospho-RB >2.

Figure 2. Prognostic significance of IHC3: **(A)** Patients with IHC3 score high had a worse iDFS compared to patients with IHC3 score low (MVA HR 2.29 95%CI [1.79-2.93], p<0.0001). **(B)** IHC3 was not predictive.

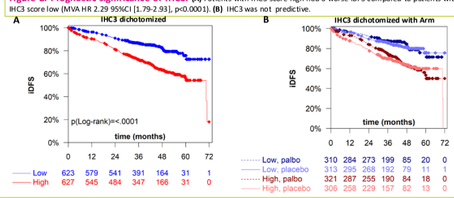


Table 2. Association of IHC3 with AIMS subtypes

Parameter	Value	IHC3 score (post-NACT) Low	High	Overall	p-value
Pre-NACT AIMS	Basal	0 (0.0)	11 (3.5)	11 (1.8)	<.001
	HER2E	8 (2.5)	14 (4.5)	22 (3.5)	
	LumB	113 (35.5)	157 (50.5)	270 (42.9)	
	LumA	197 (62.0)	127 (40.8)	324 (51.5)	
	NormL	0 (0.0)	2 (0.6)	2 (0.3)	
	missing	305	316	621	
Post-NACT AIMS	Basal	1 (0.3)	14 (3.5)	15 (1.9)	<0.001
	HER2E	4 (1.0)	22 (5.5)	26 (3.3)	
	LumB	5 (1.3)	59 (14.8)	64 (8.2)	
	LumA	336 (88.0)	263 (65.8)	599 (76.6)	
	NormL	36 (9.4)	42 (10.5)	78 (10.0)	
	missing	241	227	468	

Figure 3. Predictive significance of IHC3 in luminal A/normal like tumors: **(A/B)** Patients with luminal-A/normal-like tumors (Pre-NACT AIMS) and IHC3 low had an improved iDFS with the addition of palbociclib to ET (MVA HR 0.35 95%CI (0.14-0.90), test for interaction p=0.01). **(C)** Patients with luminal-B/HER2/Basal tumors (Pre-NACT AIMS) IHC3 was not predictive.

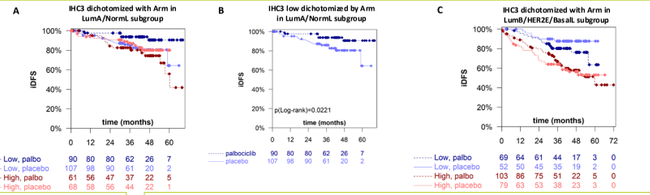


Figure 4. Prognostic significance of Cyclin D1: **(A)** Cyclin D1>1 is prognostic for iDFS (MVA HR 0.62 95%CI [0.41-0.94], p=0.023), LRRFI (MVA HR 0.30 95%CI (0.15-0.63), p=0.001) and OS (MVA HR 0.50 95%CI [0.28-0.89], p=0.019). Similar results when Cyclin D1 was analysed as continuous variable (not shown). **(B)** Cyclin D1>1 has no predictive value.

Figure 5. Role of phospho-RB and Ki67: **(A)** Bubble chart illustrating the correlation between Ki-67 and phospho-RB from resection samples (Spearman correlation coefficient 0.324, p<0.0001). The area of each bubble is proportional to the number of patients. The gray line denotes a linear regression model. **(B)** Ki-67, but not phospho-RB is prognostic at the cut-off points employed in PenelopeB.

Conclusions

- Patients with high Cyclin D1 tumor expression had a favorable prognosis independently from treatment arm.
- Phospho-RB is correlated with Ki-67, but in this analysis yields no additional prognostic or predictive information. High expression of Ki-67 was associated with poor prognosis.
- Patients with both, luminal-A/normal-like tumors and IHC3 low, had an improved outcome when receiving palbociclib in addition to adjuvant ET.
- Biomarkers can identify sub-groups of patients that experienced benefit with palbociclib in the PenelopeB study.

Future Directions

Validation of these findings in an independent cohort will be required to address the clinical benefit of the combination of palbociclib with ET in select patient sub-groups.

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Pathologic complete response and breast-conserving surgery are associated with improved prognosis in patients with early-stage triple-negative breast cancer treated with neoadjuvant chemotherapy

PD15-06

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Background

Neoadjuvant chemotherapy (NACT) is standard of care for patients with triple-negative breast cancer (TNBC). Treatment response, especially pathologic complete response (pCR), is a strong predictive factor for treatment outcome. In the setting of up-front surgery, retrospective data have suggested improved outcome in patients with early TNBC who received breast-conserving surgery (BCS) with adjuvant radiotherapy (BCT) as compared to mastectomy.

Patients and Methods

We identified 2632 patients with early TNBC from the German Breast Group (GBG) meta-database with pooled data from 8 prospective clinical trials. Patients with cT1-2 cN0 and ypN0, available surgery and follow-up data were eligible for this project. A total of 1074 patients from 8 prospective NACT trials were analyzed. Endpoints of interest were locoregional recurrence as first site of relapse (LRR, other sites of recurrence were considered competing events), disease-free survival (DFS) and overall survival (OS); analyses were performed using univariate and multivariate Fine-Gray (for LRR) and Cox models including study, age, cT, surgery type and pCR. For the analyses including pCR as covariable, only patients at risk at the landmark time were evaluated.

Patient characteristics are shown in Table 1. Median follow-up was 64.4 (range 3-224.8) months.

Table 1: Patient characteristics

Parameter	Category	BCS (N=916) N (%)	Mastectomy (N=158) N (%)	Total (N=1074) N (%)	P-value (BCS vs. M)
Age, years	≤50	549 (59.9)	115 (72.8)	664 (61.8)	0.002
	>50	367 (40.1)	43 (27.2)	410 (38.2)	
cT	cT1	278 (30.3)	49 (31.0)	327 (30.4)	0.852
	cT2	638 (69.7)	109 (69.0)	747 (69.6)	
Grading	G1-2	218 (24.1)	42 (26.9)	260 (24.6)	0.481
	G3	685 (75.9)	114 (73.1)	799 (75.4)	
	missing	13	2	15	
Histological type	NST*	773 (84.4)	138 (87.3)	911 (84.8)	0.629
	ILC*	13 (1.4)	2 (1.3)	15 (1.4)	
	other	130 (14.2)	18 (11.4)	148 (13.8)	
ypT	ypT0/is	512 (60.0)	80 (55.2)	592 (59.3)	<0.001
	ypT1/2	341 (39.9)	60 (41.4)	401 (40.1)	
	ypT3/4	1 (0.1)	5 (3.4)	6 (0.6)	
	missing	62	13	75	

*no special type (NST)
*invasive lobular cancer (ILC)

Results

Median age was 48 years, 69.6% of patients had cT2 tumors and 85.3% underwent BCS (Table 1). Patients who underwent mastectomy (N=158) were significantly younger (age ≤ 50 years 72.8% vs. 59.9% for BCT [N=916]; p=0.002). Of the 1074 analyzed patients, 48.8% pCR was reported. There were 94 (8.8%) locoregional events as first site of relapse (Table 2). Upon univariate analysis, absence of pCR (hazard ratio [HR]=2.28; 95%CI 1.44-3.61; p<0.001) and ypT-stage (ypT1-3 vs. ypT0/is HR=1.63 95%CI 1.05-2.52; p=0.028) were significantly associated with LRR, while type of surgery, age and cT-stage were not. Upon multivariate analysis (Table 3), absence of pCR was the only factor associated with increased risk of LRR (HR=2.22; 95%CI 1.38-3.58; p=0.001).

DFS and OS were significantly better in patients with pCR (Fig. 1a&b) and in patients who underwent BCT compared to mastectomy (Fig. 2a&b). In multivariate analyses (Table 4), BCT was associated with a significantly better DFS and OS compared to mastectomy (DFS: HR=0.51; 95%CI 0.36-0.72; p<0.001) and OS (HR=0.43; 95%CI 0.27-0.68; p<0.001), whereas absence of pCR was associated with significantly worse DFS and OS (DFS: HR=2.43; 95%CI 1.78-3.31; p<0.001; and OS: HR=3.15; 95%CI 1.94-5.10; p<0.001).

Fig. 1a Disease-free survival according to pCR-status

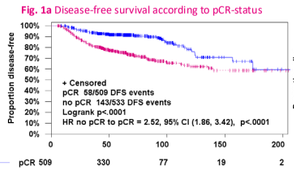


Fig. 1b Overall survival according to pCR-status

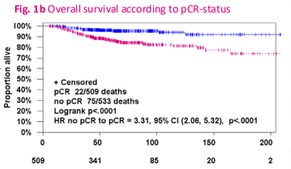


Fig. 2a Disease-free survival according to surgery

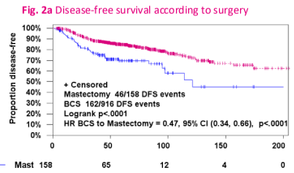


Fig. 2b Overall survival according to surgery

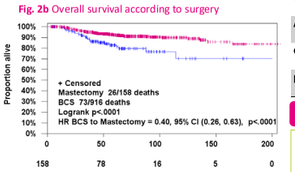


Table 2: Listed events

Event	N	N in %
Loco-regional	94	8.8
Distant	77	7.2
Secondary malignancy	21	2.0
Death	16	1.5

Table 3: Locoregional recurrence rates (LRR) and results of multivariate Cox-regression analysis

Parameter	Category	5-year LRR (%)	Hazard ratio (95%CI)	P-value
Surgery type	BCS	6.71 (5.11-8.60)	1.213 (0.673-2.187)	0.5209
	mastectomy	12.31 (7.17-18.93)		
Age	≤50	7.59 (5.60-9.97)	1.090 (0.709-1.675)	0.6949
	>50	7.25 (4.85-10.27)		
cT	cT1	6.66 (4.14-9.98)	1.088 (0.622-1.902)	0.7676
	cT2	7.74 (5.85-9.97)		
ypT (3 groups)	ypT0/is	4.88 (3.24-7.01)	not included	not included
	ypT1	8.64 (5.68-12.36)		
	ypT2/3	13.34 (6.99-21.75)		
pCR (landmark)	no pCR	10.11 (7.57-13.06)	2.223 (1.381-3.578)	0.0010
	pCR	3.57 (2.12-5.61)		

Table 4: Disease-free survival + overall survival

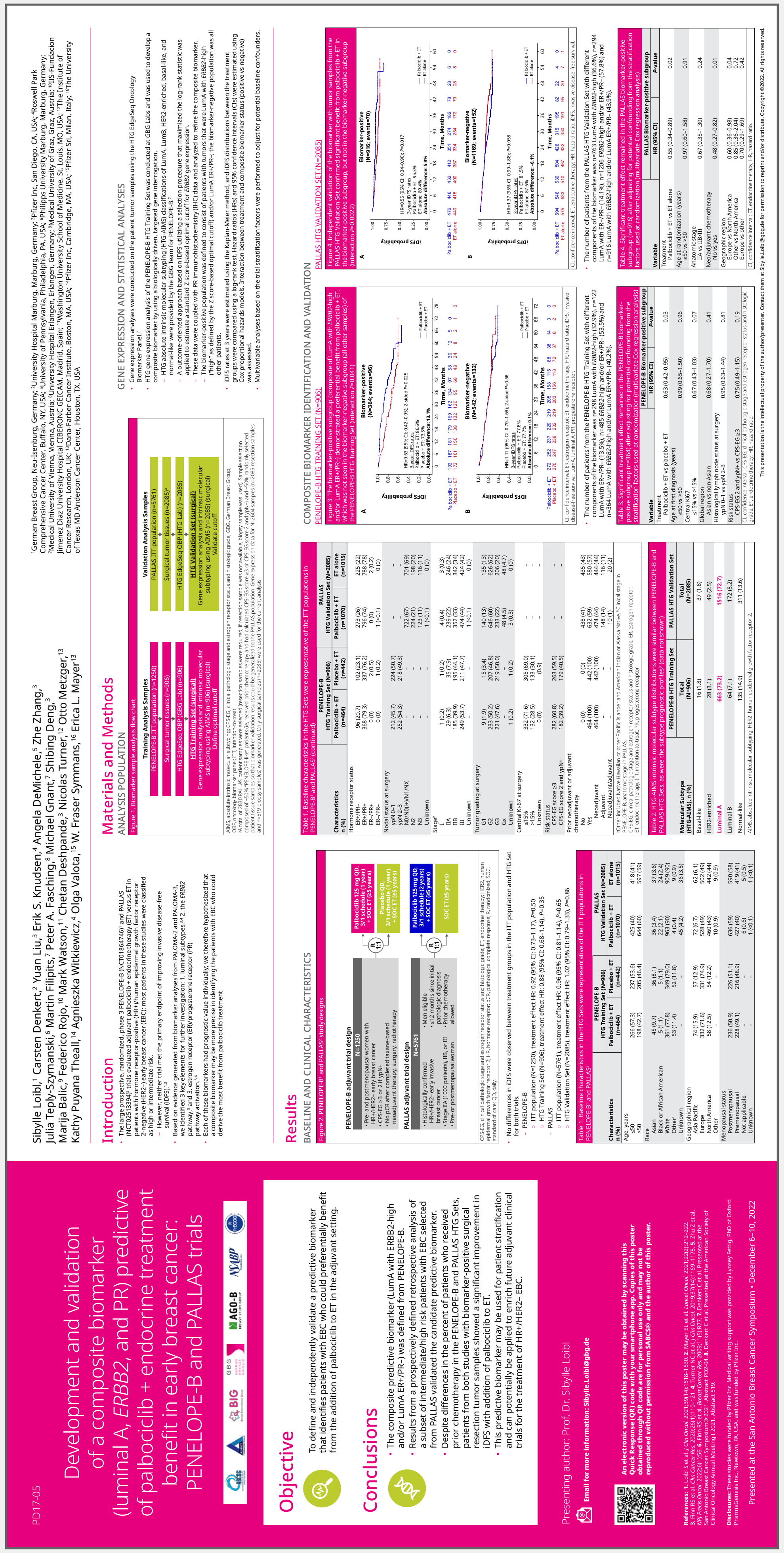
Parameter	Category	Multivariate Cox-regression analysis - DFS Hazard ratio (95%CI)	P-value	Multivariate Cox-regression analysis - OS Hazard ratio (95%CI)	P-value
Surgery type	BCS mastectomy	0.51 (0.36-0.72)	<0.001	0.43 (0.27-0.68)	<0.001
Age	≤50 >50	1.03 (0.77-1.37)	0.855	1.01 (0.67-1.53)	0.948
cT	cT1 cT2	0.71 (0.50-1.01)	0.058	0.76 (0.46-1.28)	0.306
pCR (landmark)	no pCR pCR	2.43 (1.78-3.31)	<0.001	3.15 (1.94-5.10)	<0.001

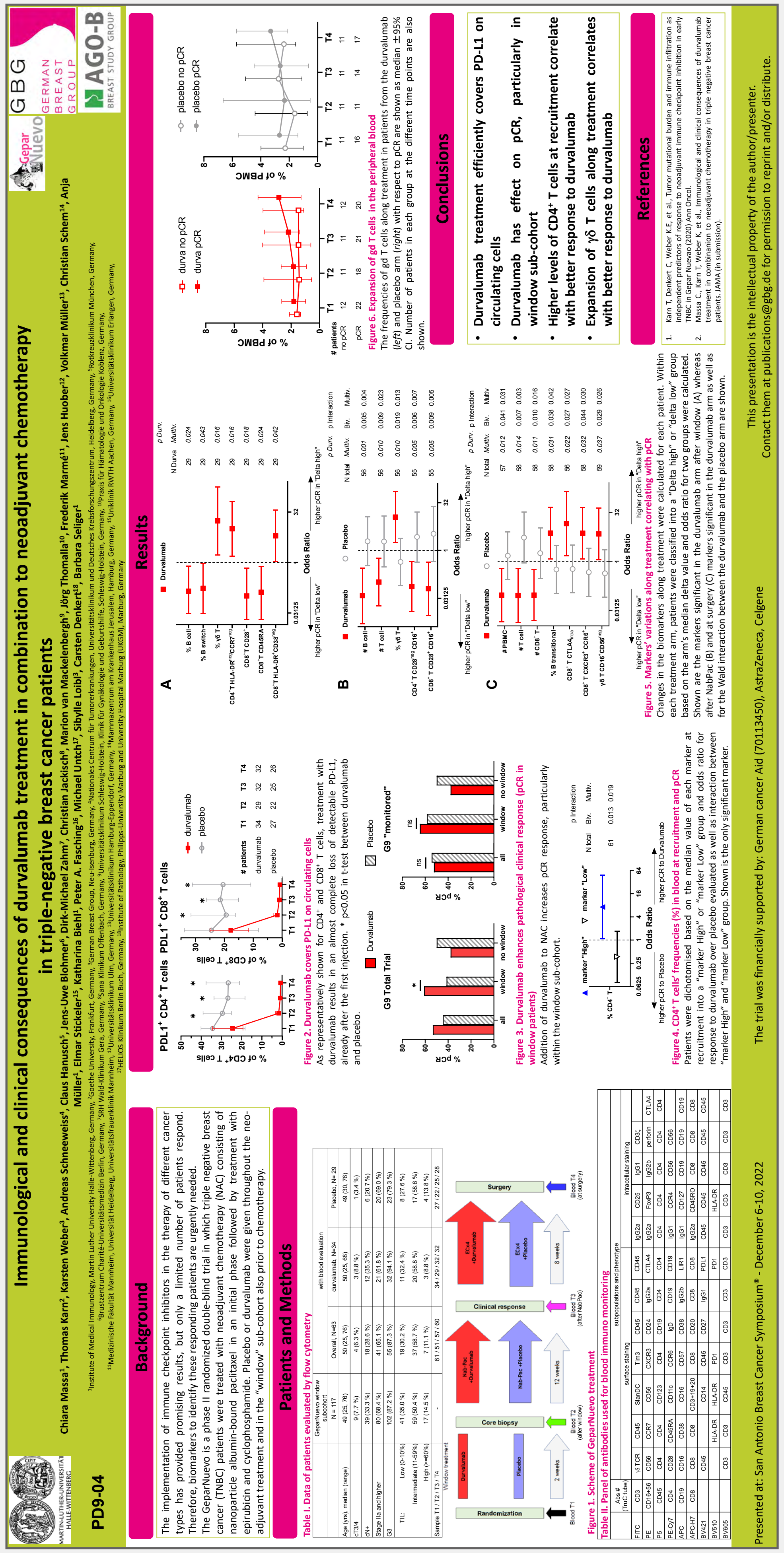
Conclusions

In this retrospective analysis from the GBG meta-database, treatment response, e.g. pCR, was the main determinant of locoregional recurrence in patients with early stage TNBC treated with NACT, while type of surgery had no impact. BCT was associated with improved DFS and OS compared to mastectomy, which may reflect favorable patient selection.

Presented at: San Antonio Breast Cancer Symposium® - December 6-10, 2022

Corresponding Author: PD Dr. med. David Krug (david.krug@uksh.de)


PD17-05
Development and validation of a composite biomarker (luminal A, ERBB2, and PR) predictive of palbociclib + endocrine treatment benefit in early breast cancer: PENELOPE-B and PALLAS trials
Introduction
Materials and Methods
Results
Objective
Conclusions
Presented at the San Antonio Breast Cancer Symposium - December 6-10, 2022


PD9-04
Immunological and clinical consequences of durvalumab treatment in combination to neoadjuvant chemotherapy in triple-negative breast cancer patients
Background
Patients and Methods
Results
Conclusions
References
GBG German Breast Group
Presented at: San Antonio Breast Cancer Symposium® - December 6-10, 2022
The trial was financially supported by: German cancer Aid (70113450), AstraZeneca, Celgene
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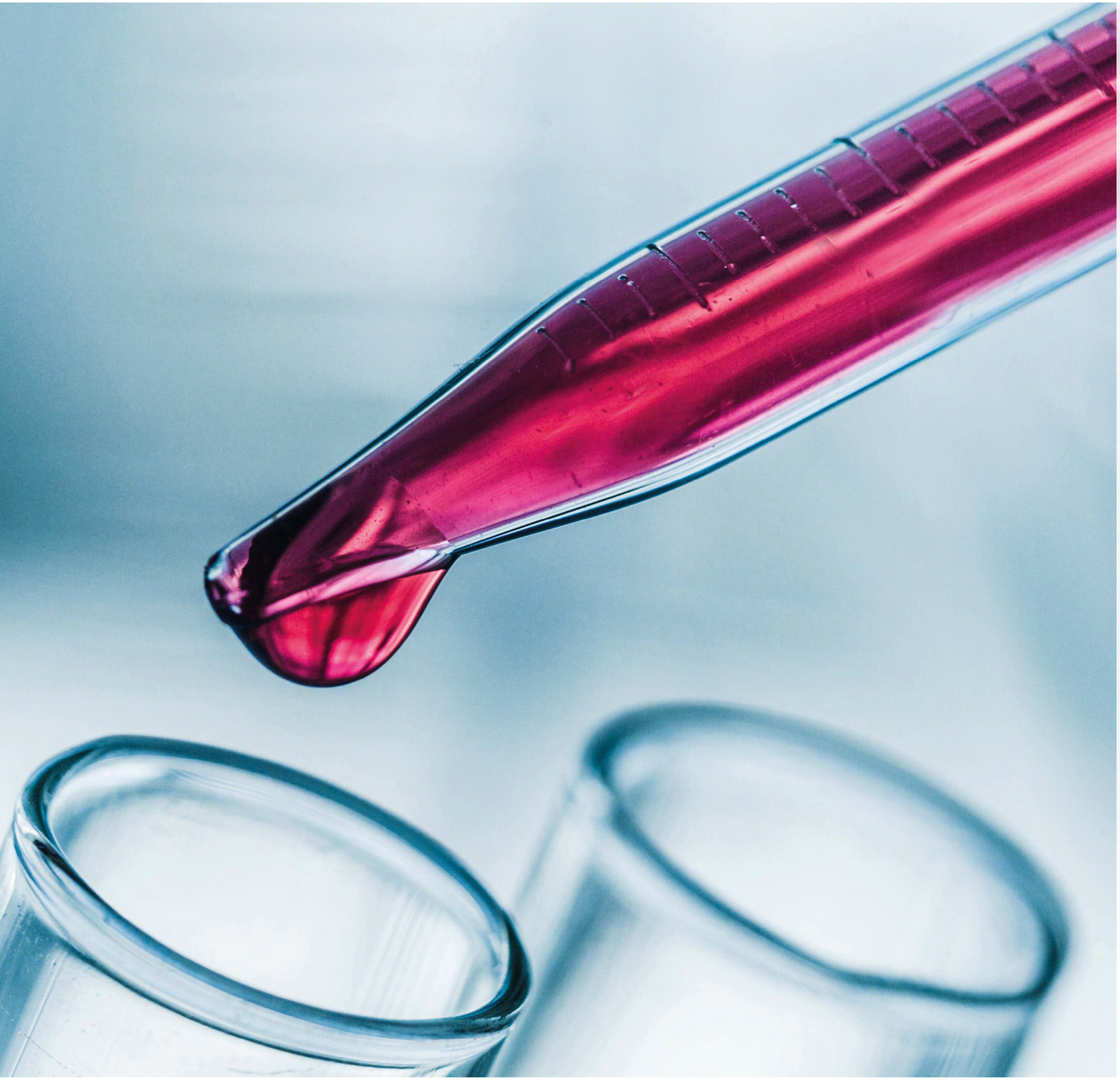

New Study Concepts and Methodologies

GBG 110: Cambria-1
Interview with Univ.-Prof. Dr. Elmar Stickeler, coordinating investigator of the Cambria-1 trial

A phase III, open-label, randomised study to assess the efficacy and safety of switching to AZD9833 (a next generation, oral SERD) vs continuing standard endocrine therapy (aromatase inhibitor or Tamoxifen) in patients with HR+/HER2- early breast cancer and an intermediate or high risk of recurrence who have completed definitive locoregional therapy and at least 2 years of adjuvant endocrine therapy without disease recurrence

Univ.-Prof. Dr. Elmar Stickeler
UKA | Universitätsklinikum Aachen

1. Cambria-1 study will use Camizestrant (AZD9833) as an oral, next generation selective estrogen receptor degrader (SERD). What is the difference between Camizestrant and other SERDs?

Selective estrogen receptor down-regulators or degraders represent one of three major classes of endocrine therapeutic drugs with different mechanisms of action. SERDs are high-affinity competitive antagonists of estrogen receptor (ER) that immobilize and target ERα for proteasome-dependent degradation. In contrast to Fulvestrant, which must be administered i.m., Camizestrant is a potent, orally delivered, non-steroidal SERD and a pure ER antagonist, that was developed to improve ER degradation and avoid an ER agonism, which was observed with the first-generation of oral SERDs. In addition, the drug demonstrated anti-cancer activity in preclinical models, including those with ER-activating mutations.

2. In which trials was Camizestrant used, and can you comment briefly on the results?

Camizestrant was evaluated in the multi-part, open-label phase I SERENA-1 (NCT03616587) trial in ER+, HER2- advanced breast cancer. Despite extensive pre-treatment, including chemotherapies, CDK4/6 inhibitor and Fulvestrant usage, Camizestrant given alone or in combination with Palbociclib exhibited encouraging clinical activity and a favourable toxicity profile with no dose interruptions or reductions due to a Camizestrant-related adverse event. In addition, no grade ≥3 adverse events were observed.

The phase II SERENA-2 trial compared Camizestrant 75mg and 150mg dose levels vs Fulvestrant 500mg. In this study, 240 patients with HR+/HER2- advanced breast cancer were included with recurrence or progression on at least one line of endocrine treatment, no more than one line of chemotherapy (20%) and one line of endocrine therapy in advanced breast cancer setting. 58% of patients had visceral disease and 36% an ESR1 mutation, and 69% of patients were in the second line situation with 50% prior CDK4/6 inhibitor therapy. Camizestrant met, for both dosages, the primary endpoint, demonstrating a statistically significant and clinically meaningful improvement of PFS with 7.2 months (75mg) and 7.7 months (150mg) versus 3.7 months with Fulvestrant (with hazards ratio (HR) of 0.58 and 0.67, respectively). This benefit was observed across all pre-specified subgroups including post CDK4/6 inhibitor treatment, visceral disease, as well as ER-driven disease, and it underlines the potential of this drug.

3. What is the rationale for setting up Cambria-1?

For patients with HR+/HER2- early breast cancer, an ongoing and clinically relevant risk of disease recurrence over the next 5-10 years exists despite the implementation of risk adapted adjuvant endocrine treatment strategies. These strategies include aromatase inhibitor usage in postmenopausal women, the LHRH combination with aromatase inhibitor in premenopausal patients, and the recent approval of Abemaciclib in the high risk situation. Furthermore, we have evidence that a switch to more effective therapies can create substantial benefit for patients at risk in the adjuvant setting, underlining the medical need to explore better substances for extended therapy. The Cambria-1 phase III study will therefore evaluate the potential for extended adjuvant therapy with Camezistrant to improve the clinical outcome in HR+/HER2- early breast cancer in the intermediate and higher risk situation.

4. Which patients and how many will be enrolled in Cambria-1?

As mentioned before, patients with an HR+/HER2- early breast cancer with an intermediate to high risk of recurrence after completed loco-regional therapy and 2 to 5 years of standard adjuvant endocrine therapy including CDK4/6 inhibitor without disease recurrence will be included. The risk estimation is based on clinical and genomic features. Approximately 4,300 patients will be enrolled in the trial.

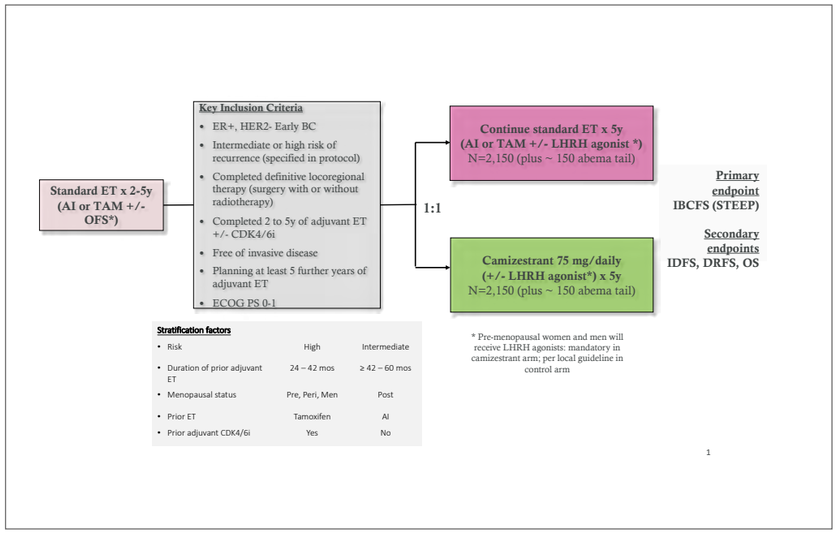

Figure 1: Cambria-1 study design

IN COOPERATION WITH

GBG 112: PREcoopERA
Interview with Prof. Dr. Sibylle Loibl, coordinating investigator of the PREcoopERA trial

A Window-of-Opportunity (WOO) trial of giredestrant +/- LHRHa versus anastrozole + LHRHa in premenopausal patients with estrogene receptor (ER) positive/HER2-negative early breast cancer

Prof. Dr. Sibylle Loibl
GBG | German Breast Group
Neu-Isenburg

This is a randomized, multicenter, open-label, three-arm, WOO trial to evaluate the activity and safety of giredestrant (A) vs. giredestrant plus triptorelin (B) vs. anastrozole plus triptorelin (C). The randomization profile demonstrates a 2 to 2 to 1 distribution of giredestrant to giredestrant plus triptorelin to anastrozole plus triptorelin arm. The primary endpoint of the study will be the change of the well-established proliferation biomarker Ki-67 after four weeks of treatment compared with baseline.

1. Could you describe the hypothesis that will be tested in this Window of Opportunity trial? What is the biological background?

In this WOO trial, we aim to test the hypothesis that the new oral selective estrogen receptor degrader (SERD) giredestrant with triptorelin offers higher biological activity as compared to anastrozole with triptorelin. This comparison will proceed in the preoperative setting in premenopausal patients with ER-positive/HER2- negative early breast cancer. Further, we aim to demonstrate that the biological activity of giredestrant alone is similar to the combination of giredestrant with triptorelin in order to support the hypothesis that using LHRH agonist with giredestrant for treatment of PREcoopERA trial patients may not be necessary.

2. What is the primary objective of this trial?

The primary objectives of this trial are to determine if four weeks of giredestrant plus triptorelin provides greater anti-proliferative activity than anastrozole plus triptorelin among premenopausal patients with ER-positive/HER2-negative localized breast cancer. Furthermore, it is interesting to determine if four weeks of giredestrant without triptorelin provides anti-proliferative activity that is similar to giredestrant plus triptorelin.

The primary endpoint of the study will be the change of Ki-67 between pre-treatment tumor biopsy and a post-treatment tumor re-biopsy on day 29 (+/-3 days). The change of Ki-67 will be represented in a Ki-67-labeling index that demonstrates the percentage of immunostaining cells measured by IHC in central laboratory.

3. Which patients qualify for PREcoopERA?

In the PREcoopERA trial, premenopausal patients with histologically confirmed ER-positive/HER2-negative untreated breast, invasive breast cancer (stage I, stage II or operable stage III and excluded T4), with available tumor tissue and baseline Ki-67 will be enclosed.

4. The planned study design looks very interesting. Can you please tell us about the planned main study procedures?

The study consists of a screening period of approximately five weeks to determine eligibility, a window-of-opportunity phase of four weeks (29 days ±3days), followed by re-biopsy or surgery. Finally, an end-of-study visit is planned 29 days ±3 days after re-biopsy or surgery.

5. How many patients are planned for the recruitment?

For the recruitment of approximately 200 patients, 40 -50 sites will be included.

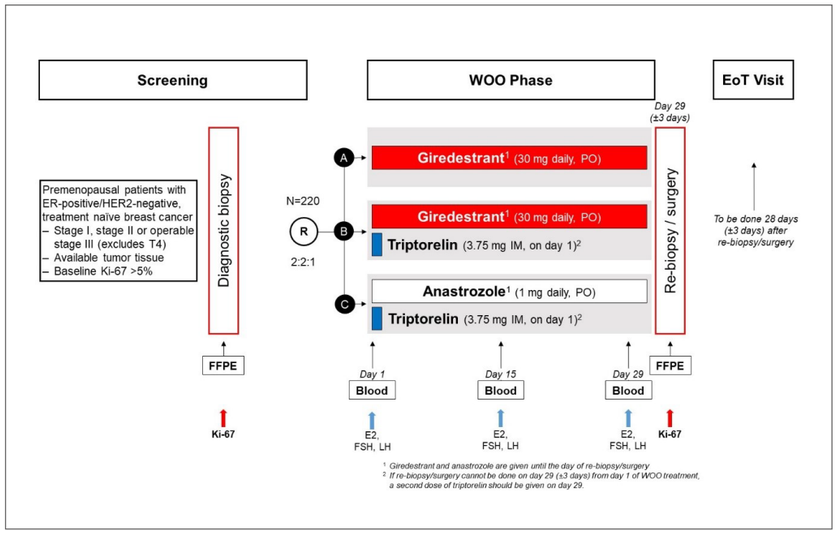

Figure 1: PREcoopERA study design

NeoRad

NeoRad
Interview with Univ.-Prof. Dr. Wilfried Budach, study chairman deputie of the NeoRad trial

A prospective, randomized multicenter-phase III trial to address the optimal timing of radiotherapy in patients, who are candidates for neoadjuvant chemotherapy.

Univ.-Prof. Dr. Wilfried Budach
UKD | Universitätsklinikum Düsseldorf

1. The standard of care for high-risk breast cancer consists of neoadjuvant chemotherapy and surgery followed by postoperative whole breast/chest wall irradiation. Please describe the background of NeoRad.

NeoRad is a prospective, randomised multicenter-phase III trial investigating the potential advantage of preoperative radiotherapy compared to postoperative standard radiotherapy in high risk breast cancer patients, who received neoadjuvant chemotherapy +/- antibody therapy. The hypothesis is that preoperative radiotherapy improves disease free survival by obtaining earlier locoregional clearance of tumor cells and improved systemic clearance by triggering an immune response. Radiation induced tumor cell death has been shown to be particularly immunogenic in preclinical models. In a retrospective re-analysis of a large randomized trial testing postoperative radiotherapy after mastectomy (DBCG82), a significantly larger survival benefit in the radiotherapy arm was observed, if the tumor contained CD8 positive immune cells in the initial biopsy. This effect is expected to be larger, if preoperative radiotherapy is used. In addition, preoperative radiotherapy is anticipated to results in better cosmetic results, especially in patients, who undergo immediate breast reconstruction.

2. What are the primary objectives and end-point?

The primary objective of the trial is to prove the superiority of preoperative radiotherapy terms of disease-free survival (DFS) at 10 years follow up.

3. Which sample size is planned and how much sites planned to participate in this study?

The hypotheses is that preoperative radiotherapy after NACT will improve 10-year DFS from 70% in control arm to 76.5% in the experimental arm of the trial (HR=0.75). In order to detect a difference of this magnitude and a power of 80%, a recruitment time of 4 years and in additional follow up of at least 6 years, 379 events and a sample size of 1826 patients, 913 in each arm using a 1:1 randomisation, are required to reject the null hypothesis of no improvement on a two-sided type I error level of 0.05. A cumulative drop-out rate of 10% in 10 years is included in these calculations. The participation of approximately 40 breast cancer centers is planned.

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

In the radiation oncology community, the benefits of preoperative radiotherapy are well known, since preoperative radiotherapy is standard of care in rectal and esophageal cancer and also an established option in lung cancer and soft tissue sarcomas. Accordingly, most radiation oncologist will be in favor of the tested concept. Many breast surgeons are not accustomed to the use of preoperative radiotherapy and may have reservation, because of potentially more wound healing complications. However, the available experience in breast cancer and the large experience in rectal and esophageal cancer indicate that this is a minor problem, if surgery is performed 3 - 6 weeks after completion of radiotherapy. Gynecologists and Medical Oncologist may express the apprehension that due to the expected increased pathological complete response (pCR) rate after preoperative radiotherapy, less patients could qualify for postneoadjuvant systemic treatment. However, data from phase II trials indicate that pCR after preoperative radiotherapy after neoadjuvant chemotherapy also indicates superior clinical outcome. To minimize possible disadvantage from this consideration, biopsies from the tumor and suspected involved lymph nodes are intended before preoperative radiotherapy. In case of residual tumor, patients qualify for postneoadjuvant treatments even in case of pCR after preoperative radiotherapy.

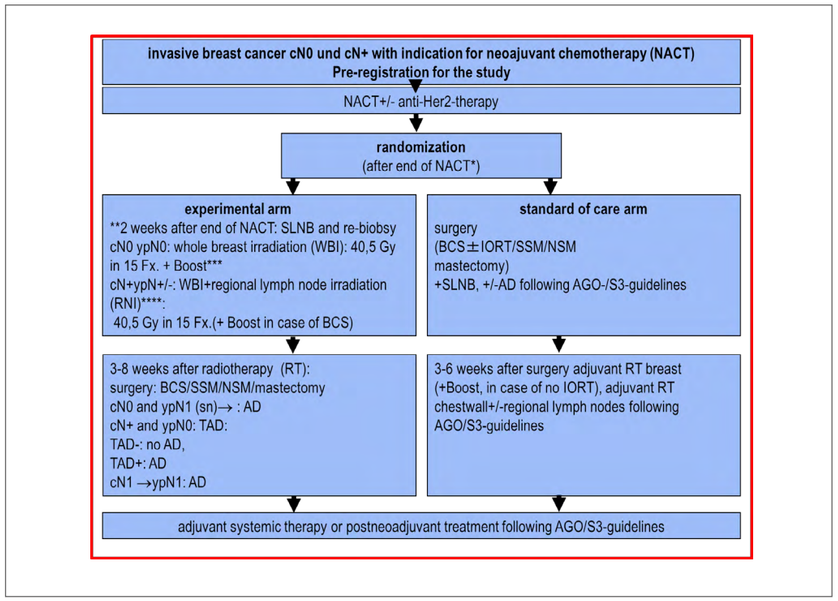

Figure 1: NeoRad study design

Recruiting Studies

GBG 105: GeparPiPPa

Phase II neoadjuvant study of Trastuzumab, Pertuzumab with or without Inavolisib, a PI3K inhibitor, in early breast cancer patients with HER2-positive, HR-positve and *PIK3CA* mutation

NCT05306041

GeparPiPPa is a randomized, open-label, phase II trial comparing neoadjuvant endocrine therapy in combination with trastuzumab, pertuzumab +/- the PI3K inhibitor inavolisib in patients with HER2-positive, HR-positive, *PIK3CA* mutant early breast cancer.

Background

PIK3CA mutations can be found in about 20-30% of HER2+ breast cancer with a higher rate in HR+ than HR-/HER2+. It could be demonstrated that the pCR rate with standard treatment is lower in patients in *PIK3CA* mutant HER2+ breast cancer, especially in HR+ breast cancer (Loibl et al. Ann Oncol 2016).
The rationale of the GeparPippa study is based on experimental and clinical evidence concerning the alteration of the PI3K pathway. The PI3K pathway is frequently altered in HR+ breast cancer and seems to be involved in resistance to endocrine therapies. Approximately 40% of HR+ breast cancers harbor a *PIK3CA* mutation leading to estrogen receptor independent growth (Miller et al. J Clin Invest 2010, Crowder et al. Cancer Res 2009). Therefore, combination therapies targeting both estrogen receptor and PI3K pathways may be warranted.

Study design and objectives

Patients with *PIK3CA* mutant breast cancer are randomized in a 1:1 ratio to receive neoadjuvant endocrine therapy in combination with dual anti-HER2 blockade consisting of ready-to-use fixed-dose combination of pertuzumab and trastuzumab as subcutaneous (PH-FDC SC) formulation q3w for 6 cycles (18 weeks) with inavolisib (6 cycles) or without inavolisib. Endocrine therapy consists of either tamoxifen 20mg or an aromatase inhibitor +/- GnRH analogue for premenopausal women and men.
All patients will undergo surgery or biopsy after completing study therapy to assess pCR rate. In case of ycT0 and no tumor residuals in the biopsy, it is recommended to undergo surgery; in case of tumor residuals in the biopsy, further ((neo-) adjuvant) treatments may be given, which will be captured within a registry.
Primary objective of GeparPiPPa is to compare pathological complete response (pCR=ypT0/is ypN0) rates between both study arms.
GeparPiPPa study will also address translational research questions to evaluate potential new biomarkers for HER2+/HR+ breast cancer and its association with responses and resistance to therapies.

Study report

The GeparPiPPa recruitment will start in January 2023. The planned enrollment period is approximately 36 months.

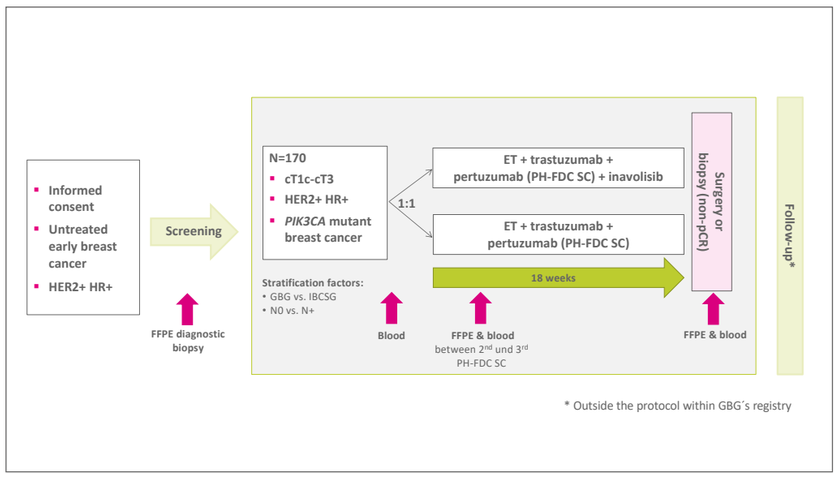

Figure 1: GeparPiPPa study design

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Clinical Project Management
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COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

COORDINATING INVESTIGATOR:
PD Dr. Mattea Reinisch
Evang. Klinikum Essen-Mitte

GBG 103: TruDy / DESTINY-Breast05

A Study of Trastuzumab Deruxtecan (T-DXd) Versus Trastuzumab Emtansine (T-DM1) in High-risk HER2-positive Participants With Residual Invasive Breast Cancer Following Neoadjuvant Therapy

NCT04622319

DESTINY-Breast05 (TruDy-GBG103; AGO-B-050; NSABP B-60; SOLTI-2001) is a global, multicenter, randomized, open-label, phase III study of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients with high-risk human epidermal growth factor 2 (HER2)-positive primary breast cancer (BC) who have residual invasive disease in breast or regional lymph nodes following neoadjuvant chemotherapy (NACT).

Background

Although the KATHERINE study (T-DM1 vs. trastuzumab) showed a clinically meaningful improvement in iDFS in the post neoadjuvant setting, further unmet medical need exists in HER2+ BC patients who do not achieve a pCR following neoadjuvant treatment.
While the overall 3-year iDFS rate in the KATHERINE study was 88.3% for T-DM1 treated subjects, there were subgroups with 3-year iDFS rates for T-DM1 that were considerably lower. Among these subgroups, the 3-year iDFS rates for patients with inoperable disease were 76.0% (24.9% of T-DM1 patients; hazard ratio (HR)=0.54), 83.0% for node-positive patients (46.2% of T-DM1 patients; HR=0.52) and 82.1% for hormone receptor (HR)-negative patients (28.1% of T-DM1 patients; HR=0.50) (von Minckwitz et al. N Engl J Med 2019).
On the other hand, lymph node metastasis is widely known to be a poor prognostic factor (Harbeck et al. 2019, National Comprehensive Cancer Network (NCCN) Guideline Breast Cancer, Version 2. 2020), and long-term follow-up results in the APHINITY study of the anti-HER2 therapy pertuzumab as adjuvant therapy identified a delayed risk of recurrence in the node-positive group (6-year iDFS: pertuzumab group 87.9%, trastuzumab 83.4%) compared with the node-negative group (6-year iDFS: pertuzumab group 95.0%, trastuzumab 94.9%) (von Minckwitz et al. N Engl J Med 2017; Piccart et al. J Clin Oncol 2021). For this reason, patients with node-positive breast cancer will be included in the target population for the DESTINY-Breast05 study, while patients with nodal-negative disease are excluded.
It is recognized that patients who do not achieve pCR after appropriate NACT are at a higher risk of disease recurrence. This is a clinical setting where the application of more effective therapies would have a potentially large absolute impact on patient outcomes and can be considered an area of unmet medical need. In addition, compared to T-DM1, T-DXd has a novel mechanism of cytotoxic action (topoisomerase I inhibitor vs. tubulin polymerization inhibitor), a higher drug-to-antibody ratio with better plasma stability, and a bystander cytotoxic activity due to higher cell membrane permeability (Ogitani et al. Cancer Sci 2016; Takegawa et al. Int J

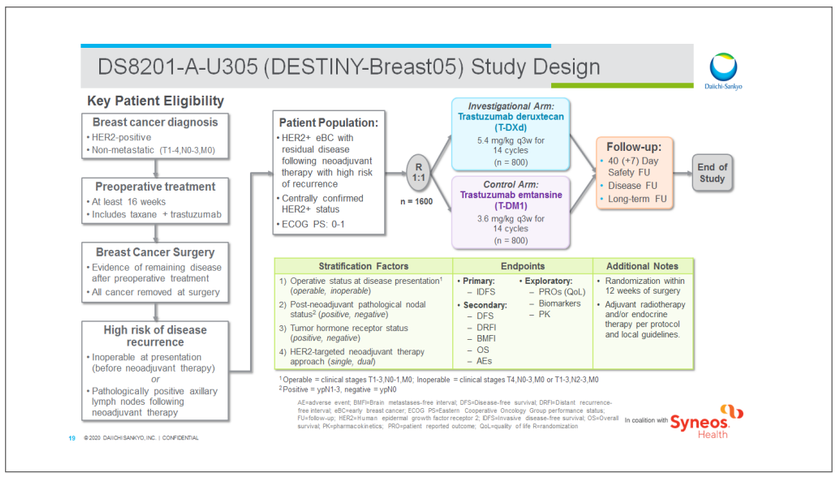

Figure 1: TruDy study design

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Cancer 2019). In patients with unresectable and metastatic BC, T-DXd has demonstrated high, durable response rates after treatment with T-DM1 (Modi et al. N Engl J Med 2020). Furthermore, T-DXd showed a statistically significant improvement in progression-free survival vs. T-DM1 (HR=0.28) in patients with HER2+ metastatic BC previously treated with trastuzumab and taxane (Cortés et al. Ann Oncol 2021).
Based on the differentiating features of T-DXd and the anticancer activity in metastatic BC patients after failure of T-DM1, T-DXd is anticipated to be effective even in the high-risk adjuvant subpopulation in which T-DM1 had not demonstrated compelling efficacy.

Study design and objectives
Patients (adults ≥18 years) with high-risk HER2+ BC and residual disease in the breast or axillary lymph nodes following NACT are eligible. High-risk disease is defined as inoperable at disease presentation (cT4, cN0-3, M0 or cT1-3, cN2-3, M0) or operable at presentation (cT1-3, cN0-1, M0) with positive pathological node status (ypN1-3) after NACT. HER2+ expression must be centrally confirmed prior to randomization. Further key inclusion criteria are left ventricular ejection fraction (LVEF) ≥50% prior to randomization, an interval of no more than 12 weeks between the date of last surgery and the date of randomization, and adequate organ function before randomization.
This study is designed to randomize at least 1,600 patients in a 1:1 ratio to receive T-DXd or T-DM1. Randomization is stratified by i) operative status at disease presentation, prior to NACT (operable cT1-3, cN0-1, M0 vs inoperable cT4, cN0-3, M0 or cT1-3, cN2-3, M0), ii) HR status (positive vs negative), iii) post-NACT pathologic nodal status (ypN1-3 vs ypN0), and iv) HER2-targeted NACT (single vs dual). Patients receive assigned study drug for a total of 14 cycles of treatment.
The primary objective is to compare invasive disease-free survival (iDFS) between T-DXd and T-DM1 treatment arms in this population. Key secondary objective includes evaluation of DFS with T-DXd treatment as compared to T-DM1. Further secondary endpoints are to evaluate overall survival (OS), distant recurrence-free interval (DRFI) and brain metastases-free interval (BMFI) with T-DXd treatment as compared to T-DM1; and to evaluate safety, pharmacokinetics, and immunogenicity of T-DXd. Exploratory objectives include assessment of correlations between biomarker status and efficacy and/or safety, evaluation of health economics, and outcomes research endpoints including patient reported health-related quality of life, symptoms, physical functioning, and healthcare resource utilization for T-DXd compared to T-DM1.

Study report:
The TruDy/Destiny-Breast05 worldwide recruitment started in December 2020 and on 13th of September 2021 in Germany. As of 31st December 2022, there are 31 patients enrolled in the study (global 866 patients). Global enrollment is targeted to be completed in 2024, and the end of study is estimated for the year 2027.

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

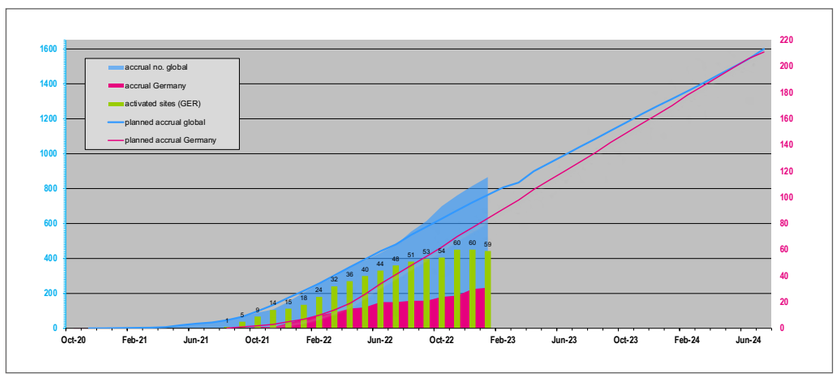

Figure 2: TruDy recruitment as of 31st December 2022

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

NSABP Foundation, Inc.

SOLTI INNOVATIVE BREAST CANCER RESEARCH

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

GBG 102: SASCIA

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

NCT04595565

SASCIA is a prospective, multi-center, randomized, open-label, parallel group, phase III study to evaluate the efficacy and safety of post-neoadjuvant treatment with sacituzumab govitecan compared to treatment of physician's choice with capecitabine or platinum-based chemotherapy or observation in primary HER2-negative breast cancer patients with residual disease after standard neoadjuvant treatment.

Background
Neoadjuvant chemotherapy (NACT) allows monitoring of tumor response to treatment and a pathological complete response (pCR) is associated with superior survival. This association is strongest in the most aggressive subtype, i.e., in patients with triple-negative breast cancer (TNBC). Patients with TNBC not achieving a pCR have a 5-year event-free survival rate of about 50% (Hahnen et al. JAMA Oncol 2017; Sikov et al. J Clin Oncol 2015; Petrelli et al. Breast Cancer Res Treat 2014). The association between pCR and prognosis is less pronounced in hormone receptor (HR)-positive/HER2-negative patients. However, the CPS+EG scoring system for prognosis after NACT, taking into account clinical stage, post treatment pathological stage, estrogen receptor status and grade allows to select patients at high risk of relapse for post-neoadjuvant therapy (Marmé et al. Eur J Cancer 2016). Patients with TNBC not achieving a pCR as well as those with HR-positive/HER2-negative tumors and a CPS+EG score of ≥3 or 2 with nodal involvement after NACT (ypN+) are at a high risk of relapse, warranting additional experimental therapies after NACT.
There is proof of concept that post-neoadjuvant therapy can significantly improve survival. Several randomized trials in patients with residual tumor after NACT reported on disease-free survival (DFS) and overall survival (OS). The CREATE X study demonstrated a significant improvement in DFS and OS in the overall population, which was confined to the TNBC subgroup (Masuda et al. N Engl J Med 2017). The phase III KATHERINE study showed an improved invasive DFS (iDFS) in HER2-positive patients without pCR after trastuzumab +/- pertuzumab treated postoperatively with T-DM1 compared to trastuzumab (von Minckwitz et al. N Engl J Med 2019).
The post-neoadjuvant approach, in contrast to the adjuvant setting (Piccart-Gebhart et al. J Clin Oncol 2016; von Minckwitz et al. N Engl J Med 2017), avoids overtreatment and limits sample size and risk of trial failure from lack of events by selecting a high-risk population. In contrast to neoadjuvant trials, which so far have mainly been powered for pCR rates, post-neoadjuvant trials result in a survival endpoint that is relevant for patients. Thus, post-neoadjuvant trials are probably a more appropriate setting to introduce new therapies into clinical routine for early breast cancer.
Sacituzumab govitecan is an antibody-drug conjugate composed of a humanized monoclonal antibody which binds to Trop-2 (trophoblast cell-surface antigen-2). SN-38, an active metabolite of irinotecan and a topoisomerase I inhibitor, is covalently bound to the antibody by a hydrolysable linker. Due to the characteristics of the linker connecting SN-38 to the antibody, not only can sacituzumab govitecan kill tumor cells expressing Trop-2, but it can also kill adjacent tumor cells (bystander effect). Sacituzumab govitecan has demonstrated unprecedented activity in heavily pretreated patients with metastatic triple-negative (TNBC) and HR-positive/HER2-negative breast cancer, even after prior immune-checkpoint inhibitors or CDK4/6 and mTOR inhibitors (Bardia et al. J Clin Oncol 2018; Bardia et al. N Engl J Med 2019). The phase III ASCENT trial led to the approval of sacituzumab govitecan (10mg/kg, days 1, 8 of 21-day cycles) in patients with advanced or metastatic TNBC who have received ≥2prior systemic therapies, at least one of them for metastatic disease (Bardia et al. N Engl J Med 2021). The phase III TROPiCS-02 study in advanced HR-positive breast cancer is ongoing (Rugo et al. Future Oncology 2020). As sacituzumab govitecan constitutes a compound with strong activity against highly resistant clones of metastatic breast cancer, it may represent a new option against the resistant residual disease after standard NACT regardless of HR status. Therefore, the SASCIA study will evaluate the activity of sacituzumab govitecan in HER2-negative patients at high risk of relapse after NACT.

SASCIA

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Study design and objectives

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

Patients will be allocated (1:1) to receive either sacituzumab govitecan (days 1, 8 q3w for eight cycles; experimental arm) or treatment of physician's choice (TPC, defined as capecitabine or platinum-based chemotherapy for eight cycles or observation/endocrine therapy; control arm). The implementation of protocol amendment 1 (planned Q1/2023) allows the use of pembrolizumab as monotherapy in the TPC arm in patients with TNBC who received pembrolizumab as neoadjuvant therapy (according to the approval). Adjuvant pembrolizumab may be given until the completion of radiotherapy and before randomization in the SASCIA trial. Patients with known g*BRCA1/2* mutation are not allowed to participate in the trial if adjuvant olaparib is indicated or planned.

Randomization will be stratified by HR status (HR-negative vs HR-positive) and ypN (ypN+ vs ypN0). In patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines for patients in the TPC arm. The start of endocrine therapy will be at the discretion of the investigator; however, it will be encouraged to start after surgery/radiotherapy in patients without additional cytotoxic agents.

Primary objective of the SASCIA trial is to compare iDFS between patients treated with sacituzumab govitecan versus treatment of physician's choice; primary endpoint is iDFS. Secondary objectives and endpoints include comparison of OS, distant DFS and locoregional recurrences-free interval between both treatment groups, iDFS and OS in the stratified subgroups, iDFS and OS in exploratory subgroups, safety and compliance, patient-reported outcomes and quality of life. The SASCIA study will also address translational research questions such as exploring circulating tumor DNA (ctDNA) dynamics as early predictors of ctDNA clearance in ctDNA-positive patients, and the predictive value of markers (including genetic and immune markers) for sacituzumab govitecan.

One interim analysis for overwhelming efficacy will be performed when 264 events (2/3 of the total events) have occurred.

Study report:

SASCIA recruitment started on November 10, 2020, in Germany. As of December 31st, 2022, there are 738 patients enrolled in the study. The other European recruiting countries are Spain, France, Austria, Ireland and Switzerland. The end of recruitment is planned for Q1/2024.

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

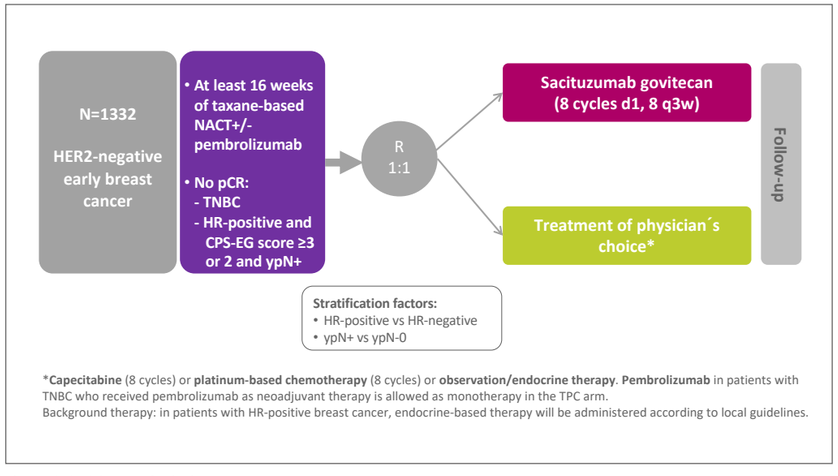

Figure 1: SASCIA study design

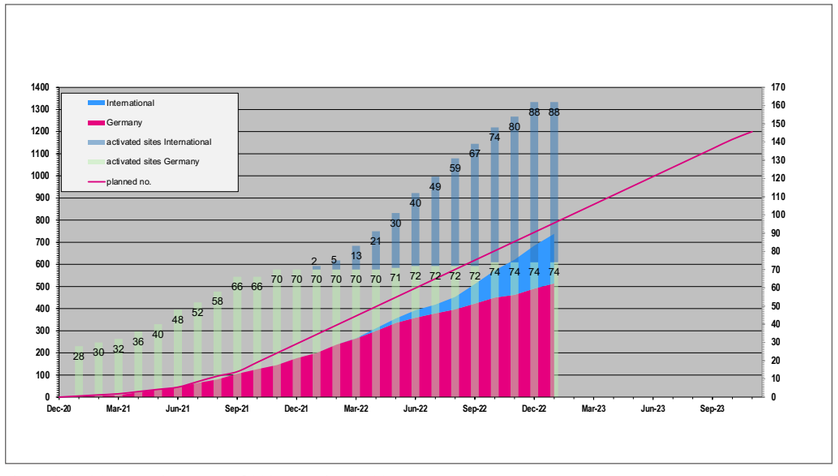

Figure 2: SASCIA recruitment as of 31st December 2022

COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

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

GBG 100: APPALACHES

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

NCT03609047

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

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

Study design and objectives:
Women or men aged ≥70 years with stage II or stage III, early invasive breast cancer fulfilling all inclusion criteria will be centrally registered at EORTC after written informed consent has been obtained. Randomization will be stratified by country, pathological TNM stage (stage II vs stage III) and potential clinical frailty as defined by the G8 geriatric assessment score (>14 vs ≤14). Patients will be randomized with a 2:1 allocation rate to receive either a standard adjuvant endocrine therapy for a duration of at least 5 years + palbociclib for a total duration of up to 2 years (experimental palbociclib arm) or adjuvant chemotherapy followed by standard adjuvant endocrine therapy for a duration of at least 5 years (control chemotherapy arm).
In the experimental arm, palbociclib 125mg orally will be administered once a day for 21 days followed by 7 days off treatment in the 28-day cycle, with an objective of 2-years total duration of study medication, in combination with standard adjuvant endocrine therapy, for a duration of at least 5 years. Longer duration can be proposed to patients according to investigators and patients. In patients for whom adjuvant radiation therapy is indicated, radiation therapy will be administered before the start of palbociclib. Patients in the control treatment arm will be treated with adjuvant chemotherapy as initial adjuvant systemic treatment. The investigator needs to select for each patient one out of the four following schemes: 1) 4 cycles docetaxel 75mg/m2 / cyclophosphamide 600mg/m2 q3w; 2) 4 cycles doxorubicin 60mg/m2 / cyclophosphamide 600mg/m2 q3w; 3) 4 cycles epirubicin 90mg/m2 / cyclophosphamide 600mg/m2 q3w; 4) 4 cycles weekly paclitaxel 80mg/m2 D1, D8, and D15 q3w. Chemotherapy can start after sufficient wound healing is achieved according to the investigator, but in any case, ≤13 weeks after last surgery. Prophylactic use of G-CSF is recommended after each cycle of the 3-weekly regimens, with type and length decided per local institutional guidelines. In patients for whom radiation therapy is indicated, radiation therapy will be administered after the last dose of chemotherapy.
Primary objective of APPALACHES trial is to assess the efficacy of the combination of at least 5 year-endocrine therapy and 2 year-palbociclib as adjuvant systemic treatment instead of adjuvant chemotherapy followed by endocrine therapy in older patients with stage II-III ER+/HER2-early breast cancer. Secondary objectives include evaluation of the efficacy with respect to different time-to-event endpoints (distant recurrence-free interval (DRFI), breast cancer specific survival (BCSS), and OS) at 3, 6, and 10 years in both arms; evaluation of toxicity, treatment discontinuation, and dose reduction rates in both arms, as well as reasons for treatment discontinuation; assessment of completion of oral therapy in the experimental arm; Health-Related Quality of Life (HRQoL) in both arms; and prognostic and predictive effects of geriatric assessment in both arms.
APPALACHES study will also address translational research questions such as the evaluation of biomarkers of aging during treatment and their correlation with treatment-related toxicity. Thus, blood samples will be collected at baseline, 6 months, and 3 years after treatment start. All samples will be stored centrally at the Integrated BioBank of Luxembourg (IBBL), Luxembourg.

Study report:
APPALACHES recruitment started in March 2020 and ended in October 2022 with 373 patients enrolled, 30 of them in Germany. The study duration is approximately 54 months.

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

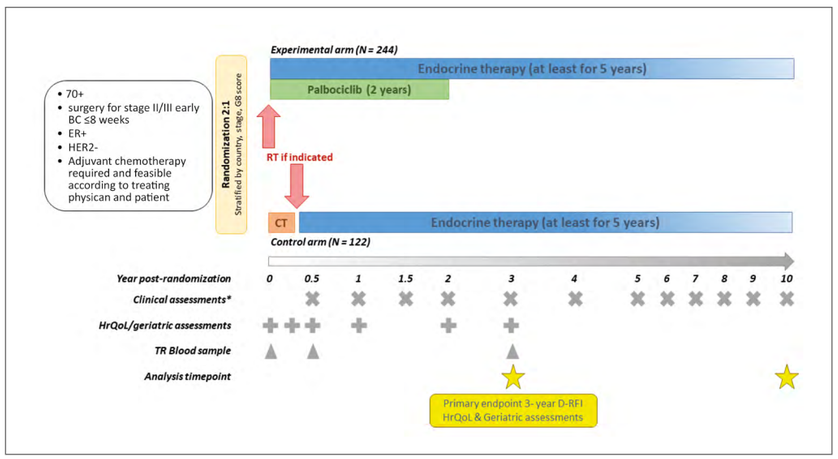

Figure 1: APPALACHES study design

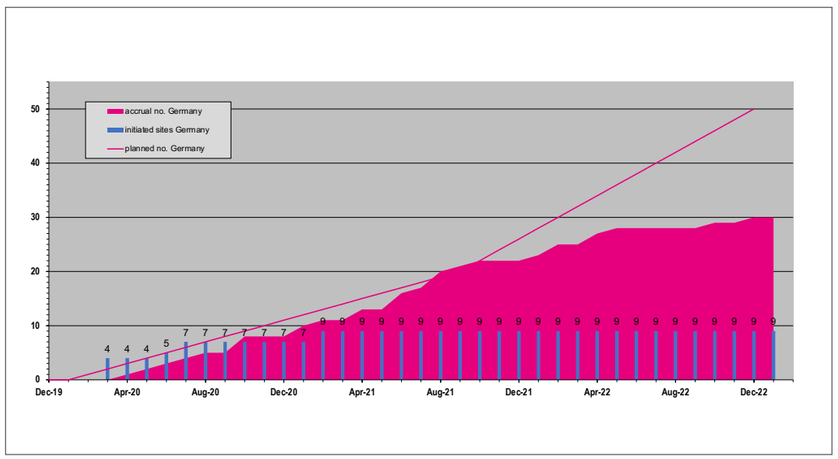

Figure 2: APPALACHES recruitment as of 31st December 2022

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

EORTC European Organisation for Research and Treatment of Cancer
The future of cancer therapy

SPONSOR:
EORTC

STUDY CHAIR:
PD Dr. Mattea Reinisch
Kliniken Essen-Mitte

GBG 98: ALEXANDRA/IMpassion030

CONTACT:
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A phase III, multicenter, randomized, open-label study comparing atezolizumab (anti PD-L1 antibody) in combination with adjuvant Anthracycline/Taxane-based chemotherapy versus chemotherapy alone in patients with operable triple-negative breast cancer

NCT03498716

ALEXANDRA/Impassion30 (BIG 16-05/AFT-27/WO39391) is an international, multicenter, randomized, open-label, controlled phase III trial that will recruit approximately 2,300 patients at approximately 370-450 sites globally within 4 years.

Background
Patients with TNBC exhibit a poor clinical outcome, generally with rapid progression and a shorter time to local and distant relapse (Dent et al. Clin Cancer Res 2007). Three-year invasive disease-free survival (iDFS) rates of 81% have been reported for patients with TNBC who have received adjuvant anthracycline/taxane therapy (Sparano et al. J Clin Oncol 2015). Upon systemic relapse, patients with metastatic TNBC have poor outcomes, with rapid progression and decreased overall survival (Kassam et al. Clin Breast Cancer 2009).
Atezolizumab is a humanized immunoglobulin G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in an improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). TNBC may be more immunogenic compared to other breast cancer subtypes, and promising clinical activity has been reported with atezolizumab in phase I/Ib metastatic TNBC trials (Adams et al. JAMA Oncol 2019). Furthermore, the results of the randomized phase III Impassion130 study demonstrated enhanced anti-tumor activity when atezolizumab was co-administered with chemotherapy in the first line metastatic setting, with benefit mainly observed in PD-L-positive cohort.
Atezolizumab has been generally well tolerated. Atezolizumab in combination with taxanes (including paclitaxel and nab-paclitaxel) has shown toxicities similar to those experienced with paclitaxel or nab-paclitaxel alone and have generally been manageable. The benefit-risk ratio for atezolizumab in combination with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide is expected to be acceptable in this setting.

Study design and objectives:
ALEXANDRA/Impassion030 primarily aims to evaluate the efficacy, safety, and pharmacokinetic profile of adjuvant atezolizumab plus standard chemotherapy versus chemotherapy alone in early TNBC. Patients with operable stage II or III TNBC, confirmed by central pathology review, will be randomized to receive either adjuvant atezolizumab in combination with paclitaxel followed by atezolizumab, dose-dense doxorubicin or epirubicin (investigator's choice), and cyclophosphamide (atezolizumab+T-AC/EC) or paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide alone (T-AC/EC). Patients are stratified by type of surgery, nodal status, and centrally assessed PD-L1 status. Adjuvant treatment will consist of weekly paclitaxel 80mg/m2 for 12 weeks followed by dose dense anthracycline (epirubicin 90mg/m2 or doxorubicin 60mg/m2) and cyclophosphamide 600mg/m2 for 4 doses every 2 weeks or the same chemotherapy regimen (T-AC/EC) given concomitantly with atezolizumab 840mg every 2 weeks, followed by maintenance atezolizumab 1200mg every 3 weeks until completion of 1 year of atezolizumab. The primary endpoint is to evaluate iDFS of adjuvant atezolizumab+T-AC/EC compared with T-AC/EC alone in patients with TNBC. Secondary endpoints include iDFS by PD-L1 and lymph node status, overall survival, safety, patient functioning, and health-related quality of life (HRQoL). Furthermore, tumor tissue and blood samples will be collected for biomarker research.

Study report:
ALEXANDRA/IMpassion030 worldwide recruitment started in July 2018, and in Germany in June 2019. As of December 31st, 2022, there are 52 patients enrolled in the study. On August 25th, 2022, the recruitment stopped in Germany. A global recruitment stop was implemented on November 9th, 2022.

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

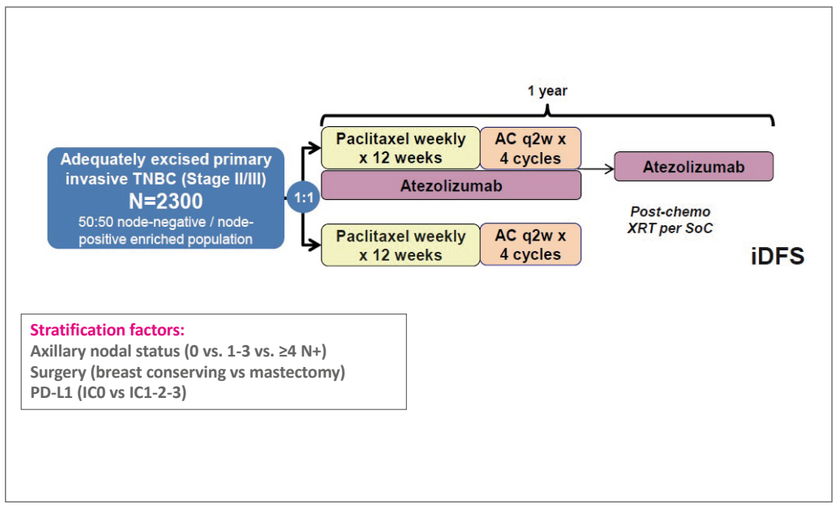

Figure 1: ALEXANDRA/IMpassion030 study design

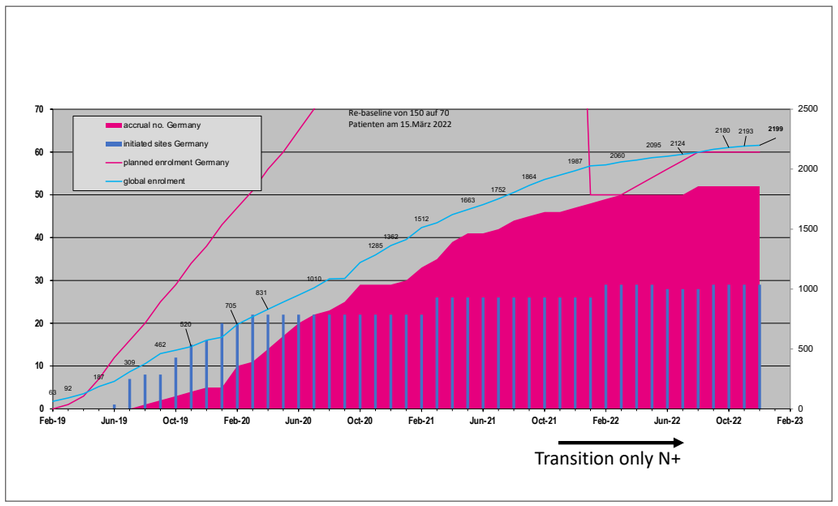

Figure 2: ALEXANDRA/IMpassion030 recruitment as of 31st December 2022

COLLABORATING STUDY GROUPS:
GBG GERMAN BREAST GROUP
BIG Breast International Group
frontier science foundation
ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY
INSTITUT JULES BORDET INSTITUUT

SPONSOR:
Hoffmann-La Roche

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

GBG 93: PADMA

CONTACT:
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Clinical Project Management
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A randomised, 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 (PADMA)

NCT03355157

PADMA is an international, prospective, randomized, open-label, multicenter, controlled phase IV low intervention trial to test whether endocrine therapy (ET) 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). PADMA will be conducted in approximately 70 sites in Europe.

Background
ET is the recommended option for hormone receptor (HR)-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 et al. Ann Oncol 2014; Gradishar et al. Natl Compr Canc Netw 2016; Schneeweiss et al. Geburtshilfe Frauenheilkd 2021). With the novel CDK4/6 inhibitors in addition to either an aromatase inhibitor (AI) or fulvestrant, the treatment landscape is changing rapidly. Data comparing ET alone with chemotherapy (CT) are scarce and not informative about which strategy would benefit patients most. In the real world, most patients with MBC receive CT to obtain a quick response, although it has not been proven that achieving a quick response will have an impact on patient benefit. Since palbociclib in combination with ET is superior to ET alone, PADMA investigates if palbociclib + ET is superior to mono-chemotherapy with or without ET maintenance. Many clinical studies have rigid inclusion and exclusion criteria, they predefine study treatment, and they strictly define patient monitoring intervals, which do not reflect the situation in clinical practice. Therefore, PADMA is planned as a low-intervention real-world trial investigating two treatment strategies that are commonly used in real-world practice. In addition, we are collecting patient reported outcomes (PROs) using the FACT-B questionnaire, and a novel composite endpoint of well-being and healthcare utilization as measured by daily monitoring treatment impact (DMTI).

Study design and objectives:
PADMA will provide evidence if palbociclib + ET can replace CT with or without ET maintenance. Patients are randomized in a 1:1 ratio to receive either ET with palbociclib or CT with or without endocrine maintenance therapy. Stratification factors for randomization are: i) hormone resistant (relapse on or within 12 months of end of adjuvant ET) versus hormone sensitive (relapse beyond 12 months after end of ET or de novo metastatic HR-positive/HER2-negative breast cancer); ii) symptomatic versus asymptomatic (both defined by investigator). In both study arms, treatment is given until disease progression, unacceptable toxicity, 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 ET. The TTF is defined as time from randomization until discontinuation of treatment due to disease progression, treatment toxicity, patient's preference, or death. Main secondary objectives include progression-free survival, time-to-first subsequent treatment, time-to-first subsequent chemotherapy, time-to-second subsequent treatment regimen, and overall survival between treatment arms; and to compare patient well-being and health care utilization, quality of life, safety, and treatment compliance between the two arms. Furthermore, the PADMA study will also address translational research questions such as an investigation of biomarkers (e.g., cyclines, RB expression, p27 and p16 expression) which might predict the response to CDK inhibition in MBC, as well as the evaluation of circulating tumor DNA (ctDNA) at various time points to monitor tumor progression.
The protocol was amended in July 2018. The main changes included in amendment 1 were a reduction of the number of planned patients, and the removal of an initially planned interim analysis as well as an activity tracker monitoring sleep and activity levels.
With amendment 2 of the study protocol, the number of planned patients was reduced again, and the study duration was prolonged. In addition, a molecular screening is offered to all patients included in the study to identify molecular changes of therapeutic relevance within the context of precision medicine.

Study report:
The PADMA study recruitment started in March 2018 in Germany. As of December 31st, 2022, there are 113 patients enrolled in the study. The end of the study (i.e., last visit of the last patient randomized) is estimated for mid of 2025.

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

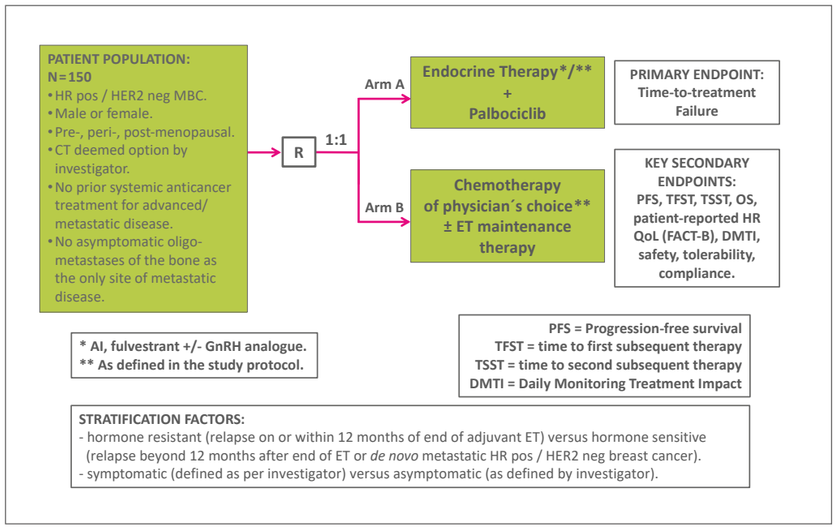

Figure 1: PADMA study design

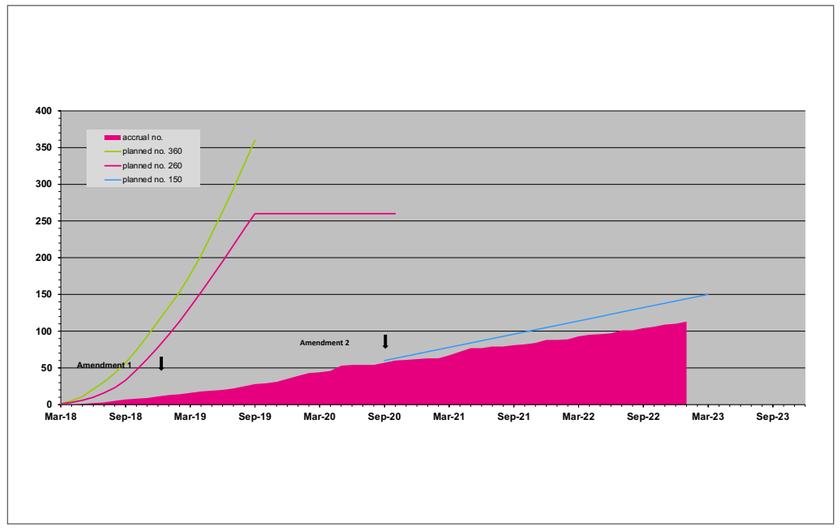

Figure 2: PADMA recruitment as of 31st December 2022

COLLABORATING STUDY GROUPS:
GBG GERMAN BREAST GROUP

SPONSOR:
GBG Forschungs GmbH

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 104: EUBREAST-01

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

NCT04101851

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EUBREAST-01 (GBG 104) is a single-arm, multicenter, prospective trial to investigate the omission of sentinel lymph node biopsy (SLNB) in triple-negative and HER2-positive breast cancer patients with radiologic and pathologic complete response (pCR) in the breast after neoadjuvant systemic therapy (NAST).

Background

Currently, axillary surgery for breast cancer is considered as staging procedure that does not seem to influence breast cancer mortality, since the risk of developing metastasis depends mainly on the biological behavior of the primary tumor (seed-and-soil model). Thus, the postsurgical treatment strategy should be rather based on biologic tumor characteristics than nodal involvement.
Improvements in systemic treatments for breast cancer have increased the rates of pCR in patients receiving NAST, offering the opportunity to decrease, and perhaps eliminate, surgery in patients who have a pCR.

Study design and objectives

The investigators designed a clinical trial in which only patients with the highest likelihood of having a pCR after NAST will be included, and the type of surgical strategy will be defined according to the response to NAST rather than on the classical T and N status at presentation. Axillary surgery will be eliminated completely (no axillary sentinel lymph node biopsy [SLNB]) for initially cN0 patients with radiologic complete remission (rCR) and a breast pCR as determined in the lumpectomy specimen.
Patients ≥18 years of age with triple-negative or HER2-positive invasive breast cancer and no evidence for distant metastasis (M0) can be included. Additional key inclusion criteria are imaging techniques with estimated tumor stage between cT1c-T3 prior to NAST, and clinically also as sonographically tumor-free axilla prior to core biopsy (cN0/iN0). In cases with cN0 and iN+, a negative core biopsy or fine needle aspiration (FNA) biopsy of the sonographically suspected lymph node is required. Standard NAST with radiological complete response (rCR) and planned breast-conserving surgery (R0 resection) with postoperative external whole-breast irradiation (conventional fractionation or hypofractionation) are a prerequisite.
The trial is designed as a multicenter single-arm study with a limited number of patients (N=267) which might give practice-changing results in a short period of time, sparing the time and the costs of a randomized comparison. Patients will be recruited in European countries (Austria, Germany, Italy, and Spain) over a period of 24 months.
All patients with confirmed breast pCR after lumpectomy (BCS) will be selected for the single study arm (no axillary therapy) leading to omission of any axillary treatment (axillary SLNB, ALND, axillary radiotherapy). These patients will thus be finally staged as ypNx.
Patients with non-pCR in the breast will be treated with axillary SLNB in a second procedure in concordance with current guidelines. In case of a tumor-free SLNB (ypN0[sn]), no completion ALND is performed. If micro- or macrometastases are found in the SLNB (ypN+[sn]), completion ALND and/or axillary radiotherapy is mandatory according to local decision. Postoperative systemic treatment should be based on local multidisciplinary tumor board recommendations according to current international or national guidelines.
All study patients must receive CT-based WBRT with 3-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiotherapy (IMRT) to the remaining breast (50 Gy in 25 fractions or 50.4 Gy in 28 fractions) delivered in supine position. In addition, the hypofractionated regimen with a single dose of 2.66 Gy in 15 fractions according to the START B trial (Haviland SJ et al. Lancet Oncol 2013) is an option. A boost to the tumor bed is recommended according to local guidelines (dose [10-]16 Gy). The irradiation of regional lymph nodes (axillary, supra-/infraclavicular, internal mammary) must be avoided in cases with pCR in the breast (ypT0).
The primary objective is the 3-year rate of axillary recurrence-free survival (ARFS) after breast-conserving surgery (no SLNB arm). Secondary objectives are the 5-year invasive disease-free survival, overall survival, locoregional disease-free survival (no tumor in the ipsilateral breast or ipsilateral supraclavicular, infraclavicular, internal mammary, or axillary nodes), ipsilateral axillary recurrence rate, distant disease-free survival, and the diagnostic accuracy of imaging methods for pathologic complete response (breast pCR) after NAST.

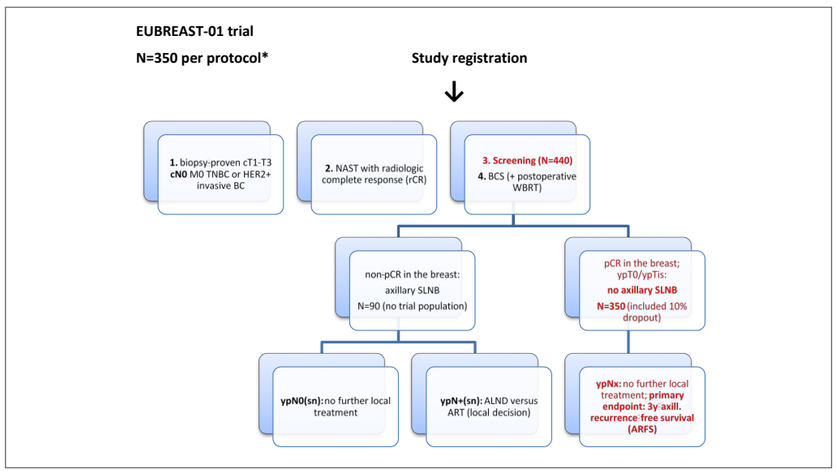

Figure 1: EUBREAST-01 flow chart (Amendment #2)

Publications

1. Reimer T, Glass Ä, Botteri E, Loibl S, Gentilini OD. Avoiding axillary sentinel lymph node biopsy after neoadjuvant systemic therapy in breast cancer: Rationale for the prospective, multicentric EUBREAST-01 trial. Cancers 2020; 12: E3698

We thank all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients.

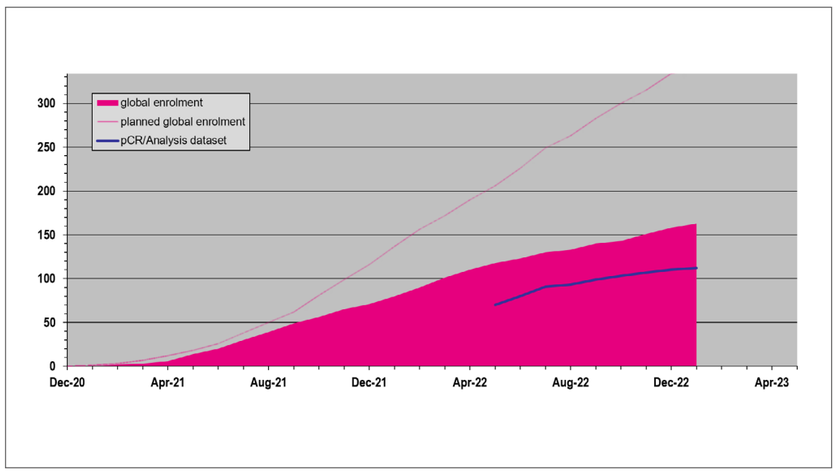

Figure 2: EUBREAST-01 recruitment as of 31st December 2022

COLLABORATING STUDY GROUPS:

SPONSOR:
University Medicine Rostock (UMR, Germany)

CO-SPONSOR:
San Raffaele Hospital (Milan, Italy)

COORDINATING INVESTIGATOR:
Prof. Dr. Toralf Reimer
Universitäts-Frauenklinik am Klinikum Südstadt

GBG 101: TAXIS

TAXIS

CONTACT:
Jan Steffen
Clinical Project Management
taxis@GBG.de

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

NCT03513614

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

Background

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

Study design and objectives

Women aged ≥18 years with node positive breast cancer (histologically or cytologically proven both in primary tumor and in lymph node) AJCC/UICC stage II-III (all molecular subtypes) fulfilling all inclusion criteria at randomization are eligible. Patients will be assigned to either TAS followed by ALND and regional nodal irradiation excluding the dissected axilla as a target volume (arm A) or to TAS followed by regional nodal irradiation including the full axilla (arm B). It is planned to enroll a total of 1,500 patients (750 per treatment arm) in the trial. All patients will undergo adjuvant whole-breast irradiation after breast conserving surgery and chest wall irradiation after mastectomy. Radiation therapy (RT) should start preferably within 8 weeks from the last breast surgical procedure and not later than 12 weeks. In case chemotherapy was applied, RT should start within 6 weeks after the end of the last cycle of chemotherapy and not later than 8 weeks. Dose to the breast/thoracic wall as well as the regional nodal pathways is: 50 Gy in 25 fractions of 2 Gy or 50.4 Gy in 28 fractions of 1.8 Gy; daily, five days a week. Hypofractionated schedule is allowed: 40 Gy in 15 fractions of 2.67 Gy to the same volume. Patients will be followed up to 20 years after randomization of the last patient.

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

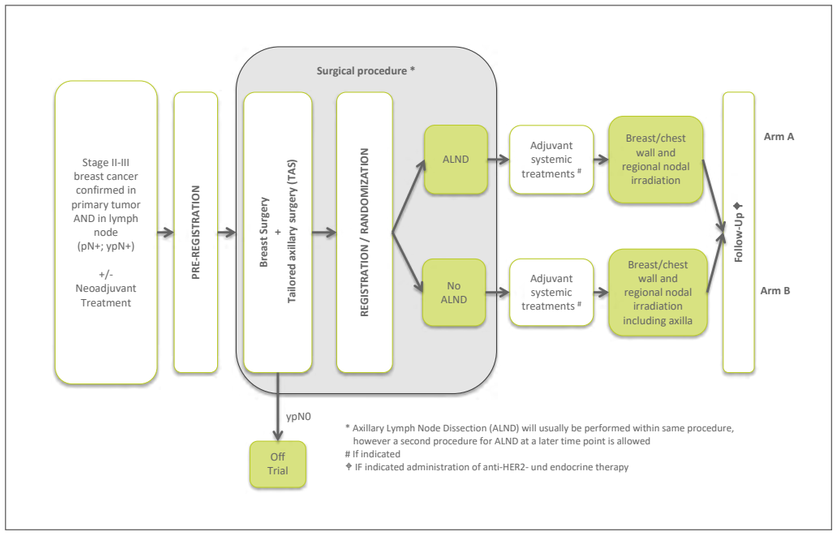

Figure 1: TAXIS study design

Study report:

TAXIS recruitment started in August 2019 in Germany. Recruitment was stopped at the end of 2020, and then the trial reopened again for recruitment in January 2022 in collaboration with a new sponsor (Universitätsspital Basel). As of December 31st, 2022, there were 39 patients enrolled in the study in Germany. Follow-up is planned for up to 20 years. The end of the study (i.e., last visit of the last patient randomized) is planned for QIV/2043 [1].

Data on a pre-specified subproject to study the difference in surgical extent between TAS and ALND and to quantify the extent of tumor load reduction by TAS was recently published. This report included 296 patients from the early stage of patient accrual, and data showed that TAS selectively reduced the tumor load in the axilla and remained much less radical than ALND (Weber et al. Breast 2021).

Publications:

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

We thank all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients.

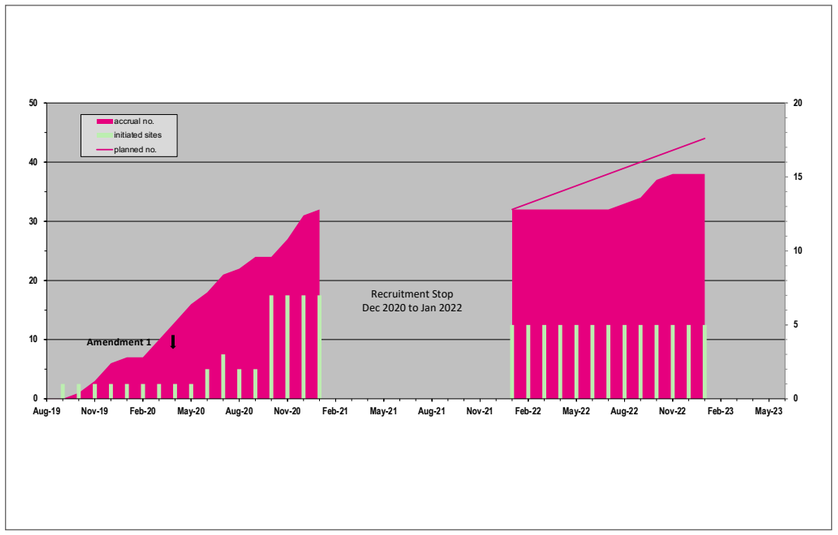

Figure 2: TAXIS recruitment as of 31st December 2022

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

SAKK WE BRING PROGRESS TO CANCER CARE

Universitätsspital Basel

SPONSOR:
Universitätsspital Basel

COORDINATING INVESTIGATOR
Prof. Dr. Jörg Heil
Universitätsklinikum Heidelberg

GBG 107: ETERNITY[B] Registry

ETERNITY[B] is a prospective and retrospective, international, multicenter, non-interventional, observational study for collection of long-term safety and efficacy parameters of former GBG study participants from prospective clinical trials on early breast cancer. The B stands for Breast.

Background

Although the impact on long-term patient survival and safety is a decisive factor for drawing conclusions on the benefit-risk ratio of investigational treatment strategies, treatment recommendations for early and advanced stage breast cancer are mostly based on the primary results of randomized clinical trials with a relatively short follow-up time at read out.

Longer collection of survival and safety data is important to provide a better understanding of the efficacy of certain investigational treatment strategies as well as to identify late onset toxicities and long-term quality of life.

To address this issue, we have successfully established a patient-self-reported outcome (PSRO) registry (GBG 71) in Germany. However, as GBG 71 is not available for our European and non-European partners, we have set up the international registry study ETERNITY[B] to collect a similar data set to that of GBG 71, also focused on long-term outcomes.

Study design and objectives

Patients will be eligible for ETERNITY[B] if they have participated and received treatment in a GBG clinical trial for early breast cancer. Patients will be informed about the registry by the treating physician at the study site. Inclusion and registration can take place after informed consent of the patient. Documentation of follow- up should start after the regular end of study or with the start of follow-up period as defined in the respective study protocol. A correlation of the follow-up registry database with the respective study databases is possible via the patient identification number of the participant. In consequence, the long-term effects of the study therapy can be analyzed per therapy group, and the effectiveness can be correlated with possible late-onset toxicities.

The post study long-term-outcome follow-up will be assessed according to local/national guidelines. Data should be documented at least once a year in the registry.

Relapse and safety assessment will be performed, and survival status will be collected in all registered patients. Here, the investigator may conduct evaluations or assessments within regular follow-up visits. However, telephone contact or contact in writing with the patient or treating physician or relatives in case of death is also acceptable. Imaging tests (e.g., mammography and/or staging workup) are recommended according to local/national guidelines for follow up and in case of symptoms suspicious for locoregional or distant relapse.

In case of disease recurrence, it is recommended to confirm diagnosis by histological examination. If performed, a FFPE tumor tissue block from the metastatic lesion should be provided to GBG; however, participation in ETERNITY[B] is not linked to the provision of biomaterials.

Study report

The ETERNITY[B] recruitment started in September 2022. As of December 31st, 2022, there are 3 patients enrolled in the study. The end of study is estimated for 2030.

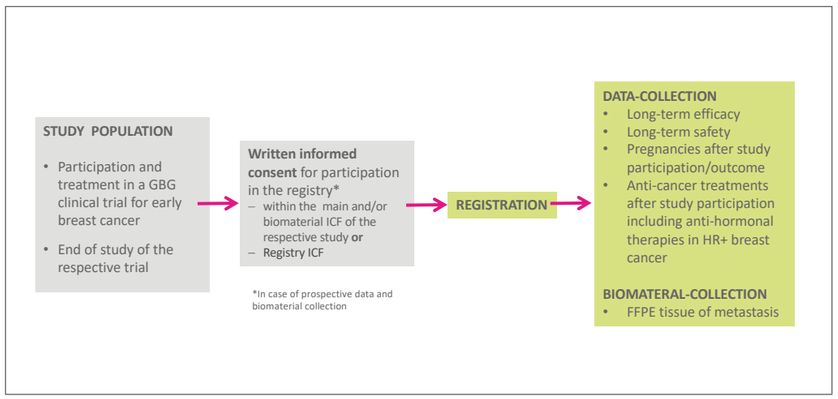

Figure 1: ETERNITY[B] study design

GBG 79: Brain Metastases in Breast Cancer

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

Background

The development of brain metastases reduces quality of life and survival in breast cancer patients. The incidence of brain metastases has increased during the last years (Frisk et al. Br J Cancer 2012). Around 10-40% of patients with metastatic breast cancer 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, as well as a 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 insufficiently analyzed. Improved treatment strategies are required, as the incidence of patients with brain metastases is expected to increase over the next years given the better control of systemic disease outside the central nervous system. 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 breast cancer patients with brain metastases diagnosed in the year 2000 and beyond. 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 the data is captured anonymously.

The registry study is conducted in collaboration with Prof. Dr. Volkmar Müller, Prof. Dr. Isabell Witzel, Priv. Doz. Dr. Elena Laakmann, and Dr. med. Kerstin Riecke from the University Hospital 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 tumors.

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,

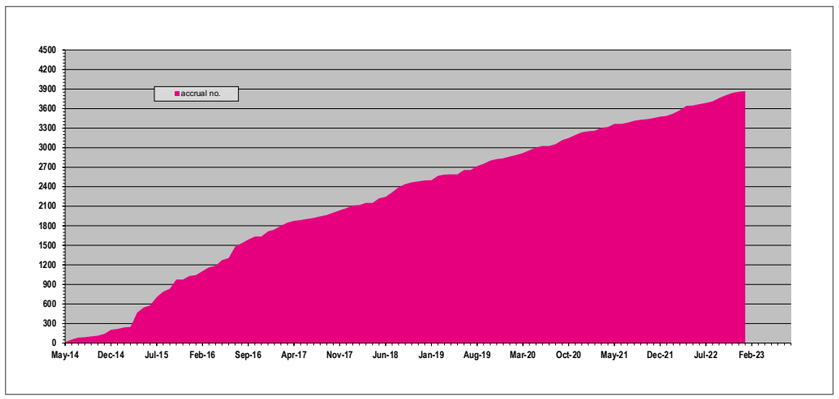

Figure 1: BMBC recruitment as of 31st December 2022

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COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

PROJECT LEADER:
Prof. Dr. med. Sibylle Loibl

CONTACT:
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Clinical Project Management
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resistance mechanisms against HER2-targeted therapies, the role of the blood brain barrier, and the evaluation of markers of radio-resistance 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 December 31st, 2022, 3,867 patients have been registered and 547 tissue samples have been received. Registration of patients is ongoing.

A project using data from the BMBC registry was presented at the ESMO Breast Cancer Congress 2021. This retrospective analysis involved a total of 2948 patients, including 1,311 patients with HER2+ disease and identified factors associated with the prognosis of HER2+ patients with brain metastases. A significantly longer overall survival was observed for the HR+ subcohort, and this finding warrants further research [2].

Up to 40% of patients with metastatic HER2+ breast cancer develop brain metastases. To understand clinical features of patients with HER2+ breast cancer and brain metastases, subanalyses of the BMBC registry have been implemented (Laakmann et al. 2021 [1]; 2022 [2]).

Publications:

1. Laakmann E, Witzel I, Neunhöffer T, et al. 95MO - Characteristics of patients with brain metastases from HER2-positive breast cancer. Ann Oncol 2021; 32 (suppl_2): S60-S78.

2. Laakmann E, Witzel I, Neunhöffer T, et al. Characteristics of patients with brain metastases from human epidermal growth factor receptor 2-positive breast cancer: subanalysis of Brain Metastases in Breast Cancer Registry. ESMO Open. 2022 Jun;7(3):100495.

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
Prof. Dr. Volkmar Müller
Universitätsklinikum Hamburg-Eppendorf, Klinik und Poliklinik für Gynäkologie

GBG 71: Patient Self-Reporting Outcome Registry

PSRO (Patient Self-Reporting Outcome) is a multicenter registry designed to capture long-term follow-up data of former trial participants.

Background

Long-term follow-up of early breast cancer trials is considered highly important as treatment efficacy might increase, maintain, or decrease over time, and to understand and document late or chronic toxicities. This might result in a different assessment of the overall patient benefit of an investigational treatment strategy as compared to the initial assessment when the primary endpoint was read out. However, collection of data over a long time is often not feasible due to the logistical and financial burdens for study sites and sponsors.

To address this issue, we have set up a registry in 2010 where patients are consented and contacted in writing, and they send back information about their health status.

Methods

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 collected, and they agree to regularly receive health status questionnaires.

German privacy laws and good clinical practice (GCP) regulations do not allow the storage of patient-identifying data by the sponsor. Therefore, we developed the registry with a strict separation of patient-identifying data and pseudonymized medical data via a data trustee. The data trustee is financially and organizationally independent from the GBG. The data trustee handles names and addresses of patients through a database that is not accessible by GBG.

Once informed 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 out by a third person in case of death. Forms are 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.

Study report

We accept participants from most GBG trials for early breast cancer. Currently, over 13,000 participants from 20 trials and 450 sites are included in this registry.

Publications:

1. von Minckwitz G, Steffen J, Wiest W et al. Patient Self-reported Outcome for Long-term Follow up of Early Breast Cancer Trials. Eur J Cancer. 2012; 48, suppl 1, S52

2. von Minckwitz G, Steffen J, Costa S et al. Quality of patient-reported outcome for long-term survival of early breast cancer trials. J Clin Oncol. 2016; 34:15_suppl, e18121-e18121

We encourage all study centers and practices to enter patients from eligible trials into the registry.
We thank all sites that have already entered patients into the registry and have contributed to this important project so far.

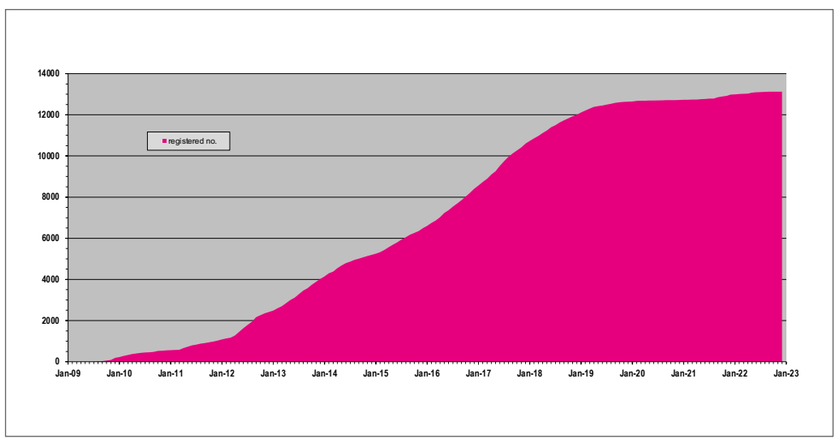

Figure 1: Recruitment into PSRO-registry as of 31th December 2022

PSRO

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PARTNER:
As data trustee, we partnered with the Center for Clinical Studies at the University of Cologne.
Zentrum für Klinische Studien (ZKS), Universität Köln

ZKS Köln ZENTRUM FÜR KLINISCHE STUDIEN

SPONSOR:
GBG Forschungs GmbH

GBG 29: Breast Cancer in Pregnancy

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

NCT 00196833

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 recent years (Eisemann et al. Geburtshilfe Frauenheilkd 2013; DeSantis 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 pregnant patients with breast cancer as controls treated in everyday clinical practice.
All patients with histologically confirmed breast cancer who are pregnant, as well as patients who are 40 years old 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 placental tissue from patients with breast cancer during pregnancy.

Study report

As of December 31st, 2022, a total. of 3,437 patients have been registered, 3,062 in Germany (702 pregnant and 2,360 non pregnant women).
A recent evaluation of the outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls in cooperation with INCIP (International Network on Cancer, Infertility and Pregnancy) revealed that pregnancy-induced alterations in chemotherapy concentration do not seem to affect maternal prognosis. After a median follow-up of 66 months, the observed disease-free survival and overall survival were comparable for pregnant and non-pregnant patients. These results support initiation of chemotherapy for breast cancer during pregnancy when indicated according to clinical guidelines [1,2].

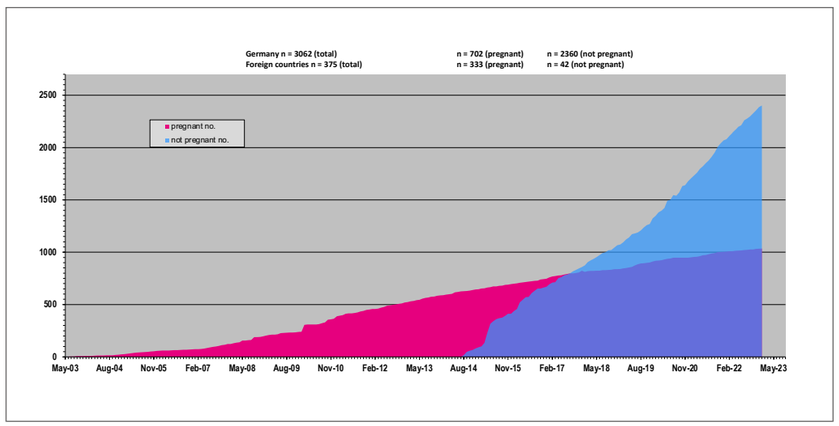

Figure 1: BCP recruitment as of 31st December 2022

Publications:

1. Amant F, Nekljudova V, Maggen C, et al. Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. J Clin Oncol 39, no. 15_suppl (May 20, 2021) 515-515.

2. Amant F, Nekljudova V, Maggen C, et al. Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. Eur J Cancer. 2022 Jul;170:54-63.

Thanks to all participating sites and practices that have entered their patients into the registry and have supported 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 from the GBG website: https://gbg.de/de/studien/bcp.php

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

BIG Breast International Group

SPONSOR:

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

STUDY CHAIR:

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

Follow-up Activities

Follow-up Activities 2022

Long-term follow-up of early breast cancer trials is considered highly important as treatment efficacy might increase, maintain, or decrease over time, and to understand and document late or chronic toxicities. This might result in a different assessment of the overall patient benefit of an investigational treatment strategy as compared to the initial assessment when the primary endpoint was analyzed. However, collection of data over a long period is often not feasible due to the logistical and financial burdens for study sites and sponsors.

Patient self-reported outcome (PSRO) registry

To improve follow-up and reduce the workload for the trial sites, we developed a concept to use a patient self-reported outcome (PSRO) registry for long term follow-up in the GBG early breast cancer trials. Detailed information on the PSRO registry can be found on page 75.

General follow-up database and eCRF

Follow-up documentation across different studies over a long time is a significant burden for study 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 care without trial specific examinations.
Results from the PSRO are also entered into this database.

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 33	GAIN	2,994	1,015	62%
GBG 66	GeparSixto	588	338	63%
GBG 68	GAIN-2	2,857	2,284	71%
GBG 69	GeparSepto	1,203	792	69%
GBG 70	Dafne	65	52	59%
GBG 74	Genevieve	333	205	58%
GBG 75	Insema	5,195	3,146	74%
GBG 78	Penelope[B]	1,244	109	75%
GBG 84	GeparOcto	945	733	73%
GBG 88	GeparX	768	596	68%
GBG 89	GeparNuevo	174	133	75%
GBG 90	GeparOla	106	64	73%
GBG 96	GeparDouze	978	0	78%

Table 1: Status of the GBG trials in follow-up as of December 2022 (FU-completeness according to Clark, Lancet 2002;359:1309)

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

Neoadjuvant studies

GeparDouze
(GBG 96, NSABP B-59, NCT03281954)
is an international, multicenter, prospective, randomized, double-blind, phase III trial that has recruited 1550 patients worldwide.

This trial of neoadjuvant and adjuvant administration of atezolizumab/placebo in patients with high-risk triple-negative breast cancer aims to evaluate the efficacy and safety of neoadjuvant administration of atezolizumab/placebo with a sequential regimen of weekly paclitaxel with every-3rd-week carboplatin, followed by neoadjuvant administration of atezolizumab/placebo with epirubicin/cyclophosphamide or doxorubicin/cyclophosphamide (EC/AC). After surgery, patients reinitiated atezolizumab/placebo as adjuvant therapy to complete one year of treatment.
GeparDouze is a collaborative study conducted by NSABP Foundation, Inc., in partnership with the German Breast Group. Study recruitment was completed in May 2021 with a total of 978 patients enrolled in Europe (805 patients in Germany). Patients are now in the follow-up period. The first interim analysis of event-free survival (EFS) is expected in Q1/2023.

For timely analysis of the primary study endpoints, we would like to encourage all participating sites to respond to potential queries in a timely manner.

GeparOLA
(GBG 90, NCT 02789332)
is a multicenter, prospective, randomized open-label phase II study that has recruited 107 patients.

The study evaluated the efficacy of paclitaxel and olaparib in comparison to paclitaxel and carboplatin followed by epirubicin/cyclophosphamide (EC) as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and homologous recombination deficiency (HRD; defined as deleterious *BRCA1/2* tumor or germline mutation and/or high HRD score). While the addition of olaparib to paclitaxel was well tolerated, a pCR rate of 55.1% (90%CI 44.5%-65.3%) was not sufficient to exclude the predefined pCR rate of 55% in the olaparib arm. Subgroup analyses revealed higher pCR rates in the olaparib group compared to the carboplatin group in patients younger than 40 years and in those with hormone receptor positive status (Fasching et al. Ann Oncol 2020).
Long-term data revealed an overall inferior outcome in patients with no *BRCA1/2* tumor or germline mutation treated with olaparib instead of carboplatinum. On the other hand, in patients with such mutations, no difference was found in survival outcomes between olaparib and carboplatin. Results pertaining to the long-term survival in GeparOLA were presented at SABCS 2022.

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

GeparX
(GBG 88, NCT 02682693)
is a multicenter, prospective, 2x2 randomized, open-label, phase IIb study that has recruited 780 patients.

The study investigated efficacy and safety of adding denosumab to anthracycline/taxane-containing neoadjuvant chemotherapy and preference for weekly or 2-of-3 weeks nab-paclitaxel schedules for primary breast cancer. The addition of denosumab to neoadjuvant chemotherapy did not increase the pCR rate (41% with denosumab vs. 43% without denosumab, p=0.582), while the weekly schedule of nab-paclitaxel resulted in significantly higher pCR rates than those seen with the 2-of-3 weeks regimen (45% vs. 39%, respectively, p=0.062,

to the significance level of α=0.1). However, weekly nab-paclitaxel resulted in higher rates of serious adverse events and treatment discontinuations mainly due to adverse events (Blohmer et al. Cancer Res 2020; Blohmer et al. JAMA Oncol 2022). Among predefined subgroups, patients receiving epirubicin/cyclophosphamide every two weeks and patients receiving denosumab benefitted from the weekly nab-paclitaxel schedule. A high RANK expression was associated with significantly higher pCR rates, an effect that was pronounced in patients with luminal breast cancer. However, a clinical benefit of denosumab in relation to RANK expression could not be shown (Link et al. Ann Oncol 2020). Moreover, quality of life analyses revealed that weekly nab-paclitaxel was associated with decreased quality of life compared to the 2-of-3 weeks regimen, which is consistent with the higher toxicity reported for the former. Therefore, benefits and risks of these regimens need to be discussed with patients (Blohmer et al. JAMA Oncol 2022).

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

KATHERINE
(GBG 77, NCT 01772472)

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

The trial investigated whether adjuvant T-DM1 was more effective than trastuzumab in patients with HER2-positive primary breast cancer who received neoadjuvant chemotherapy including trastuzumab and had residual invasive disease after surgery.
Interim analyses showed a significantly improved invasive disease-free survival (iDFS) with adjuvant T-DM1 compared to trastuzumab. Safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone (von Minckwitz et al. N Engl J Med 2019). Moreover, patient reported outcomes revealed generally stable health-related QoL assessments in both study arms over the course of treatment (Conte et al. Cancer 2020).
Additional safety and efficacy exploratory analyses of factors potentially associated with i) the higher rates of peripheral neuropathy and thrombocytopenia observed with T-DM1; ii) efficacy implications of the numerically higher rate of central nervous system (CNS) recurrence as the first iDFS event observed in the T-DM1 arm; iii) efficacy in patients treated with non-anthracycline (AC) versus AC-based neoadjuvant chemotherapy; and iv) mutually exclusive, particularly high-risk patient cohorts were recently conducted. The results of these subgroup analyses were generally consistent with the findings in the primary study. T-DM1 treatment provides benefit in all subgroups analyzed, including small tumors and particularly high-risk tumors, and it does not increase the overall risk of CNS recurrence. Neoadjuvant chemotherapy had a minimal impact on safety (Mamounas et al. Ann Oncol 2021).

Follow-up is still ongoing for this study to collect the remaining data necessary for the full analysis. We would like to encourage all participating sites to provide follow-up data for their patients.

Post-neoadjuvant studies

Penelope[B]
(GBG 78, NCT 01864746)

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

The study evaluated the addition of the CDK4/6 inhibitor palbociclib as postneoadjuvant treatment for HER2-/HR+ patients with high relapse risk after neoadjuvant chemotherapy (NACT). The addition of one-year palbociclib to endocrine therapy in Penelope[B] did not improve invasive disease-free survival (iDFS). No new safety signals were observed (Loibl et al. J Clin Oncol 2021). Subgroup analyses of 616 premenopausal women revealed no difference in iDFS between palbociclib and placebo overall. However, in the small subgroup of patients treated with tamoxifen + gonadotropin-releasing hormone analogue (GnRHa), a tendency for a better iDFS with palbociclib was found, with no additional side effects compared to the combination with aromatase inhibitor + GnRH (Marmé et al. J Clin Oncol 2021). An evaluation of health economic properties of palbociclib in Penelope[B] found that one year of palbociclib added to endocrine therapy is not likely to be cost-effective in women with residual invasive disease after NACT (Galactionova et al. Ann Oncol 2021). Analyses of patient-reported outcomes showed that global quality of life was generally maintained during Penelope[B] in both treatment arms. Slight differences, in terms of global health status, physical functioning, and fatigue, statistically favored the placebo arm, but none met published clinically meaningful thresholds (García-Sáenz et al. Ann Oncol 2021).
Analyses of ovarian function in young patients demonstrated that treatment with palbocicilib does not significantly influence follicle-stimulating hormone, estradiol, and ovarian reserve when added to endocrine therapy after NACT. These results were presented at the ESMO Breast 2022. Furthermore, biomarkers (ER, PgR, Ki-67, HER2, Cyclin D1 and phospho-RB) were analyzed to identify potential subgroups of patients deriving benefit from palbociclib. These data (n=1250) were presented at SABCS 2022 and results in a favorable prognosis for patients with high Cyclin D1 expression independent of treatment arm. Patients with luminal-A/normal-like tumors and IHC3 low after NACT had an improved outcome when receiving palbociclib in addition to adjuvant ET.
Within the large translational program, gene expression profiling in 906/1250 post-NACT surgical residual tumor tissue samples (HTG Molecular Diagnostics Inc.) revealed that the small group of patients with a luminal-B tumor after NACT (n=64) potentially derived a benefit from palbociclib (numerically, not statistically significant) (Denkert et al. J Clin Oncol 2021). This analysis was later extended to include a cohort of 540 paired pretherapeutic and post-NACT samples and the results were presented at the SABCS 2021. It could be shown that a switch from high-risk (in particular luminal-B) to low-risk molecular subtypes (in particular luminal-A) is common in neoadjuvant therapy of luminal tumors. The adaptation of luminal high-risk tumors to chemotherapy-induced stress is crucial for the clinical outcome and molecular defined tumor subtypes might not be as stable as originally thought (Denkert et al. Cancer Res 2021).
The incidence of mutations in *gBRCA1/2* and other breast cancer (BC) disposition genes and their impact on patient outcome in Penelope[B] was analyzed and results were presented at the SABCS 2021. This case-cohort analysis of 442 patients revealed that patients with mutations in *gBRCA1/2* or other BC disposition genes had a comparable outcome to non-carriers overall and irrespective of treatment. This is the largest investigation of BC predisposition genes in HR+ patients to date (Loibl et al. Cancer Res 2021).
Further presentation at SABCS 2022 included the evaluation of the molecular phenotype and clinical outcomes of HER2-low compared to HER2-zero patients. In the Penelope[B] cohort of HR+ tumors, a HER2-low status in pretherapeutic core biopsies is related to improved disease-free survival, especially for those tumors that have a more aggressive intrinsic subtype. A shift of HER2-low status was observed before and after chemotherapy, indicating an adaptation of the pathway activity to therapy-induced stress.

We would like to thank all participating sites for their ongoing dedication and tremendous efforts taken on this important trial. We encourage all participating sites to provide further follow-up data for their patients since analysis of overall survival and an update on iDFS is planned in 2023.

Adjuvant studies

TAMENDOX
(GBG 91, IKP275, NCT03931928)

is a prospective, multicenter, single-blinded, three treatment arms, placebo controlled, pharmacogenetics/pharmacokinetic phase II study that has recruited 248 patients.

The study aimed 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. TAMENDOX is currently being analysed by the sponsor IKP. Publication of the results is planned for 2023.

We would like to thank the centers for their commitment in recruiting, documentation, as well as the excellent support of monitoring procedures despite the difficult conditions brought by the pandemic.

PALLAS
(GBG 87, NCT 02513394)

is a multicenter, prospective, international, randomized, open-label, adjuvant phase III study that has recruited 5,796 patients worldwide.

The trial was designed to determine if the addition of two years of palbociclib to adjuvant endocrine therapy improves invasive disease-free survival (iDFS) over endocrine therapy alone in patients with HR+/HER2- early-stage breast cancer. At the planned second interim analysis (at a median follow-up of 23.7 months), the futility boundary was crossed. The addition of 2 years of adjuvant palbociclib to adjuvant endocrine therapy did not improve iDFS compared with adjuvant endocrine therapy alone (Mayer et al. Lancet Oncol 2021). This result was confirmed at the final analysis of the PALLAS trial at a median follow-up of 31 months (Gnant et al. J Clin Oncol 2022). Results pertaining to the quality of life and symptom severity in PALLAS were presented at SABCS 2021. No clinically significant differences in either patient-reported quality of life or symptom severity were found; hence, the addition of palbociclib in the adjuvant breast cancer setting did not contribute to increased symptom burden within this survivorship population (Naughton et al. Cancer Res 2022). Long-term follow-up and additional clinical and translational analyses to explore the effect of palbociclib are ongoing.

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

OLYMPIA
(GBG 82, NCT 02032823)

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

The OLYMPIA study investigated for the first time the efficacy of olaparib compared with placebo in an adjuvant/post-neoadjuvant approach in patients with germline *BRCA1/2* mutations and high-risk HER2- early breast cancer. Analysis of the primary endpoint showed that adjuvant olaparib following completion of local treatment and neoadjuvant or adjuvant chemotherapy significantly improved invasive and distant disease-free survivals compared to placebo. The adverse event profile of olaparib was similar to previous reports, and limited effects on global patient-reported quality of life were reported (Tutt et al. N Engl J Med 2021). The full protocol-specified patient-reported outcome analyses were presented at the SABCS 2021 showing that increased treatment-emergent symptoms with olaparib were small and resolved after treatment. Quality of life scores were similar in olaparib and placebo treated patients and slowly improved during the 24 months after (neo)adjuvant chemotherapy (Ganz et al. Cancer Res 2022). Finally, with 3.5 years of median follow-up, OLYMPIA demonstrated statistically significant improvement in overall survival with adjuvant olaparib compared to placebo in this patient population (89.8% vs. 86.4%), and it maintained improvements in the previously reported invasive and distant disease-free survivals with no new safety signals (Geyer et al. Ann Onc 2022).

The analysis and publishing of further time-to-event endpoints are planned for 2028. Therefore, we would encourage all participating sites to provide follow-up data for their patients.

APHINITY
(GBG 67, NCT 01358877)

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

The study compared safety and efficacy of a combination therapy with two anti-HER2 agents (trastuzumab and pertuzumab) in addition to chemotherapy in the adjuvant setting, compared to chemotherapy and trastuzumab alone. Addition of pertuzumab significantly improved the rates of invasive disease-free survival (iDFS) when it was added to trastuzumab and chemotherapy. Diarrhea was more common with pertuzumab than with placebo (von Minckwitz et al. N Engl J Med 2017). The recently published preplanned second interim OS and descriptive updated iDFS analysis with 74 months median follow-up confirmed an iDFS benefit from adding pertuzumab to standard adjuvant therapy for patients with node-positive, HER2+ early breast cancer, while a modest OS benefit did not reach statistical significance (Piccart et al. J Clin Oncol 2021). Moreover, a health-related quality of life assessment of the patient cohort revealed that the addition of pertuzumab to trastuzumab and chemotherapy did not adversely affect the ability to conduct activities of daily living compared to trastuzumab and chemotherapy alone. Patient-reported diarrhea worsened during taxane therapy in both arms, persisting during HER2-targeted treatment in the pertuzumab arm (Bines et al. Br J Cancer 2021).
Data on the cardiac safety of the dual anti-HER2 blockade with pertuzumab plus trastuzumab within APHINITY were reported at ASCO 2021. While the dual blockade was not associated with an increased risk of cardiac events compared to placebo and trastuzumab alone, the use of anthracycline-based chemotherapy increased the risk of cardiac events. Therefore, non-anthracycline chemotherapy may be considered, particularly in patients with other cardiovascular risk factors (de Azambuja et al. J Clin Oncol 2021). New results of a large translational project using BluePrint RNA sequencing, an 80-gene molecular subtyping test that classifies breast tumors as Basal-, Luminal- or HER2-subtype, have been reported at SABCS 2021. BluePrint subtype was evaluated as a biomarker for predicting response to trastuzumab-containing neoadjuvant chemotherapy with or without pertuzumab in a large nationwide cohort of patients, and it confirmed previous results that the benefit of adding pertuzumab to (neo)adjuvant trastuzumab-based chemotherapy seems most pronounced in patients with a molecularly defined single-activated HER2-subtype. In other subtypes, pathological complete response rates and long-term outcomes are worse overall, and no clear benefit of pertuzumab was seen, although tests for interaction between pertuzumab treatment and BluePrint subtype were not significant (Liefaard MC et al. Cancer Res 2022).

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

Metastatic studies

PATINA
(GBG 94, AFT-38, NCT02947685)

is a collaborative study conducted by Alliance Foundation Trials (AFT), LLC in partnership with the German Breast Group (GBG) and supported by AFT, LLC. This is an international, multicenter, randomized, open-label, phase III trial evaluating the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy versus anti-HER2 therapy + endocrine therapy after induction treatment for HR-positive/HER2-positive metastatic breast cancer.

The primary objective of PATINA is to demonstrate that the combination of palbociclib with anti-HER2-based therapy + endocrine therapy is superior to anti-HER2-based therapy + endocrine therapy alone in prolonging progression-free survival. Key secondary objectives are measures of tumor control, overall survival, safety and quality of life.
Between July 2018 and May 2021, 34 patients were enrolled in Germany. Enrollment was completed in QII 2021 worldwide, and the last patient last visit is expected in 2026. The study is now in the follow-up period.

For timely analysis of the primary endpoint, we would like to encourage all participating sites to provide regular follow-up data for their patients.

AURORA
(GBG 85, NCT02102165)

is an exploratory, multinational, collaborative molecular screening program aiming to recruit and collect biomaterial globally from more than 1,000 patients with metastatic breast cancer.

The main objectives of AURORA are to better understand the genetic aberrations in metastatic breast cancer, and to discover the mechanisms of response or resistance to therapy, in order to ultimately identify the right therapy for each individual patient. At the same time, patients with genetic aberrations that are targeted by new drugs in development will be offered the possibility to participate in clinical trials once approved and available in their countries.
Recruitment under protocol version 2.0 was completed in March 2021 with 1,160 patients included in the study. Follow-up is ongoing. Genomic and transcriptomic analyses performed on 318 patients with metastatic breast cancer who were enrolled by February 28, 2018, in the AURORA program were published in 2021. For these analyses, matched primary and metastatic samples (252 for targeted gene sequencing, 152 for RNA sequencing and 67 for single nucleotide polymorphism arrays) were used. Results showed that metastatic samples were enriched in ESR1, PTEN, CDH1, *PIK3CA*, and RB1 mutations; MDM4 and MYC amplifications; and ARID1A deletions. An increase in clonality was observed in driver genes such as ERBB2 and RB1. Intrinsic subtype switching occurred in 36% of cases. Luminal A/B to HER2-enriched switching was associated with TP53 and/or *PIK3CA* mutations. High tumor mutational burden was associated with shorter time to relapse in HR-positive/HER2-negative breast cancers. ESCAT tier I/II alterations were detected in 51% of patients and matched therapy was used in 7% (Aftimos et al. Cancer Discov 2021).
Additional integrative analyses of matched samples collected within the AURORA program are ongoing.

We would like to thank all participating centers for their commitment and efforts so far.

Surgical studies

INSEMA
(GBG 75, NCT 02466737)

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

The trial aims to compare the invasive disease-free survival after breast-conserving surgery between patients who received no axillary surgery versus patients who received sentinel lymph node biopsy (SLNB) (first randomization), and between node positive patients who received SLNB alone versus patients with completion of axillary lymph node dissection (cALND) (second randomization).
Follow-up for this surgical trial is ongoing, and analysis of the primary endpoint invasive disease-free survival is planned for 2024. Data on patient-reported outcomes in INSEMA were presented at SABCS 2021 and published in November 2022 (Reimer et al. EClinicalMedicine 2022). Patient-reported outcomes were assessed at baseline (pre-surgery) and at 1, 3, 6, 12, and 18 months after final axillary surgery. Questionnaire completion response remained high throughout the trial with over 70% at all time points. There were significant differences for the BRBS (breast symptoms) and BRAS (arm symptoms) scores favoring the no SLNB group in all post-baseline assessments. Patients in the SLNB group showed significantly and clinically relevant higher scores for BRAS, including pain, arm swelling, and impaired mobility in all postoperative visits, with the highest difference at one month after surgery. Scoring of the QLQ-C30 questionnaire revealed no relevant differences between the treatment groups, although some comparisons were statistically significant (Reimer et al. EClinicalMedicine 2022).

We would like to thank all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the INSEMA study by providing regular follow-up data or transferring participants to the patient self-reported outcome registry (PSRO, Patienten-Selbstauskunft, GBG 71).

Completed Studies

GBG 97: AMICA

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Anti-hormonal maintenance treatment with the CDK4/6 inhibitor Ribociclib after 1st line chemotherapy in hormone receptor positive / HER2 negative metastatic breast cancer: A phase II trial (AMICA)

NCT 03555877

AMICA is a multicenter, prospective, open-label, single-arm, phase II trial that has recruited 53 patients from 13 sites in Germany.

Background

At the time of study conception, clinical practice guidelines recommended the use of endocrine therapy (ET) as 1st line therapy in patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (BC). Despite that, about 30% of patients received chemotherapy. Even if 1st line chemotherapy is effective in this subset of patients, progression-free survival (PFS) is usually around 6-8 months.
In contrast, maintenance treatment strategies are standard of care, not only in breast cancer, but also in other tumor entities, like lung cancer (Gentzler et al. Ther Adv Med Oncol 2014), colorectal cancer (Esin et al. Cancer Treat Rev 2016), and lymphoma (Hagemeister et al. Curr Oncol Rep 2010). Maintenance treatment with ET is also an accepted treatment strategy in everyday clinical practice in the management of patients with HR+/HER2- advanced BC, and at the time of study conception, prospective data were lacking.
Cyclin-dependent kinase (CDK) 4/6 inhibitors combined with ET are the standard-of-care for ER+/HER2- metastatic BC, with improved PFS and overall survival (OS), and a good toxicity profile seen in several trials (Finn et al. N Engl J Med 2016; Hortobagyi et al. N Engl J Med 2016; Im et al. N Engl J Med 2019; Slamon et al. N Engl J Med 2020). Also, ET plus CDK4/6 inhibition yields similar or better efficacy compared to chemotherapy (Martin et al. Ann Oncol 2021; Park et al. Lancet Oncol 2019) and is associated with less toxicity, making it the preferred treatment, unless a patient has imminent organ failure. Ribociclib is a prominent CDK 4/6 inhibitor that has been evaluated in several combination phase I-III clinical trials with ET and has shown efficacy and safety in patients with HR+/HER2- metastatic BC.
The AMICA study evaluates the impact of the addition of the CDK4/6 inhibitor ribociclib to ET maintenance treatment of physicians' choice in pre- and post-menopausal women with HR+/HER2- metastatic BC with at least stable disease after first line chemotherapy and with up to one line of ET prior to chemotherapy.

Study design and objectives:

Patients were initially randomized to receive or not receive open-label treatment with ribociclib in addition to their maintenance ET. Later, the study was amended after inclusion of 37 patients and changed into a single-arm study, and all subsequent patients received ET + ribociclib. Due to slow accrual of the trial, and in accordance with the Independent Data Monitoring Committee recommendations, the trial was prematurely stopped on December 31st, 2021.
AMICA primarily aimed to estimate the median PFS of an ET maintenance therapy with ribociclib after first line chemotherapy. Secondary objectives included the median OS, safety, treatment compliance, clinical benefit rate, as well as patient-reported outcomes. Potential biomarkers as well as the role of several mutations predicting response to treatment will be determined later.

Study report

Between March 2018 and July 2022, 53 patients were enrolled and started therapy in the AMICA study (43 received ribociclib and ET, 10 received ET only). Among patients who received ribociclib + ET, the median PFS was 18.9 months [95%CI: 13.2, 32.6]. Among patients who received ET only, the median PFS was 16.55 [2.7, 29.2]. The median OS was not reached for the cohort of patients who received ribociclib + ET, while the median OS for patients who received ET only was 22.5 months [4.4, not applicable (NA)]. For patients who received ribociclib + ET, 3 patients (7%) had a complete response, 10 patients (23.3%) had partial response, 15 patients (34.9%) had stable disease, 10 patients (23.3%) experienced progressive disease, and 5 patients (11.6%) were not evaluable.
The toxicity profile observed in the study was in line with the known safety profile of ribociclib without new safety concerns. In total, 17 serious adverse events (SAEs) were reported across 12 patients, mostly being gastrointestinal disorders (4 SAEs), infections and infestations (3 SAEs), and nervous system disorders (3 SAEs). Side effects were tolerated and were managed with dose reductions or interruptions. Most treatment discontinuations occurred due to tumor progression and were not treatment related. Quality of life was comparable between study start and the end of the study.
During treatment and in the 30 days following last treatment, 15 patients died – 14 (93.3%) of whom due to tumor-related reasons, and one patient died due to pneumonia. Of all SAEs, one was fatal but was not tumor- or treatment-related. Furthermore, 12 patients treated with ribociclib + ET reached the end-of-study period, 10 of whom (83.3%) continued ribociclib after the study ended.
The results of the AMICA study show a promising efficacy of maintenance treatment with ribociclib added to ET after at least stable disease following first line chemotherapy in patients with HR+/HER2- metastatic BC. Treatment with ribociclib has an acceptable safety profile and can delay tumor progression after chemotherapy in this patient population.

Official results of the AMICA study are expected to be published in 2023. We would like to sincerely thank all participating centers for their commitment and efforts.

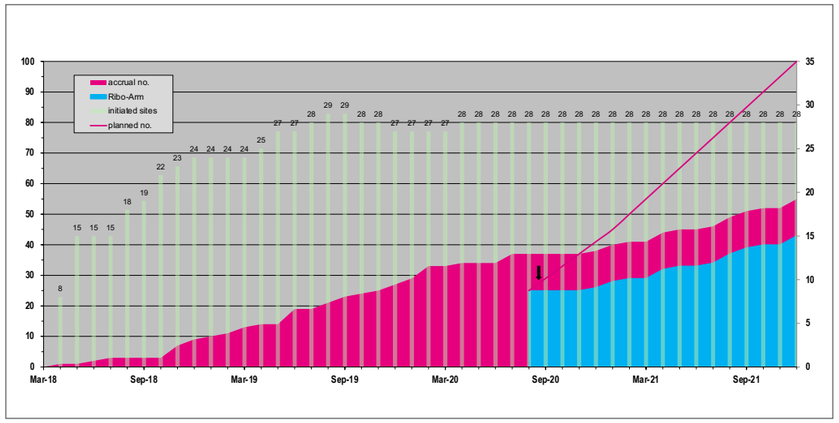

Figure 1: AMICA final recruitment as of 31st December 2022.

Publications:

1. Decker T, Denkert C, Lübbe K, et al. 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 (AMICA) GBG 98. Ann Oncol. 2018; 29 (suppl_8): viii90-viii121.

2. Decker T, Lüdtke-Heckenkamp K, Melnichuk, L, et al. Anti-hormonal maintenance treatment with the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in hormone receptor positive/HER2 negative metastatic breast cancer: a phase II trial (AMICA). San Antonio Breast Cancer Symposium, December 6-10, 2022.

COLLABORATING STUDY GROUPS:

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German Breast Group

STUDY CHAIRS:
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GBG 74: GENEVIEVE

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Randomized, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neo-adjuvant treatment in patients with operable triple negative or luminal B/HER2 normal breast cancer

NCT 01779479

GENEVIEVE is a neoadjuvant, prospective, multicenter, open-label, randomized phase II trial that has recruited 333 patients from 44 sites in Germany.

Background

Paclitaxel is among the most active agents in the treatment of metastatic breast cancer, with response rates ranging from 30 to 60% when used as a single agent. Moreover, in the neoadjuvant setting, weekly paclitaxel given before an anthracycline-based regimen in patients with resectable tumors induced a significantly higher pCR rate (Green et al. J Clin Oncol 2005).
Cabazitaxel is a new taxoid which promotes the tubulin assembly in vitro and stabilizes microtubules against cold-induced depolymerization as efficiently as docetaxel, and it was selected for development based on a better antiproliferative activity on resistant cell lines than docetaxel. A phase 2 study in patients with taxane- and/or anthracycline-resistant metastatic breast cancer demonstrated that cabazitaxel was active and well tolerated (Pivot et al. Ann Oncol 2008). These clinical data support the assessment of cabazitaxel versus an established taxane such as paclitaxel in breast cancer using the dose registered for metastatic castration-resistant prostate cancer.
In the GENEVIEVE study, cabazitaxel has been compared against weekly paclitaxel, which is currently the most widely used treatment for breast cancer patients. A head-to-head comparison in the neoadjuvant setting was sought to allow a rapid and precise comparison of efficacy and tolerability of cabazitaxel versus paclitaxel, to decide whether further development of this taxoid in breast cancer is reasonable.
GENEVIEVE primarily aimed to compare the pathological complete response (pCR, ypT0/is ypN0/+) in patients with operable HER2-negative (triple negative or luminal B/HER2-) primary breast cancer treated with either cabazitaxel or weekly paclitaxel. In addition, pCR according to other definition and in stratified subgroups, objective response rate, pCR and local recurrence free survival in patients with a clinical complete response and negative core biopsy before surgery, breast conservation rate, toxicity, compliance, invasive locoregional recurrence-free, distant-disease-free (DDFS), invasive disease-free (iDFS) and overall survival (OS) will be compared between the two treatment arms.
Patients without cCR could undergo a core biopsy to demonstrate that a pCR has not been obtained. Patients without response could then continue with an anthracycline based chemotherapy (Figure 1).
GENEVIEVE also offers the opportunity to conduct translational research in order to explore the existence of biomarkers and profiles potentially predicting response to treatment.

Study report

The study has recruited a total of 333 patients between March 2013 and June 2015 from 44 German sites. In sum, 74,7% of patients completed treatment in the cabazitaxel arm and 83.2% in the paclitaxel arm. Patients in the cabazitaxel arm had a significantly lower pCR rate compared to the paclitaxel arm (1.2% versus 10.8%; p=0.001). The study results also showed no short-term effects of cabazitaxel in triple negative or luminal B/HER2– primary breast cancer. High-grade toxicity (hematological and non-hematological) was significantly more common in the cabazitaxel arm compared to the paclitaxel arm (25.3% versus 10.2%; p<0.001), while drug exposure and patient compliance did not differ between the two arms [1, 2].
Survival analyses utilizing follow-up data with a median of 89 months (range, 87.2-90.6) demonstrated comparable long-term outcomes including an overall of 80 iDFS events (43 after cabazitaxel and 37 after paclitaxel) and 47 deaths (23 after cabazitaxel and 24 after paclitaxel). There were no significant differences in the iDFS, DDFS, and OS rates between the two arms after 3 and 5 years. Patients with HER2-primary breast cancer treated with neoadjuvant cabazitaxel showed significantly lower pCR rate, however, that did not negatively impact survival rates.

Publications:

1. Paepke S, Huober J, Kümmel S, et al. Randomized, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple negative or luminal B/HER2 normal breast cancer (GENEVIEVE). Eur J Cancer 2016; 57 (suppl.2):S99 (Poster 350)

2. Kümmel S, Paepke S, Huober J, et al. Randomised, open-label, phase II study comparing the efficacy and the safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer (GENEVIEVE). Eur J Cancer. 2017 Oct;84:1-8. doi: 10.1016/j.ejca.2017.06.037.

3. Huober J, Janni W, Untch M, et al. Long-term survival of a randomised, open-label, phase II study comparing the efficacy and safety of cabazitaxel versus weekly paclitaxel given as neoadjuvant treatment in patients with operable triple-negative or luminal B/HER2-negative breast cancer (GENEVIEVE). ASCO 2022 (Poster 168)

We thank all participating centers for their commitment and efforts.

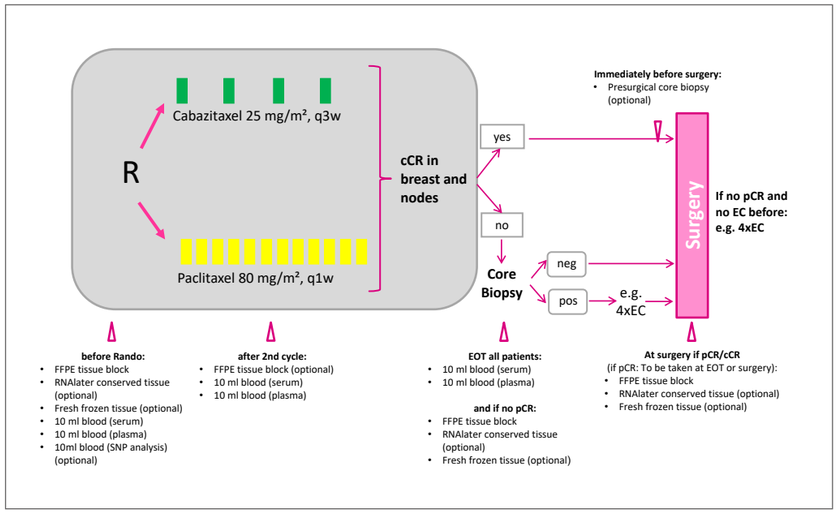

Figure 1: GENEVIEVE Study Design (Amendment 2)

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

SPONSOR:
German Breast Group

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Translational Research & Biobanking

Translational Research & Biobanking

Central Pathology and GBG Tumor Bank

In 2022, the Institute of Pathology at the University of Marburg introduced several new technical and bioinformatical infrastructures for translational research. Spatial transcriptomics reveal tumor heterogeneity by spatially resolving transcriptional activity within intact tissues and cell populations. Different techniques, such as GeoMx® (Nanostring) and Visium Spatial Gene Expression (10XGenomics), have been established to determine differences in gene expression profiles between tumor and stromal cells in FFPE tissue. In addition, a completely new pipeline for HTG's EdgeSeq RNA profiling (using macrodissected FFPE tissue) was invented to analyze bulk targeted gene expression profiles for over 2,500 genes. For protein expression analysis on tissue microarrays (TMAs), a fully automated TMA generator with a digital annotation approach was introduced to expand the institute's research equipment.

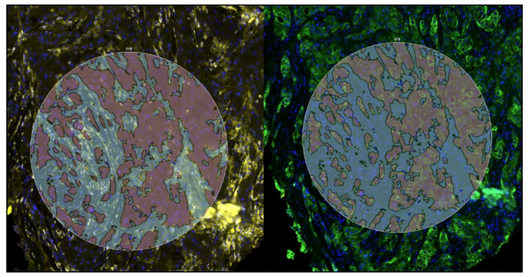

Figure 1 Biomarker analysis on TMA.
Spatial RNA gene expression profiling using immunofluorescence antibodies for identification of tumor and stromal cells.

New Research Activities

SATURN³

An interdisciplinary research network to address tumor heterogeneity – supported by BMBF grant

SATURN³ stands for "Spatial and Temporal Resolution of Intratumoral Heterogeneity in 3 hard-to-treat Cancers" (breast cancer, colorectal cancer, and pancreatic cancer). The German Federal Ministry of Education and Research (BMBF) is funding SATURN³ for 5 years as part of the initiative "Nationale Dekade gegen Krebs".
The aim of the SATURN³ consortium is to address intratumoral heterogeneity (ITH), which may be the cause for therapy resistance and the development of metastatic clones. For this purpose, it is first necessary to characterize ITH in patients using innovative tissue sampling schemes, then to functionally explore the underlying mechanisms driving therapy resistance and metastasis, and eventually to validate biomarkers and novel therapeutic strategies within clinical settings.
Nine subprojects will organize recruitment of patients and biomaterial sampling, multi-omics analyses, data modeling, data management, and clinical translation to validate emerging results.
Prof. Dr. Sibylle Loibl as the lead of subproject "Clinical Translation" will bring in GBG's longstanding expertise on clinical study protocols, biomaterial collection, and biomarker validation.

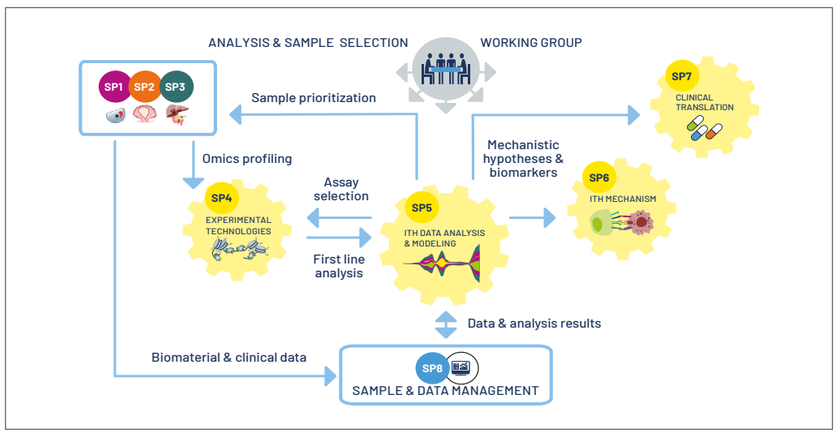

Figure 2: Saturn³ flowchart

Coordinator: Jens Siveke, West German Cancer Center, University Hospital Essen
Co-Coordinator: Andreas Trumpp, German Cancer Research Center, Heidelberg
Co-Coordinator: Wilko Weichert, Technical University Munich

Subproject Leaders:

SP1 (Breast Cancer): Andreas Schneeweiss, University Hospital Heidelberg
SP2 (Colorectal Cancer): Florian Greten, Georg-Speyer-Haus, Frankfurt
SP3 (Pancreatic Cancer): Christiane Bruns, University Hospital Cologne
SP4 (Experimental Technologies): Karsten Rippe, German Cancer Research Center, Heidelberg
SP5 (Data Analysis & Modeling): Oliver Stegle, German Cancer Research Center, Heidelberg
SP6 (ITH Mechanisms): Barbara Grüner, University Hospital Essen
SP7 (Clinical Validation): Sibylle Loibl, German Breast Group, Neu-Isenburg
SP8 (Sample & Data Management): Melanie Börries, University Hospital Freiburg
SP9 (Project Management): Jens Siveke, University Hospital Essen

Update on ongoing projects

Gut microbiome analyses within the "ONCOBIOME" project

"ONCOBIOME" is an international collaboration project, which is coordinated by Prof. Laurence Zitvogel (Institute Gustave Roussy) and funded by the EU research program Horizon 2020. The aim of the 5-year running project is to determine the relationship between intestinal microbial signatures and the prognosis and treatment resistance in four common cancer entities (breast, colon, and lung cancers as well as melanoma).

The GBG participates with sample collections (tumor tissue and stool samples) as well as expertise in clinical translational research. Collection of stool samples was successfully introduced in the study protocol of GeparDouze. Starting with amendment 1, it will also be implemented in the SASCIA study. Feces are collected in a special conservation medium and stored frozen at -20°C. Next generation sequencing of the stool samples to identify cancer-relevant microbial species is conducted at the University of Trento, Italy (Prof. Nicola Segata).
An expression analysis of pre-therapeutic FFPE tumor samples by HTG EdgeSeq is performed at the Institute of Pathology at the University of Marburg (Prof. Denkert), as well as evaluation of stromal TILs (tumor infiltrating lymphocytes).
The rationale for harnessing the gut microbiome in support of cancer therapy and the progress of clinical trials testing this new therapeutic paradigm in cancer patients were highlighted in a recent publication (Daillère et al. Oncoimmunology 2020).

DNA Damage Response (DDR) and HRD (Homologous Recombination Deficiency) in breast cancer

Prof. Andrew Tutt and his team at the ICR, London, and GBG are cooperating on a translational research project aiming to understand the mechanisms of resistance to platinum-based therapy and PARP inhibitors in breast cancer with homologous recombination deficiency (HRD).
Cancers with defects in HR-based DNA repair have characteristic chromosomal changes reflecting the use of alternative error-prone repair pathways, thus promoting the growth of cancer cells by inducing de novo driver mutations, generating tumor heterogeneity, and evading apoptosis. Triple negative breast cancer (TNBC) may have diverse defects in HR-based DNA repair through germline mutations in *BRCA1*, *BRCA2* and PALB2, promoter methylation of *BRCA1* and RAD51C, and other yet to be identified mechanisms.
The use of PARP inhibitors and platinum-containing chemotherapy regimens is now well-established in advanced breast cancers with germline *BRCA1/2* mutation. The GeparOLA, GeparOcto, and GeparSixto trials are among those that have investigated these agents in the neoadjuvant setting, and also in g*BRCA1/2* wild type but HRD-positive (homologous recombination deficient) tumors. Residual tumors collected within these trials will be analyzed (whole exome/RNA sequencing) to identify genomic and transcriptomic features that may have led to therapy resistance.

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

FURTHER INFORMATION:
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GBG Study Finder 2023*

Early Breast Cancer

Operative Studies (M0)

Operable node-positive breast cancer: • Most suspicious lymph node clipped • AJCC/UICC stage II-III • Eligible for primary axillary lymph node dissection or sentinel lymph node biopsy procedure	**GBG 101: TAXIS** Tailored axillary surgery **with or without axillary lymph node dissection** followed by radiotherapy. All patients will receive breast/chest wall and regional nodal irradiation. Patients without axillary lymph node dissection will receive additional irradiation of the axilla.
Operable HER2-positive or triple-negative breast cancer: • cT1c-T3 prior to neoadjuvant systemic therapy (NAST) and • cN0/iN0 • Standard NAST with radiological complete response	**GBG 104: EUBREAST-01** **Omission of sentinel lymph node biopsy** in patients with radiologic and pathologic complete response in the breast after neoadjuvant systemic therapy. All patients with confirmed breast pCR after lumpectomy will be selected for the single study arm leading to omission of any axillary treatment.

Neo-adjuvant Studies (M0)

HER2-positive, HR-positive breast cancer: • cT1c-T3 prior to neoadjuvant treatment • Centrally confirmed *PIK3CA* mutation (tumor) • BMI ≤30	**GBG 105: GeparPiPPa** Arm A: Endocrine therapy in combination with ready-to-use fixed-dose combination of pertuzumab and trastuzumab s.c. (PH-FDC SC) q3w and **inavolisib** (6 cycles) Arm B: Endocrine therapy and PH-FDC SC q3w (6 cycles)

Post-neoadjuvant Studies (M0)

HER2-negative breast cancer, non-pCR after NACT: HR-negative (TNBC) or HR-positive with CPS-EG score ≥3 or 2 and ypN+ At least 16 weeks of taxane-based chemotherapy	**GBG 102: SASCIA** Arm A: **Sacituzumab govitecan** 8 cycles d1,8 q3w Arm B: Treatment of physician's choice (8 cycles capecitabine or platinum-based chemotherapy or observation) In patients with HR-positive breast cancer, endocrine therapy will be administered according to local guidelines.
HER2-positive breast cancer, non-pCR after NACT: • cT4, cN0-3 or cT1-3, cN2-3 at first diagnosis or • cT1-3, cN0-1 at first diagnosis with ypN1-3 after NACT • An interval of ≤12 weeks between the date of last surgery and the date of randomization • At least 16 weeks chemotherapy, including at least 9 weeks of trastuzumab (± pertuzumab) and at least 9 weeks of taxane-based chemotherapy	**GBG 103:TruDy/DESTINY-B05** Arm A: **Trastuzumab deruxtecan** 14 cycles d1 q3w Arm B: Trastuzumab emtansine (T-DM1) 14 cycles d1 q3w

Adjuvant Studies (M0)

HR-positive / HER2-negative breast cancer: • Intermediate/high risk of relapse • 2 - 5 years endocrine therapy (ET) Adequate surgical and systemic pretreatment	**GBG 110: CAMBRIA-1**** Arm A: **Camizestrant 150mg 1x1/d** over 5 years with or without LHRH agonist Arm B: Continue the standard ET of investigator's choice (AI or tamoxifen with or without LHRH agonist)
HER2-positive breast cancer: • Stage I, II or III prior to neoadjuvant treatment and non-pCR or Stage III and pCR • Neoadjuvant chemotherapy (CT) with at least 4 cycles of a taxane-based CT and anti-HER2 therapy • Start of study treatment within 90 days after completion of adjuvant trastuzumab	**GBG: 111 Flamingo-01**** HLA-A*02 subjects will be randomized to GLSI-100 or placebo: Arm A: 11 intradermal doses of placebo (NaCl 0.9%) over 3 years Arm B: 11 intradermal doses of GLSI-100 (blinded) over 3 years A third open-label arm will explore GLSI-100 in non-HLA-A*02 positive patients (11 intradermal doses of GLSI-100 over 3 years)

Metastatic Breast Cancer

All subtypes

Brain metastases of breast cancer	**GBG79: Brain Metastases in Breast Cancer (BMBC)** Retrospective and prospective registry designed to collect tumor characteristics of the primary and metastatic tumor as well as treatment data and biomaterial from patients diagnosed with brain metastases of breast cancer.

HER2-negative Breast Cancer

HER2-negative and HR-positive metastatic breast cancer: • 1st systemic therapy for the treatment of metastatic breast cancer • Patients with asymptomatic oligometastases of the bone as the only site of metastatic disease are excluded	**GBG 93: PADMA** Endocrine therapy **+ palbociclib versus mono-chemotherapy** +/- endocrine maintenance therapy Possible mono-chemotherapies (Physician's choice): • Capecitabine p.o. • Epirubicin i.v. • Paclitaxel i.v. • Vinorelbine i.v

Breast Cancer in Special Situations

Pregnancy and Young Women

• Patients with **breast cancer during pregnancy** • Non-pregnant women with **breast cancer < 40 years** • **M1** possible	**GBG 29: BCP** Prospective and retrospective registry study for the diagnosis and treatment of breast cancer in pregnancy compared to young non-pregnant women.

Prophylaxis

• Women with a confirmed or likely deleterious *BRCA1* germline mutation • Age ≥25 years and ≤55 years • No evidence of breast cancer • No preventive breast surgery planned • No previous history of breast or ovarian cancer	**GBG 106: BRCA-P**** Study to determine the preventive effect of denosumab on breast cancer in women carrying a *BRCA1* germline mutation: **Denosumab 120mg** s.c. every 6 months vs placebo s.c. every 6 months

Follow-up

Long-term Safety and Efficacy

Former GBG study participants in Germany	**GBG 71: Patient self-reported outcome registry (PSRO)** Collection of long-term safety and efficacy parameters of former GBG study participants from prospective clinical trials. Data reporting by the patient via questionnaire.
Former GBG study participants in other countries	**GBG 107: ETERNITY[B]** Registry for collection of long-term safety and efficacy parameters of former GBG study participants from prospective clinical trials. Data collection and documentation is performed study site.

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

** Planned start of recruitment QII-III/2023

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