GBG

GERMAN
BREAST
GROUP

Heilung durch Innovation, Kompetenz und Partnerschaft

Annual Scientific Report

2021

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Annual Scientific Report 2021

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 2021 are shown below:

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

Adjuvant
Prof. Dr. 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. V. Möbus, Frankfurt am Main
Prof. Dr. T. Reimer, Rostock
Dr. M. Reinisch, Essen
Dr. S. Schmatloch, Kassel
Prof. Dr. M. Schmidt, Mainz
PD Dr. B. Sinn, Berlin
Prof. Dr. E. Stickeler, Aachen
Prof. Dr. M. Untch, Berlin

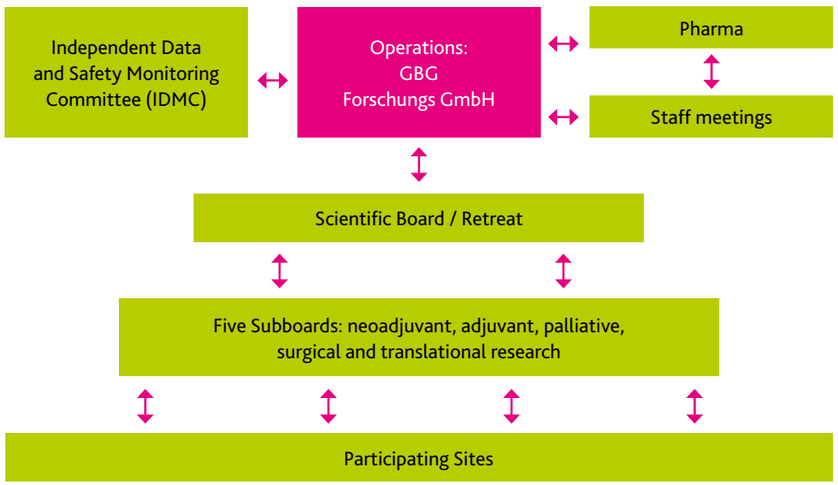

Figure 1: Structure of the German Breast Group

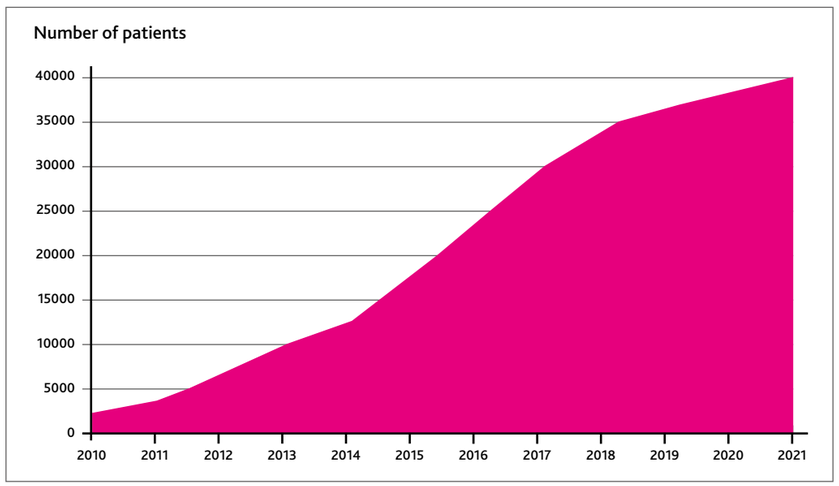

Figure 2: Annual recruitment of patients 2021

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

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

Translational Research
Prof. Dr. C. Denkert, Marburg
Prof. Dr. P. Fasching, Erlangen
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:

ABCSG:
Austrian Breast & Colorectal Cancer Study Group

AFT:
Alliance Foundation Trials

AGO:
Arbeitsgemeinschaft Gynäkologische Onkologie

AGO-B:
Breast Study Group

BREAST CANCER TRIALS GROUP

BIG:
Breast International Group

BOOG:
Borstkanker Onderzoeksgroep Nederland

CCTG:
Canadian Cancer Trials Group

CECOG:
Central European Cooperative Oncology Grou

CIRG:
Cancer International Research Group

CRUK:
Cancer Research UK

CTI:
Cancer Trials Ireland

CTRU:
Clinical Trials Research Unit

DKG:
Deutsche Krebsgesellschaft

EBCTCG:
Early Breast Cancer Trialists' Collaborative Group

EORTC:
European Organisation for Research and Treatment of Cancer

Fondazione Michelangelo:
Scientific organization based in Italy

GEICAM:
Grupo Español de Investigación del Cáncer de Mama

IBCSG:
International Breast Cancer Study Group

ICCG:
International Collaborative Cancer Group

ICR CTSU:
The Institute of Cancer Research

IDDI
International Drug Development Institute, Inc.

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

JBCRG:
Japan Breast Cancer Research Group

KCSG:
Korean Cancer Study Group

LACOG:
Latin American Cooperative Oncology Group

NOGGO:
Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie

NRG:
Oncology

NSABP:
National Surgical Adjuvant Breast and Bowel Project

PrECOG, LLC:
Cancer Clinical Trials Research Company, US

SAKK:
Swiss Group for Clinical Cancer Research

SBG:
Scandinavian Breast Cancer Group

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

UCBG:
French breast cancer intergroup UNICANCER

UNICANCER:
UNICANCER Group, France

Uniklinik Köln

Universität Rostock

Universitätsklinikum Hamburg-Eppendorf

Universitätsspital Basel, Brustzentrum

UZL:
University Hospital of Leuven

WSG:
Westdeutsche Studiengruppe

4. Publications in 2021

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 2021 are listed in 4.1., 4.2. and 4.3.

4.1. Peer-reviewed articles in 2021

1. Curigliano G, Mueller V, Borges V, et al. Tucatinib vs 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. 2021; doi: 10.1016/j.annonc.2021.12.005.

2. Loibl S, Furlanetto J. Integrating CDK4/6 inhibitors in the treatment of patients with early breast cancer. Breast. 2021; doi: 10.1016/j.breast.2021.12.008.

3. Wege AK, Rom-Jurek EM, Jank P, et al. mdm2 gene amplification is associated with luminal breast cancer progression in humanized PDX mice and a worse outcome of estrogen receptor positive disease. Int J Cancer. 2021; doi: 10.1002/ijc.33911.

4. Schneeweiss A, Michel LL, Möbus V, et al. Survival analysis of the randomised phase III GeparOcto trial comparing neoadjuvant chemotherapy of intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for patients with high-risk early breast cancer. Eur J Cancer. 2022;160:100-111 (Epub 2021).

5. Metzger-Filho O, Collier K, Asad S, et al. Matched cohort study of germline *BRCA* mutation carriers with triple negative breast cancer in brightness. NPJ Breast Cancer. 2021;7:142.

6. Jurmeister P, Weber K, Villegas S, et al. DNA methylation profiling identifies two distinct subgroups in breast cancers with low hormone receptor expression, mainly associated with HER2 amplification status. Clin Epigenetics. 2021;13:184.

7. Llop-Guevara A, Loibl S, Villacampa G, et al. Association of RAD51 with homologous recombination deficiency (HRD) and clinical outcomes in untreated triple-negative breast cancer (TNBC): analysis of the GeparSixto randomized clinical trial. Ann Oncol. 2021;32:1590-1596.

8. Bardia A, Hurvitz SA, Rugo HS, et al. A plain language summary of the ASCENT study: Sacituzumab Govitecan for metastatic triple-negative breast cancer. Future Oncol. 2021;17:3911-3924.

9. Möbus V, Lück HJ, Ladda E, et al. Phase III randomised trial comparing intense dose-dense chemotherapy to tailored dose-dense chemotherapy in high-risk early breast cancer (GAIN-2). Eur J Cancer. 2021;156:138-148.

10. Schrodi S, Braun M, Andrulat A, et al. Outcome of breast cancer patients with low hormone receptor positivity: analysis of a 15-year population-based cohort. Ann Oncol. 2021;32:1410-1424.

11. Stürken C, Möbus V, Milde-Langosch K, et al. TGFB-induced factor homeobox 1 (TGIF) expression in breast cancer. BMC Cancer. 2021;21:920.

12. Jerusalem G, Farah S, Courtois A, et al. Continuous versus intermittent extended adjuvant letrozole for breast cancer: final results of randomized phase III SOLE (Study of Letrozole Extension) and SOLE Estrogen Substudy. Ann Oncol. 2021;32:1256-1266.

13. Early Breast Cancer Trialists' Collaborative group (EBCTCG). Trastuzumab for early-stage, HER2-positive breast cancer: a meta-analysis of 13 864 women in seven randomised trials. Lancet Oncol. 2021;22:1139-1150.

14. Lefrère H, Floris G, Schmidt MK, et al. Breast cancer diagnosed in the post-weaning period is indicative for a poor outcome. Eur J Cancer. 2021;155:13-24.

15. Coombes RC, Tovey H, Kilburn L, et al. Effect of Celecoxib vs Placebo as Adjuvant Therapy on Disease-Free Survival Among Patients With Breast Cancer: The REACT Randomized Clinical Trial. JAMA Oncol. 2021 Jul 15:e212193.

16. Denkert C, Seither F, Schneeweiss A, et al. Clinical and molecular characteristics of HER2-low-positive breast cancer: pooled analysis of individual patient data from four prospective, neoadjuvant clinical trials. Lancet Oncol. 2021;22:1151-1161.

17. Marmé F, Solbach C, Michel L, et al. Utility of the CPS + EG scoring system in triple-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer. 2021 Aug;153:203-212.

18. Aftimos P, Oliveira M, Irrthum A, et al. Genomic and transcriptomic analyses of breast cancer primaries and matched metastases in AURORA, the Breast International Group (BIG) molecular screening initiative. Cancer Discov. 2021;11:2796-2811.

19. Furlanetto J, Marmé F, Seiler S, et al. Chemotherapy-induced ovarian failure in young women with early breast cancer: Prospective analysis of four randomised neoadjuvant/adjuvant breast cancer trials. Eur J Cancer. 2021;152:193-203

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20. Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant Olaparib for Patients with *BRCA*1- or *BRCA*2-Mutated Breast Cancer. N Engl J Med. 2021;384:2394-2405.

21. Cui W, Francis PA, Loi S, Hickey M, Stern C, Na L, Partridge AH, Loibl S, Anderson RA, Hutt KJ, Keogh LA, Phillips KA. Assessment of Ovarian Function in Phase 3 (Neo) adjuvant Breast Cancer Clinical Trials: A Systematic Evaluation. J Natl Cancer Inst. 2021 28;113:1770-8.

22. Rugo HS, Cristofanilli M, Loibl S, et al. Prognostic Factors for Overall Survival in Patients With Hormone Receptor-Positive Advanced Breast Cancer: Analyses From PALOMA-3. Oncologist. 2021;26:e1339-e1346.

23. Terrisse S, Derosa L, Lebba V, et al. Intestinal microbiota influences clinical outcome and side effects of early breast cancer treatment. Cell Death Differ. 2021;28:2778-2796.

24. Mamounas EP, Untch M, Mano MS, et al. Adjuvant T-DM1 versus Trastuzumab in Patients with Residual Invasive Disease after Neoadjuvant Therapy for HER2-Positive Breast Cancer: Subgroup Analyses from KATHERINE. Ann Oncol. 2021;32:1005-1014.

25. Bardia A, Hurvitz SA, Tolaney SM, et al. Sacituzumab Govitecan in Metastatic Triple-Negative Breast Cancer. N Engl J Med. 2021;384:1529-1541.

26. Loibl S, Marmé F, Martin M, et al. Palbociclib for Residual High-Risk Invasive HR-Positive and HER2-Negative Early Breast Cancer-The Penelope-B Trial. J Clin Oncol. 2021; 39:1518-1530.

27. Ciruelos EM, Rugo HS, Mayer IA, et al. Patient-Reported Outcomes in Patients With PIK3CA-Mutated Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Advanced Breast Cancer From SOLAR-1. J Clin Oncol. 2021;39:2005-2015.

28. Villegas SL, Nekljudova V, Pfarr N, et al. Therapy response and prognosis of patients with early breast cancer with low positivity for hormone receptors - An analysis of 2765 patients from neoadjuvant clinical trials. Eur J Cancer. 2021;148:159-170.

29. Riecke K, Müller V, Weide R, et al. Predicting Prognosis of Breast Cancer Patients with Brain Metastases in the BMBC Registry-Comparison of Three Different GPA Prognostic Scores. Cancers (Basel). 2021;13:844.

30. Filho OM, Stover DG, Asad S, et al. Association of Immunophenotype With Pathologic Complete Response to Neoadjuvant Chemotherapy for Triple-Negative Breast Cancer: A Secondary Analysis of the

BrighTNess Phase 3 Randomized Clinical Trial. JAMA Oncol. 2021;7:603-608.

31. Sinn BV, Loibl S, Hanusch CA, et al. Immune-related gene expression predicts response to neoadjuvant chemotherapy but not additional benefit from PD-L1 inhibition in women with early triple-negative breast cancer. Clin Cancer Res. 2021;27:2584-2591.

32. Edlund K, Madjar K, Lebrecht A, et al. Gene expression-based prediction of neoadjuvant chemotherapy response in early breast cancer: results of the prospective multicenter EXPRESSION trial. Clin Cancer Res. 2021;27:2148-2158.

33. Reinisch M, Seiler S, Hauzenberger T, et al. Efficacy of Endocrine Therapy for the Treatment of Breast Cancer in Men: Results from the MALE Phase 2 Randomized Clinical Trial. JAMA Oncol. 2021;7:565-572.

34. Denkert C, Untch M, Benz S, et al. Reconstructing tumor history in breast cancer: signatures of mutational processes and response to neoadjuvant chemotherapy. Ann Oncol. 2021;32:500-511.

35. Mayer EL, Dueck AC, Martin M, et al. Palbociclib with adjuvant endocrine therapy in early breast cancer (PALLAS): interim analysis of a multicentre, open-label, randomised, phase 3 study. Lancet Oncol. 2021;22:212-222.

4.2. Peer-reviewed reviews in 2021

1. El Bairi K, Haynes HR, Blackley E, et al. The tale of TILs in breast cancer: A report from The International Immuno-Oncology Biomarker Working Group. NPJ Breast Cancer. 2021;7:150.

2. Loi S, Michiels S, Adams S, Loibl S, Budczies J, Denkert C, Salgado R. The journey of tumor-infiltrating lymphocytes as a biomarker in breast cancer: clinical utility in an era of checkpoint inhibition. Ann Oncol. 2021 Oct;32(10):1236-1244.

3. Polley MC, Dickler MN, Sinnwell J, et al. A clinical calculator to predict disease outcomes in women with hormone receptor-positive advanced breast cancer treated with first-line endocrine therapy. Breast Cancer Res Treat. 2021;189:15-23.

4. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. Lancet. 2021;397:1750-1769.

5. Dubsky P, Pinker K, Cardoso F, et al. Breast conservation and axillary management after primary systemic therapy in patients with early-stage breast cancer: the Lucerne toolbox. Lancet Oncol. 2021;22:e18-e28.

4.3. Congress contributions in 2021

SABCS:
San Antonio Breast Cancer Symposium, December 7-10, 2021

Gerber B, Stachs A, Veselinovic K et al. Patient-reported outcomes (PROs) for the intergroup sentinel mamma study (INSEMA, GBG75, ABCSG43): Persistent impact of axillary surgery on arm and breast symptoms in early breast cancer. SABCS 2021; abstract GS4-03, oral presentation.

Denkert C, Marmé F, Martin M, et al. Molecular plasticity of luminal breast cancer and response to CDK 4/6 inhibition - The biomarker program of the PENELOPE-B trial investigating post-neoadjuvant palbociclib. SABCS 2021; abstract PD2-04, poster discussion.

Wege AK, Vladimirova V, Solbach C, et al. Mdm2 gene amplification in estrogen receptor-positive breast cancer cells is associated with enhanced solid tumor growth and pronounced metastatic potential in humanized tumor mice (HTM) and a poor outcome of patients with luminal breast cancer. SABCS 2021; abstract PD9-07, poster discussion.

Marmé F, Schmidt M, Furlanetto J, et al. Phase III postneoadjuvant study evaluating sacituzumab govitecan (SG), an antibody drug conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment – SASCIA. SABCS 2021; abstract OT1-02-01, TIP.

Galas K, Gleitsmann M, Rey J, et al. Immunological markers in patients with breast cancer occurring during pregnancy - Results from GBG BCP study. SABCS 2021; abstract P4-04-14, poster.

Loibl S, Hauke J, Gelmon K, et al. Germline *BRCA*1/2 and other predisposition genes in high-risk early-stage HR+/HER2- breast cancer (BC) patients treated with endocrine therapy (ET) with or without palbociclib: A secondary analysis from the PENELOPE-B study. SABCS 2021; abstract P5-13-36, poster.

Regan MM, Walley BA, Fleming GF, et.al. Randomized comparison of adjuvant aromatase inhibitor exemestane + ovarian function suppression (OFS) vs tamoxifen + OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer: update of the TEXT and SOFT trials. SABCS 2021; abstract GS2-05, oral presentation.

Gnant M, Dueck AC, Frantal S, et al. Adjuvant palbociclib in HR+/HER2- early breast cancer: Final results from 5,760 patients in the randomized phase III PALLAS trial. SABCS 2021; abstract PD2-09, poster discussion.

Naughton MJ, Zahrieh D, Gnant M, et al. Quality of life and symptom severity in the PALLAS randomized trial of palbociclib with adjuvant endocrine therapy in early breast cancer (AFT-05). SABCS 2021; abstract P4-10-01, poster.

Ganz PA, Bandos H, Spanic T, et al. Quality of life results from OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)-adjuvant chemotherapy in patients with germline *BRCA*1/2 mutations and high-risk HER-2 negative early breast cancer. SABCS 2021; abstract GS4-09, oral presentation.

Geyer, Jr CE, Untch M, Prat, et al. Trastuzumab deruxtecan (T-DXd; DS-8201) vs trastuzumab emtansine (T-DM1) in high-risk patients with HER2-positive, residual invasive early breast cancer after neoadjuvant therapy: A randomized, phase 3 trial (DESTINY-Breast05). SABCS 2021; abstract OT1-02-03, TIP.

Loibl S, Tolaney SM, Punie K, et al. Assessment of health-related quality of life by clinical response from the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC). SABCS 2021; abstract P5-16-01, poster.

ESMO:
European Society for Medical Oncology, September 16-21, 2021, Virtual Meeting

Loibl S, Schmidt M, Lübbe K, et al. A multicenter, randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer (mBC) (DESIREE). Ann Oncol. 2021; 32 (suppl_5): S1292-S1293, LBA19 mini oral presentation.

García-Saenz J, Marmé F, Rugo H, et al. Quality of life from the Penelope-B study on high-risk HR+/HER2- early breast cancer patients treated with endocrine therapy with or without palbociclib. Ann Oncol. 2021; 32 (suppl_5): S407-S446, 122MO mini oral presentation.

Galactionova K, Loibl S, Salari P, et al. Health economic properties of Palbociclib in breast cancer patients with high risk of relapse following neoadjuvant therapy – results from the Penelope-B trial. Ann Oncol. 2021; 32 (suppl_5): S407-S446, 132P ePoster.

Marmé F, Hanusch C, Furlanetto J, et al. Phase III postneoadjuvant study evaluating Sacituzumab Govitecan (SG), an antibody drug conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment – SASCIA. Ann Oncol. 2021; 32 (suppl_5): S407-S446, 199TiP ePoster.

Loibl S, Sikov W, Huober J, et al. Event-free survival (EFS), overall survival (OS), and safety of adding veliparib (V) plus carboplatin (Cb) or carboplatin alone to neoadjuvant chemotherapy in triple-negative breast cancer (TNBC) after ≥4 years of follow-up: BrighTNess, a randomized Phase 3 trial. Ann Oncol. 2021; 32 (suppl_5): S408, 119O oral presentation.

Loibl S, Loirat D, Tolaney SM, et al. Health-related quality of life (HRQoL) in the ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). Ann Oncol. 2021; 32 (suppl_5): S457-S515, 257P ePoster.

Franzoi MA, Martel S, Agbor-Tarh D, et al. Impact of body mass (BMI) and weight change after adjuvant treatment in patients (pts) with HER2-positive early breast cancer. Ann Oncol. 2021; 32 (suppl_5): S415-S416, 131P ePoster.

Senologiekongress 2021,
June 17-19, 2021, Virtual Meeting

Laakmann E, Witzel I, Neunhöffer T et al. Characteristics of patients with brain metastases from HER2-positive breast cancer. oral presentation.

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

ASCO:
American Society of Clinical Oncology, Annual Meeting June 4-8, 2021, Virtual Meeting
Loibl S, Schneeweiss A, Huober J, et al. Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/ taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC). J Clin Oncol. 2021; 39.15_suppl.506, oral presenation.

Denkert C, Marmé F, Matrtin M, et al. Subgroup of post-neoadjuvant luminal-B tumors assessed by HTG in PENELOPE-B investigating palbociclib in high risk HER2-/HR+ breast cancer with residual disease. J Clin Oncol. 2021; 39.15_ suppl.519, poster discussion.

Marmé F, Martin M, Untch M, et al. Palbociclib combined with endocrine treatment in breast cancer patients with high relapse risk after neoadjuvant chemotherapy: Subgroup analyses of premenopausal patients in PENELOPE-B. J Clin Oncol. 2021; 39.15_suppl.518, poster discussion.

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. 2021; 39.15_suppl.515, poster discussion.

Marmé F, Stickeler E, Furlanetto J, et al. 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. J Clin Oncol. 2021; 39.15_ suppl.TPS602, TIP.

De Azambuja E, Eiger D, Procter MJ, et al. Cardiac safety of dual anti-HER2 blockade with pertuzumab plus trastuzumab (P+T) in the APHINITY trial. J Clin Oncol. 2021; 39.15_ suppl.510, poster discussion.

Tutt A, Garber JE, Kaufman B et al. OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo) adjuvant chemotherapy in patients with germline *BRCA*1/2 mutations and high-risk HER2-negative early breast cancer. J Clin Oncol. 2021; 39.15_suppl. LBA1, oral presentation.

Kalinsky K, Oliviera M, Traina TA, et al. Outcomes in patients (pts) aged ≥65 years in the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). J Clin Oncol. 2021; 39.15_suppl.1011, oral presentation.

Carey LA, Loirat D, Punie K, et al. Assessment of sacituzumab govitecan (SG) in patients with prior neoadjuvant/adjuvant chemotherapy in the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC). J Clin Oncol. 2021; 39.15_suppl.1080, ePoster.

Curligliano G, Mueller V, Borges VF, et al. Updated results of tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB). J Clin Oncol. 2021; 39.15_suppl. 1043, ePoster.

ESMO-Breast Cancer
May 5-8, 2021, Virtual Meeting
Llop-Guevara A, Vladimirova V, Schneeweiss A et al. Association of RAD51 with Homologous Recombination Deficiency (HRD) and clinical outcomes in untreated triple-negative breast cancer (TNBC): analysis of the GeparSixto randomized clinical trial. Ann Oncol. 2021; 32 (suppl_2): S21-S36, O2 oral presentation.

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

Furlanetto J, Denkert C, Untch M, et al. Impact of body mass index (BMI) on prognostic and predictive value of stromal tumor-infiltrating lymphocytes (sTILs) in triple-negative breast cancer (TNBC): a pooled analysis of six neoadjuvant trials. Ann Oncol. 2021; 32 (suppl_2): S27-S28, 17P ePoster.

Vladimirova V, Schneeweiss A, Jackisch C, et al. BACH1 and HIF1α predict response to neoadjuvant nab-paclitaxel (nP) treatment in early breast cancer (BC). Ann Oncol. 2021; 32 (suppl_2): S29, 21P ePoster.

Leichsenring J, Vladimirova V, Solbach C, et al. EVI1 expression in early-stage breast cancer patients treated with neoadjuvant chemotherapy. Ann Oncol. 2021; 32 (suppl_2): S32, 28P ePoster.

Labidi-Galy I, Schneeweiss A, Sinn HP, et al. Baseline menopausal status, Ki-67 and stromal tumor-infiltrating lymphocytes (TILs) and association with outcome in triple-negative breast cancer (TNBC): exploratory analysis in GeparSixto. Ann Oncol. 2021; 32 (suppl_2): S49-S50, 66P ePoster.

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.

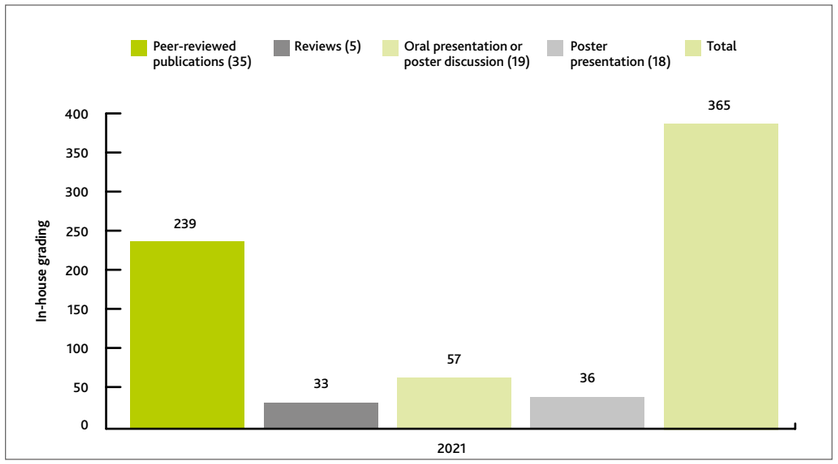


Figure 3: Overview of GBG's in-house grading for publications in 2021

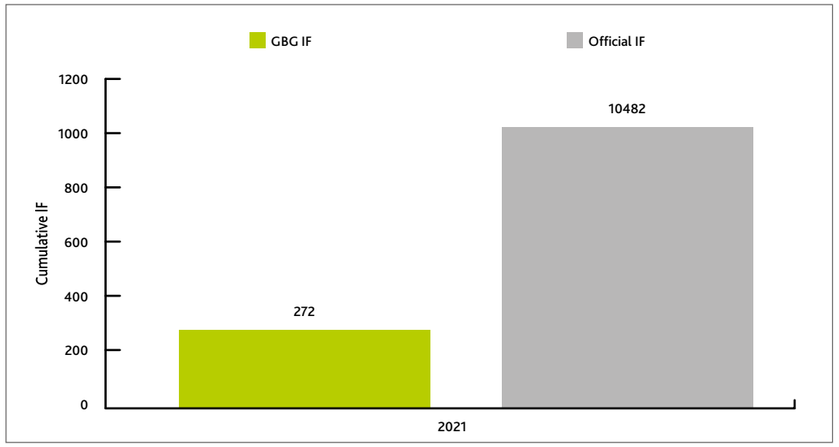


Figure 4: GBG and official Impact Factor (IF) in 2021

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

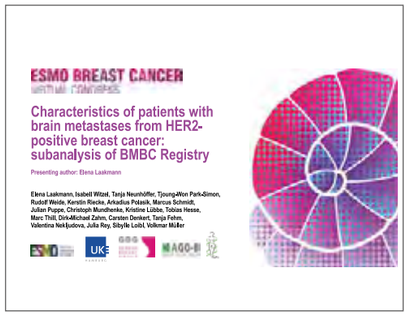
GBG Publications on translational research project

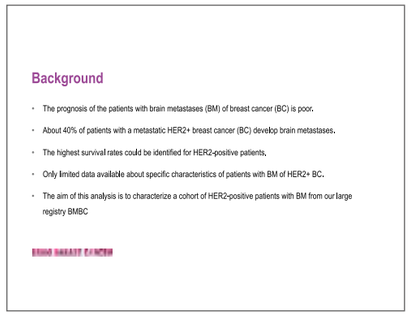
- Project leader (should prepare manuscript)
- Involved team member of this TRAFO project
- TRAFO board / protocol board members*
- Biomaterial provider
- 1-2 local pathologists providing most tumor tissue
- Biometrician
- PI (if involved in TRAFO project)

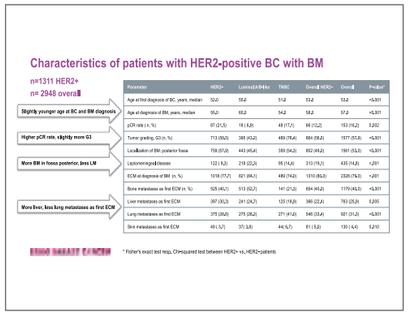
* Subboard and protocol board members will share in general authorships with best biomaterial providers on a 2:1 basis

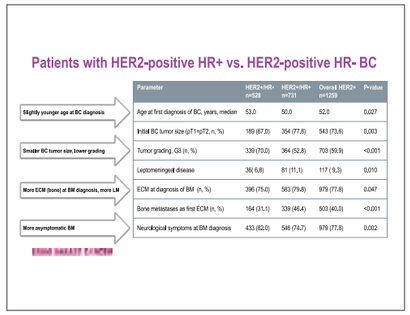
4.6. Oral and poster presentations

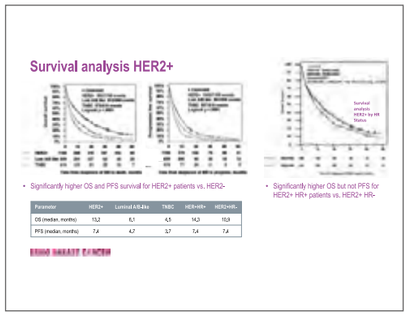
BMBC Registry
(ESMO Breast Cancer 2021)

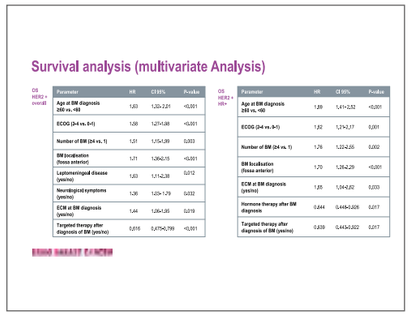


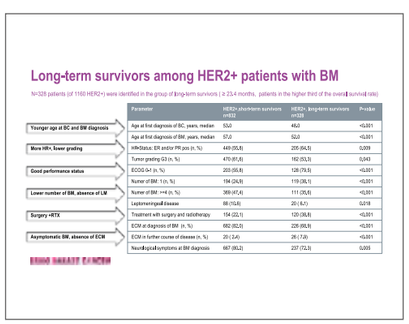


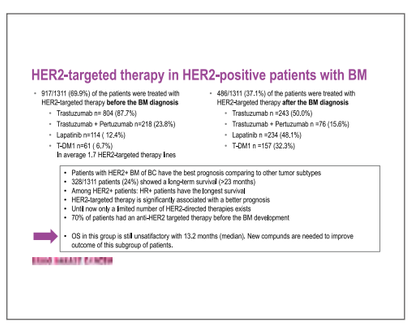




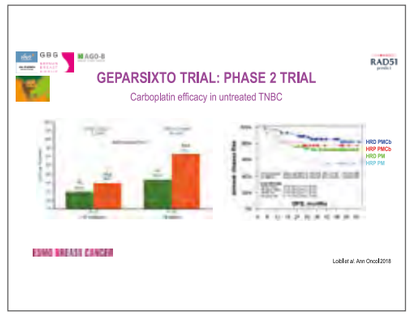


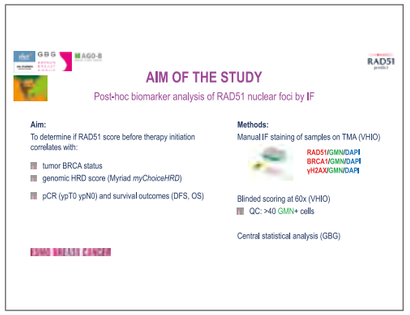


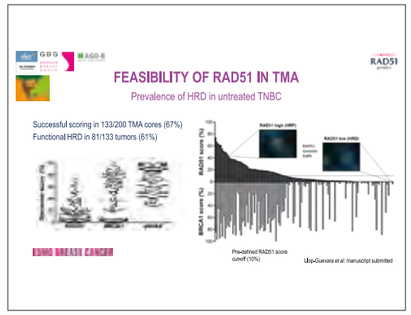


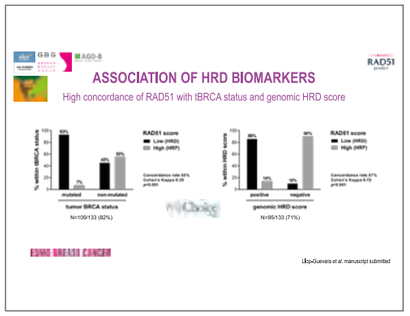


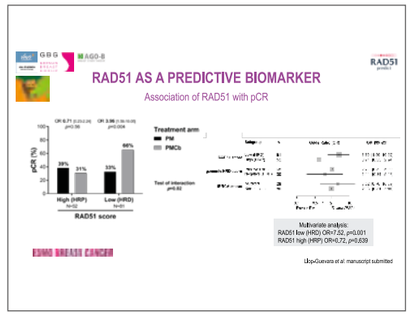
GeparSixto, RAD51
(ESMO Breast Cancer 2021)

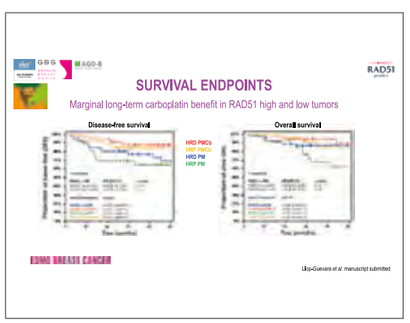




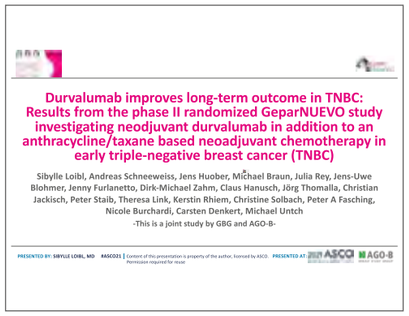


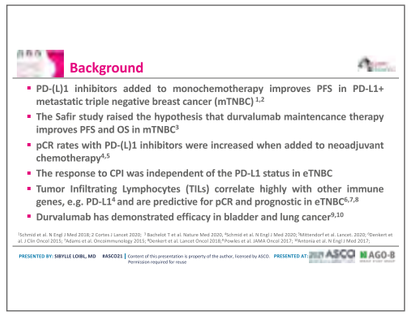


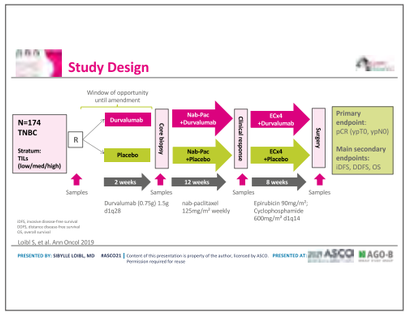


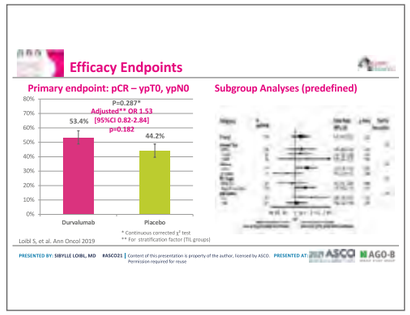


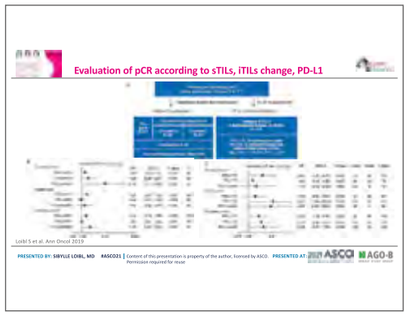
Gepar Nuevo
(ASCO 2021)

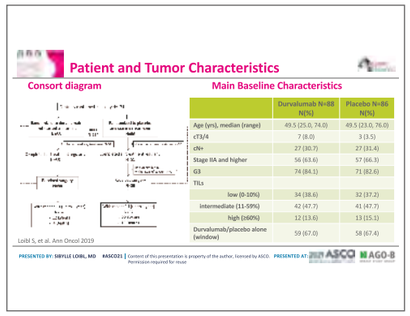


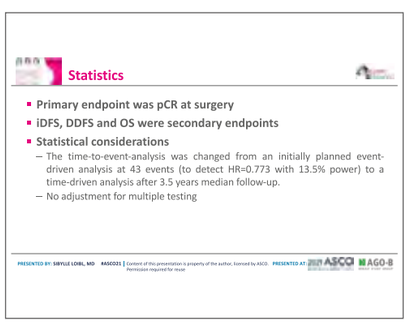


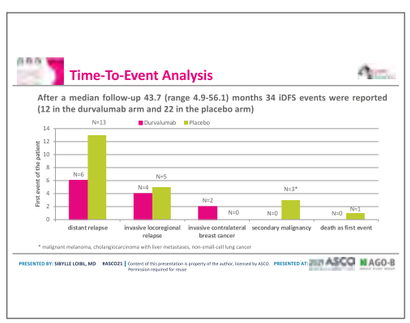












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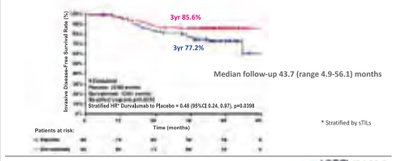
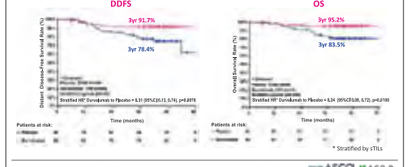
Gepar Nuevo (ASCO 2021)

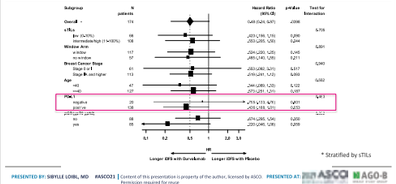
iDFS Between Treatment Arms



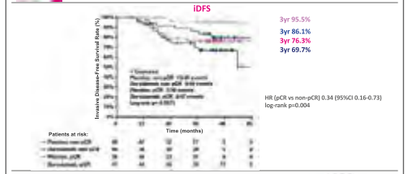
DDFS and OS Between Treatment Arms



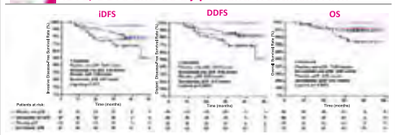
iDFS in Subgroups (univariate Cox regression model)*



iDFS by pCR and Treatment Arm



iDFS, DDFS and OS by pCR and Treatment Arm*



HR (non pCR vs pCR)=0.34 (95%CI 0.16-0.73) log-rank p=0.004

HR (non-pCR vs pCR) 0.28 (95%CI 0.11-0.69) log-rank p=0.003

HR (non-pCR vs pCR)=0.27 (95%CI 0.09-0.81) log-rank p=0.012

iDFS, DDFS and OS by pCR and Treatment Arm*

Endpoint	Category	Durvalumab 3-year rates % (95%CI)	Placebo 3-year rates % (95%CI)	HR (durvalumab vs placebo) (95%CI)	Log-rank p-value
iDFS	Non-pCR	76.3% (59.3%, 86.9%)	69.7% (53.4%, 81.2%)	0.67 (0.29-1.54)	0.346
	pCR	95.5% (83.0%, 98.8%)	86.1% (69.8%, 94.0%)	0.22 (0.05-1.06)	0.038
DDFS	Non-pCR	84.3% (68.3%, 92.6%)	71.9% (55.8%, 83.0%)	0.48 (0.18-1.25)	0.124
	pCR	100% (100%, 100%)	86.1% (69.8%, 94.0%)	0.00 (0.00-)*	0.005
OS	Non-pCR	92.0% (77.1%, 97.3%)	78.8% (63.2%, 88.4%)	0.30 (0.08-1.09)	0.053
	pCR	100% (100%, 100%)	88.9% (73.1%, 95.7%)	0.00 (0.00-)*	0.024

*no events in durvalumab arm

Summary and Conclusions

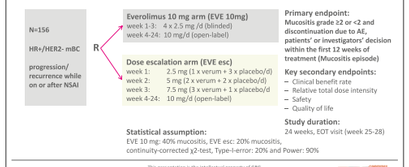
- Durvalumab added to neoadjuvant chemotherapy in TNBC significantly improved survival
  - iDFS: HR 0.48 (95%CI; 0.24, 0.97), p=0.0398
  - DDFS: HR 0.31 (95%CI 0.13, 0.74), p=0.0078
  - OS: HR 0.24 (95%CI 0.08, 0.72), p=0.0108
- Patients with pCR seem to have a better survival with durvalumab than pCR patients on placebo
- The value of PD-L1 for long-term outcome needs to be further explored
- pCR improvement with durvalumab was modest requiring further assessment of association of pCR and longer term outcomes with CPI therapies
- Given these results, the value of adjuvant therapy with CPI needs to be further assessed

DESIREE (ESMO 2021)

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

Sibylle Loibl, Marcus Schmidt, Kristina Lübbe, Thomas Decker, Marc Thill, Lelia Bauer, Volkmar Müller, Theresa Link, Jenny Furlanetto, Sherko Kümmel, Christoph Mundhenke, Oliver Hoffmann, Mark-Oliver Zahn, Lothar Müller, Carsten Denkert, Marion van Mackelenbergh, Peter A Fasching, Nicole Burchardi, Valentina Nekljudova

Study Design



Primary endpoint:
Mucositis grade ≥2 or <2 and discontinuation due to AE, patients' or investigators' decision within the first 12 weeks of treatment (Mucositis episode)

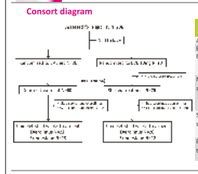
Key secondary endpoints:
- Clinical benefit rate
- Relative total dose intensity
- Safety
- Quality of life

Study duration:
24 weeks, EOT visit (week 25-28)

Statistical assumption:
EVE 10 mg: 40% mucositis, EVE esc: 20% mucositis, continuity-corrected χ2-test, Type-I-error: 20% and Power: 90%

Patient and Tumor Characteristics

Consort diagram



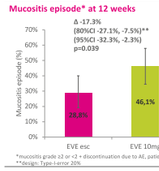
Main baseline characteristics

Parameter	Category	EVE esc N=80 N(%)	EVE 10 mg N=76 N(%)	p-value
Age, years (range)	median	64.5 (33.0-85.0)	63.0 (41.0-81.0)	0.538
BMI, kg/m² (range)	median	25.9 (16.5-45.5)	24.6 (15.9-43.9)	0.401
ECOG PS	0	57 (71.3)	63 (82.9)	0.202
	1	20 (25.0)	12 (15.8)	
	2	3 (3.8)	1 (1.3)	
No of metastatic sites	1	22 (27.5)	28 (36.8)	0.512
	2	30 (37.5)	28 (36.8)	
	3	19 (23.8)	15 (19.7)	
	≥4	9 (11.3)	5 (6.6)	
Selected metastatic sites*	Liver	45 (56.3)	32 (42.1)	0.081
	Lung	21 (26.3)	17 (22.4)	0.582
	Pleura	12 (15.0)	7 (9.2)	0.331
Previous metastatic treatment lines	0	6 (7.5)	7 (9.2)	0.849
	1-2	59 (73.8)	53 (69.7)	
	>2	15 (18.8)	16 (21.1)	

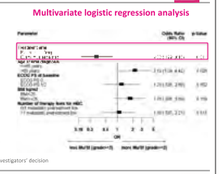
*some patients had more than one metastatic site

Primary Endpoint

Mucositis episode* at 12 weeks



Multivariate logistic regression analysis

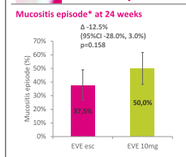


* mucositis grade ≥2 or <2 + discontinuation due to AE, patients' or investigators' decision

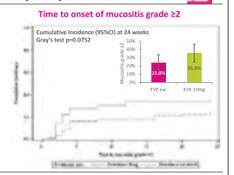
** design: Type-I-error 20%

Secondary Tolerability Endpoints

Mucositis episode* at 24 weeks

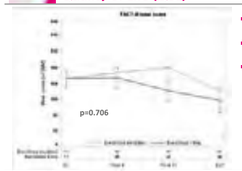


Time to onset of mucositis grade ≥2



*mucositis grade ≥2 or <2 + discontinuation due to AE, patients' or investigators' decision

Quality of Life (QoL)



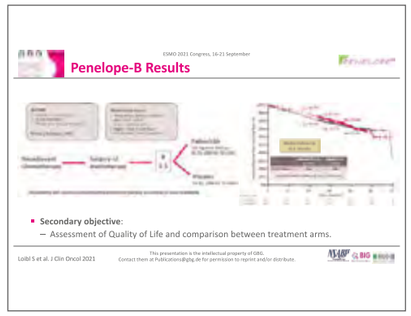
- QoL was prospectively captured by FACT-B questionnaire
- Higher FACT-B total scores (range 0-148) indicate better QoL.
- Considering the metastatic setting, FACT-B total score was generally high in both treatment arms and not significantly different between the arms:
  - Mean [SD]:
  - EVE esc 105.5 [20.5]
  - EVE 10mg 103.5 [18.6]

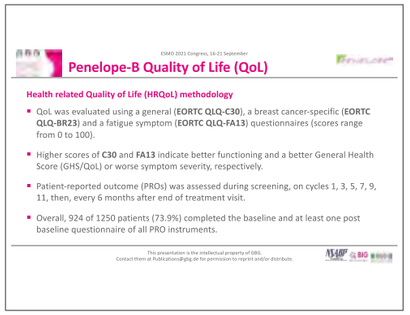
Conclusions

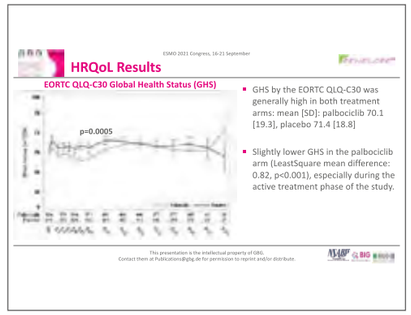
- DESIREE met its primary objective: fewer patients had mucositis grade ≥2 when the everolimus was escalated within the first 4 weeks.
- A dose escalation schema of everolimus over three weeks can be successfully used in patients with HR+/HER2- mBC to prevent the onset of mucositis grade ≥2 without affecting efficacy.
- Unirad study dose reductions of everolimus were less common in patients starting with 5mg compared to full dose (28.4% vs 46.85)[1]

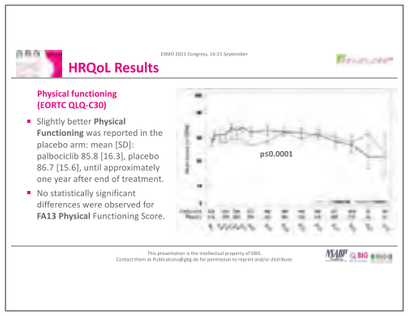
[1]Bachelot T et al. ESMO virtual plenary 2021

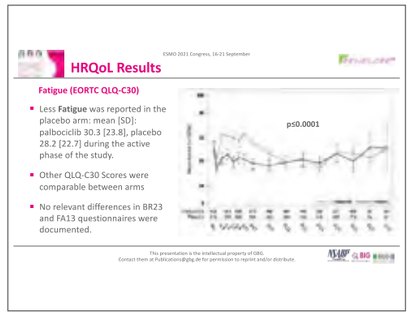
Penelope[B] (ESMO 2021)



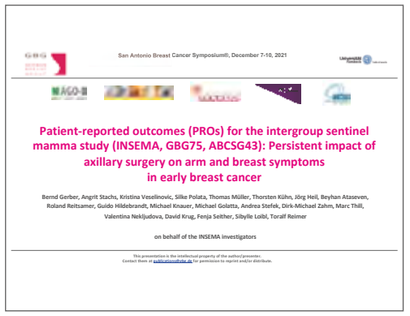


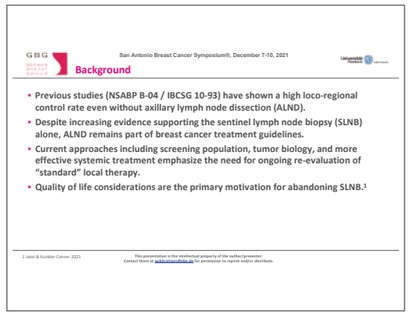


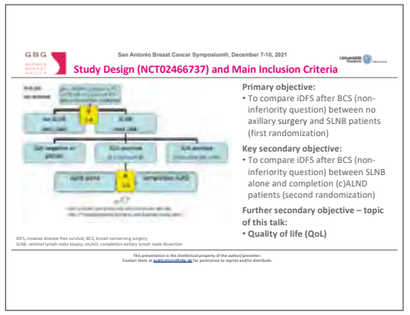


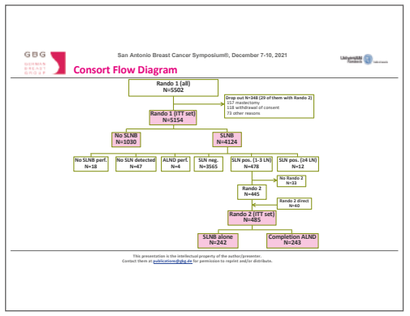


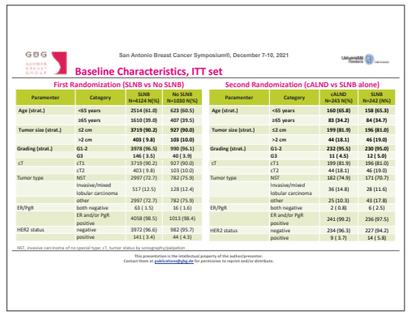
INSEMA (SABCS 2021)

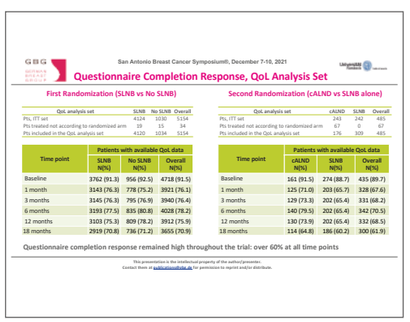


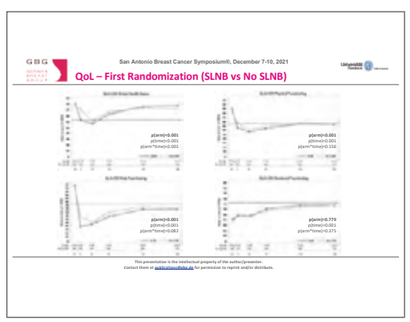












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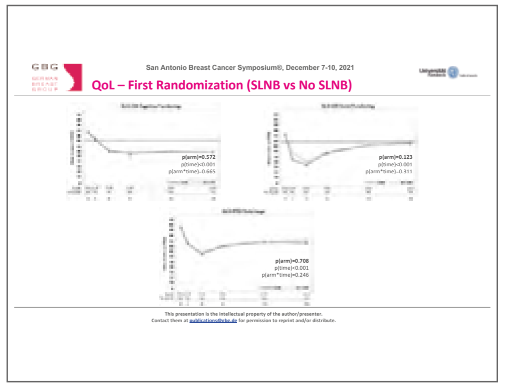
San Antonio Breast Cancer Symposium®, December 7-10, 2021
QoL – First Randomization (SLNB vs No SLNB)
p(arm)=0.572
p(time)<0.001
p(arm*time)=0.665
p(arm)=0.123
p(time)<0.001
p(arm*time)=0.311
p(arm)=0.708
p(time)<0.001
p(arm*time)=0.246
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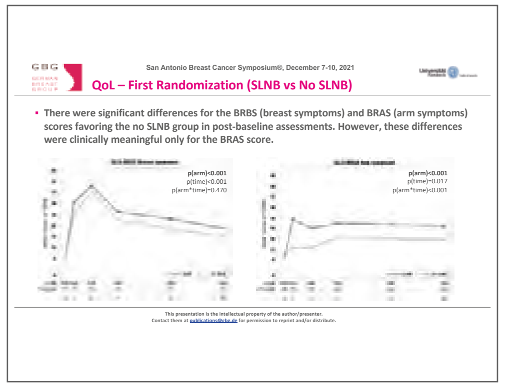
San Antonio Breast Cancer Symposium®, December 7-10, 2021
QoL – First Randomization (SLNB vs No SLNB)
There were significant differences for the BRBS (breast symptoms) and BRAS (arm symptoms) scores favoring the no SLNB group in post-baseline assessments. However, these differences were clinically meaningful only for the BRAS score.
p(arm)<0.001
p(time)<0.001
p(arm*time)=0.470
p(arm)<0.001
p(time)=0.017
p(arm*time)<0.001
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San Antonio Breast Cancer Symposium®, December 7-10, 2021
QoL – Second Randomization (cALND vs SLNB alone)
There were also no relevant differences for GHS, functional scales and body image scales/items between cALND and SLNB groups.
There were significant and clinically meaningful differences only for the BRAS (arm symptoms) scores favoring the SLNB group in post-baseline assessments.
p(arm)=0.295
p(time)<0.001
p(arm*time)=0.096
p(arm)<0.001
p(time)=0.618
p(arm*time)=0.150
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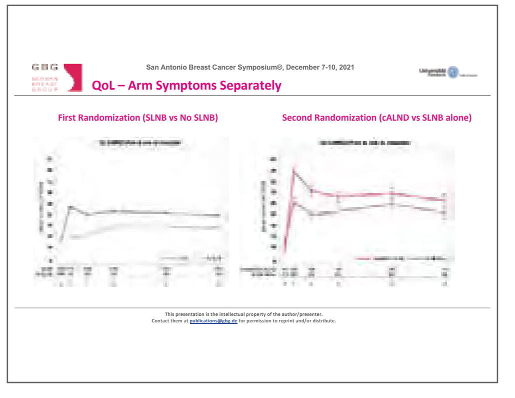
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QoL – Arm Symptoms Separately
First Randomization (SLNB vs No SLNB)
Second Randomization (cALND vs SLNB alone)
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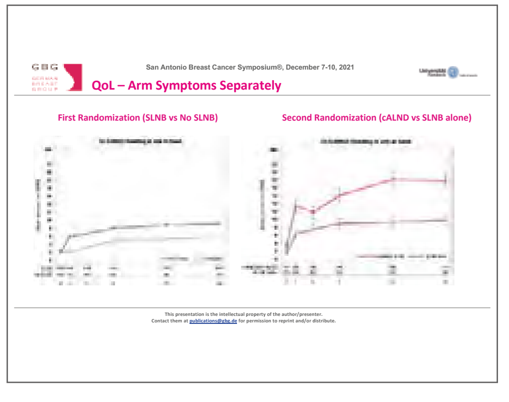
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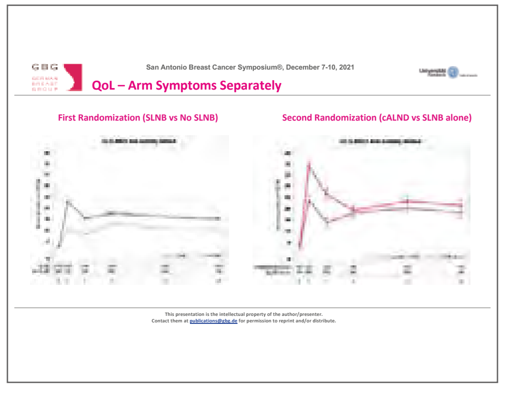
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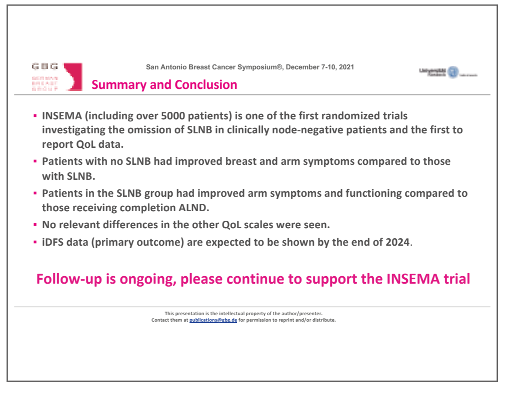
San Antonio Breast Cancer Symposium®, December 7-10, 2021
Summary and Conclusion
INSEMA (including over 5000 patients) is one of the first randomized trials investigating the omission of SLNB in clinically node-negative patients and the first to report QoL data.
Patients with no SLNB had improved breast and arm symptoms compared to those with SLNB.
Patients in the SLNB group had improved arm symptoms and functioning compared to those receiving completion ALND.
No relevant differences in the other QoL scales were seen.
iDFS data (primary outcome) are expected to be shown by the end of 2024.
Follow-up is ongoing, please continue to support the INSEMA trial
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Palbociclib combined with endocrine treatment in breast cancer patients with high relapse risk after neoadjuvant chemotherapy: Subgroup analyses of premenopausal patients in PENELOPE-B

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Background

PENELOPE-B assessed efficacy of the CDK4/6 inhibitor palbociclib for 1-year versus placebo added to endocrine therapy (ET) as post-neoadjuvant treatment in a high-risk breast cancer population. Palbociclib did not improve invasive disease-free survival (iDFS) compared to placebo (3-year iDFS 81.3% vs 77.7%)[1]. Here, we report results from the subpopulation of premenopausal women.

Patients and Methods

In PENELOPE-B (NCT01864746), patients with hormone receptor positive, HER2-negative breast cancer without pathological complete response after taxane-containing neoadjuvant chemotherapy and at high risk of relapse (CPS-EG score ≥3 or 2 and ypN+) were randomized to receive palbociclib or placebo in addition to standard endocrine treatment including tamoxifen +/- gonadotropin-releasing hormone analogue (GnRHa) or aromatase inhibitor (AI) +/- GnRHa (**Figure 1**). Menopausal status was assessed by the investigator. Survival curves were estimated using the Kaplan-Meier method and univariate Cox-proportional hazards models were used for iDFS to report hazard ratios with 95% CI. Fisher's exact test was used to compare frequencies of adverse events between arms and subgroups.

Figure 1 : PENELOPE-B Study Design

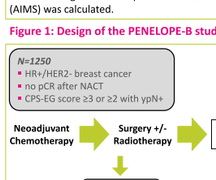


Table 1: Baseline Characteristics of Premenopausal Patients

Parameter	Category	Palbociclib N=300 N (%)	Placebo N=316 N (%)
Age, years	<30	11 (3.7)	14 (4.4)
	30-<40	83 (27.7)	77 (24.4)
	40-<50	176 (58.7)	192 (60.8)
	50-<60	30 (10.0)	33 (10.4)
	median (range)	43 (22 - 55)	43 (19 - 56)
Tumor stage at surgery	ypT0 /ypTis	14 (4.6)	8 (2.5)
	ypT1/2	218 (72.7)	251 (79.7)
	ypT3/4	68 (22.7)	56 (17.8)
Histological nodal status at surgery	ypN0	13 (4.4)	16 (5.1)
	ypN+	284 (95.6)	297 (94.9)
Histological type	lobular	24 (8.0)	24 (7.6)
Grading	G3	71 (28.0)	92 (34.1)
Ki-67%, central pathology	>15%	71 (23.7)	71 (22.5)
CPS-EG score*	1	4 (1.3)	6 (1.9)
	2	118 (39.3)	130 (41.1)
	3	147 (49.0)	141 (44.6)
	4	27 (9.0)	32 (10.1)
	5	4 (1.3)	7 (2.2)

CPS-EG, clinical, pathological stage-estrogen receptor and grading; *based on non-missing total

Table 2: Endocrine Therapy in Premenopausal Patients

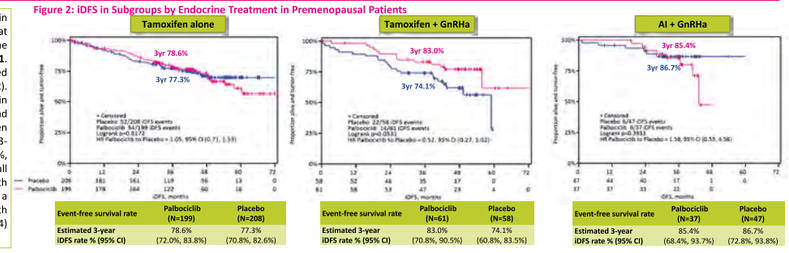
Parameter	Palbociclib N=300 N (%)	Placebo N=316 N (%)	p-value
Start ET prior to Palbociclib/Placebo	272 (90.7)	286 (90.5)	1.000
Concomitant start of ET and Palbociclib/Placebo	28 (9.3)	30 (9.5)	
First ET applied			
Tamoxifen alone	199 (67.0)	208 (66.5)	0.593
Tamoxifen + GnRHa	61 (20.5)	58 (18.5)	
AI + GnRHa	37 (12.5)	47 (15.0)	
AI alone	3	3	

AI, aromatase inhibitor ; ET, endocrine therapy; GnRHa, gonadotropin-releasing hormone analogue; *Patients received AI alone were excluded from analyses according to first ET treatment

Results

616/1250 patients randomized in Penelope-B were premenopausal at the time of enrollment, baseline characteristics are shown in **Table 1**. The majority of patients started with tamoxifen alone (**Table 2**). Overall, there was no difference in iDFS between palbociclib and placebo in premenopausal women (HR 0.95, 95% CI 0.69-1.30) with 3-year iDFS of 80.6% and 78.3%, respectively. Only in the small subgroup of patients treated with tamoxifen + GnRHa, there was a tendency for a better iDFS with palbociclib (interaction p=0.124) (**Figure 2**).

Figure 2: iDFS in Subgroups by Endocrine Treatment in Premenopausal Patients

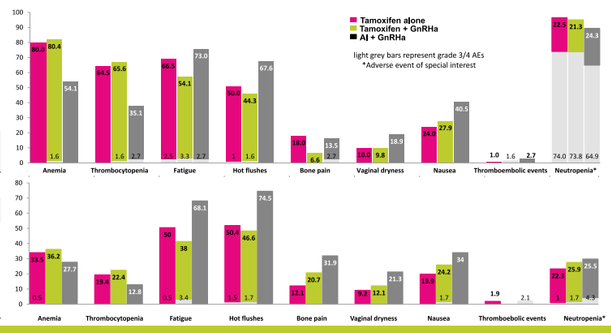


Event-free survival rate	Palbociclib (N=199)	Placebo (N=208)
Estimated 3-year iDFS rate % (95% CI)	78.6% (72.0%, 83.8%)	77.3% (70.8%, 82.6%)

Event-free survival rate	Palbociclib (N=61)	Placebo (N=58)
Estimated 3-year iDFS rate % (95% CI)	83.0% (70.8%, 90.5%)	74.1% (60.8%, 83.5%)

Event-free survival rate	Palbociclib (N=37)	Placebo (N=47)
Estimated 3-year iDFS rate % (95% CI)	85.4% (68.4%, 93.7%)	86.7% (72.8%, 93.8%)

Figure 3: Any Grade Adverse Events in Palbociclib and Placebo arm in Premenopausal Patients



Hematologic toxicity was significantly more common with palbociclib. Non-hematological toxicities any grade palbociclib vs placebo were: fatigue 67.4% vs 51.3%; hot flushes 52.2% vs 54.8%; bone pain 15.6% vs 16.6%; and vaginal dryness 11.0% vs 11.5%. Adverse events (any and high-grade) for palbociclib and placebo according to the endocrine treatment subgroups are shown in **Figure 3**.

Conclusions

1. **These are the first safety results from a phase III study for the combination tamoxifen +/-GnRHa and palbociclib.**
2. **Although the overall results did not show improvement in 3-year iDFS, an improvement was seen in the small subgroup of premenopausal women receiving tamoxifen + GnRHa. These results are mainly hypothesis generating and merit confirmation.**
3. **The addition of palbociclib to tamoxifen +/-GnRH in premenopausal women did not increase side effects compared to AI+GnRH and seems to be an alternative to AI+GnRHa.**

References

1. Loibl et al. J Clin Oncol 2021;

Presented at ASCO Annual Meeting 2021, Virtual Meeting, June 4-8.

The trial was financially supported by Pfizer, Inc.

Subgroup of post-neoadjuvant luminal-B tumors assessed by HTG in PENELOPE-B investigating palbociclib in high risk HER2-/HR+ breast cancer with residual disease

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[1]Institut für Pathologie Philipps-Universität Marburg, Germany [2]Universitätsfrauenklinik Mannheim, Germany [3]Instituto de Investigacion Sanitaria Gregorio Marañon, CIBERONC, Universidad Complutense, Madrid, Spain [4]Spanish Breast Cancer Group, GEICAM, Madrid, Spain [5]Helios Kliniken Berlin-Buch, Germany [6]Institut Bergonié and Université de Bordeaux INSERM U916, Bordeaux, France [7]Roswell Park Comprehensive Cancer Center, Buffalo NY, United States of America [8]The Asan Medical Center AMC, Seoul, South Korea [9]Penn Medicine Abramson Cancer Center, Philadelphia PA, United States of America [10]The University of California, San Francisco CA, United States of America [11]Breast Cancer Trials Australia and New Zealand and University of Queensland [12]BC Cancer, Vancouver, British Columbia, Canada [13]The Institute of Cancer Research: Royal Cancer Hospital, London, Great Britain [14]Hospital Universitario Fundación Jiménez Díaz, Madrid, Spain [15]Universitätsklinik Erlangen [16]Pfizer Inc., San Diego, United States of America [17]Breast Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan [18]Comprehensive Cancer Center, Medical University of Vienna, Vienna, Austria [19]German Breast Group, Neu-Isenburg, Germany

Poster No.519

Background

About one third of patients with hormone-receptor-positive (HR+), HER2-primary breast cancer with residual invasive disease after neoadjuvant chemotherapy will relapse despite adjuvant endocrine therapy. Therapeutic inhibition of cyclin-dependent kinase 4 and 6 (CDK 4/6) by palbociclib combined with endocrine therapy demonstrated highly relevant efficacy in metastatic breast cancer. The phase III PENELOPE-B (NCT01864746) study did not show a significant benefit from palbociclib in women with centrally confirmed HR+, HER2- primary breast cancer without a pathological complete response after taxane-containing neoadjuvant chemotherapy and at high-risk of relapse (CPS-EG score ≥3 or 2 and ypN+) for the primary endpoint[1].

Patients and Methods

After completion of neoadjuvant chemotherapy (NACT) and locoregional therapy, PENELOPE-B patients were randomized (1:1) to receive 13 cycles (1 year) of palbociclib 125 mg daily or placebo on days 1-21 in a 28d cycle in addition to standard endocrine therapy. Analysis of the primary endpoint of invasive disease-free survival (iDFS) was planned after 290 events. Secondary objective included iDFS in luminal-B group by treatment. Gene expression in post-neoadjuvant surgical residual tumor tissue samples was profiled using the HTG EdgeSeq Oncology Biomarker Panel targeting 2559 genes associated with tumor biology (HTG Molecular Diagnostics Inc.). Based on 91 genes of this panel the Absolute Intrinsic Molecular Subtyping[2] (AIMS) was calculated.

Figure 1: Design of the PENELOPE-B study

Results

Table 1. Relation of clinical variables to AIMS subtype

Parameter	Category	LumA (n=663)	LumB (n=64)	p-value
		n (%)	n (%)	
Age (years)	≤50	365 (55.1%)	21 (32.8%)	<0.001
	>50	298 (44.9%)	43 (67.2%)	
Region of site	asia	41 (6.2%)	6 (9.4%)	0.291
	other	622 (93.8%)	58 (90.6%)	
cT	cT1-2	354 (53.5%)	36 (56.2%)	0.696
	cT3-4	308 (46.5%)	28 (43.8%)	
Grade	G1-2	439 (67.0%)	23 (35.9%)	<0.001
	G3	216 (33.0%)	41 (64.1%)	
Ki-67*	≤15%	516 (77.8%)	5 (7.8%)	<0.001
	>15%	147 (22.2%)	59 (92.2%)	
ypT	ypT0-2	516 (77.8%)	52 (81.2%)	0.635
	ypT3-4	147 (22.2%)	12 (18.8%)	
ypN	ypN0-1	306 (46.2%)	29 (45.3%)	1.000
	ypN2-3	357 (53.8%)	35 (54.7%)	
Risk status	CPS-EG=2, ypN+	289 (43.6%)	15 (23.4%)	0.002
	CPS-EG≥3	374 (56.4%)	49 (76.6%)	

*post-neoadjuvant IHC

Gene expressions were measured in tumors after NACT from 906 of 1250 (72%) PENELOPE-B patients; 663 had LumA subtype, 64 LumB, 135 NormL, 16 BasalL, and 28 HER2E; for outcome see Figure 2. Compared to LumA the LumB patients were older, had higher post-neoadjuvant Ki-67, higher risk status (CPS-EG), and higher grade; no significant correlation was found for the region of participating sites, cT, ypT, and ypN (Table 1). Patients with LumB tumors had an estimated 3-year iDFS of 71.9% (Figure 3) with palbociclib vs 44.8% with placebo; the hazard ratio was 0.50 (0.24-1.05). Outcome was not different between treatment arms in patients with LumA tumors (3-year iDFS 83.9% vs 79.5%, hazard ratio 0.93 (0.68-1.28), interaction p=0.132); this was confirmed in multivariable analyses (Table2). Ki-67 by IHC and proliferation biomarkers from the HTG panel also showed no significant interaction with treatment.

Figure 2: iDFS by AIMS subtype (treatment arms combined)

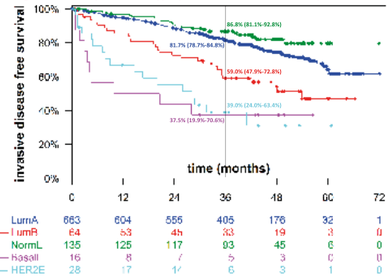

Figure 3: iDFS by AIMS subtype and treatment in the AIMS-luminal cohort

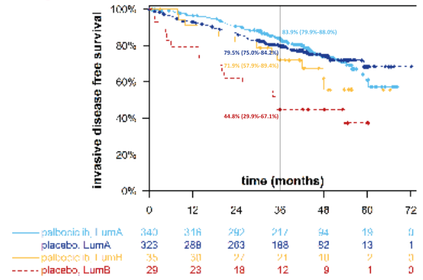

Table 2. Cox models for biomarkers defining luminal-B subgroups

Model	n	AIMS LumA HR[1] (CI)	AIMS LumB HR[1] (CI)	Interaction p-value
AIMS-arm-interaction	727	0.93 (0.68-1.28)	0.50 (0.24-1.05)	0.132
multivariable*	718	0.91 (0.66-1.25)	0.45 (0.22-0.96)	0.097
Model	**n**	**MKI67 low HR[1] (CI)**	**MKI67 high HR[1] (CI)**	**Interaction p-value**
MKI67-arm-interaction	906	1.01 (0.68-1.51)	0.79 (0.56-1.11)	0.341
multivariable*	893	1.03 (0.69-1.54)	0.79 (0.56-1.12)	0.323
Model	**n**	**Ki-67 (IHC) ≤ 15 HR[1] (CI)**	**Ki-67 (IHC) > 15 HR[1] (CI)**	**Interaction p-value**
Ki-67-arm-interaction	1250	0.88 (0.66-1.17)	1.03 (0.72-1.46)	0.504
multivariable*	1229	0.87 (0.65-1.17)	1.00 (0.70-1.43)	0.568

[1]hazard ratios (HR) and confidence interval (CI) of iDFS for palbociclib vs placebo
*additional covariables: all variables listed in Table 1

Discussion

1. **PENELOPE-B did not show a statistically significant benefit from the addition of 1 year palbociclib to endocrine therapy compared to placebo plus endocrine therapy in the entire high-risk primary breast cancer study population.**
2. **However, the small group of patients with a luminal-B tumor after NACT (n=64) potentially derived benefit from palbociclib (numerically, not statistically significant).**
3. **Further investigation is required in a larger cohort to validate a palbociclib benefit that might be confined to this group.**
4. **It would be interesting to analyze biomarker differences between the post-NACT and the metastatic situation. It has been reported for the MONALEESA trials in metastatic breast cancer that most PAM50-based subtypes (with the exception of basal-like) did benefit from the addition of ribociclib to endocrine therapy[3]**

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2. Paquet & Hallett, JNCI 2014
3. Prat et al, JCO 2021

Presented at: ASCO 2021, June 4-8, 2021

The trial was financially supported by Pfizer

Collaborating study groups:

Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls

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Poster #515

Background

Overall, a diagnosis of breast cancer during pregnancy (BCP) appears not to impact maternal prognosis if standard treatment is offered (1-3). However, caution is warranted as gestational changes in pharmacokinetics with respect to the distribution, metabolism and excretion of drugs may lead to reduced chemotherapy concentration in pregnant patients (4,5). This cohort study was designed to focus on the maternal prognosis of BCP patients that receive chemotherapy during pregnancy.

Patients and Methods

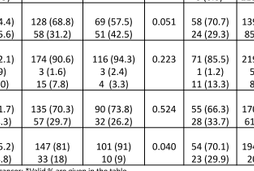
Trial design

The outcome of BCP patients treated with chemotherapy during pregnancy was compared to non-pregnant breast cancer patients treated with chemotherapy, diagnosed after 2000, excluding postpartum diagnosis and with an age limit of 45 years. The data was registered by two multicentric registries (the International Network of Cancer, Infertility and Pregnancy and the German Breast Cancer Group) that collect both retro-and prospectively breast cancer data. **Primary and secondary objectives** were to compare disease-free (DFS) and overall survival (OS), respectively, between patients treated with chemotherapy during pregnancy for BCP and patients not diagnosed in association with a pregnancy.

Statistical consideration

Cox proportional hazards regression was used to compare DFS and OS between both groups, adjusting for stage (I, II or III), grading (gr 1-2 versus gr 3), histologic tumor type (lobular versus non-lobular), estrogen receptor (ER)/progesterone receptor (PR) status (positive or negative), human epidermal growth factor receptor 2 (HER2) status (HER2-negative vs HER2-positive without or unknown anti-HER2 treatment vs HER2-positive with single anti-HER2 agent treatment) and type of chemotherapy (anthracycline-based only, anthracyclines and taxanes, non-standard treatment); and weighted by propensity scoring in order to account for the differences in baseline characteristics between pregnant patients and controls. Missing values for covariates were imputed.

Figure 1. Study Design



Results

- **662 pregnant** and **2081 non-pregnant** women who received chemotherapy for breast cancer, were eligible for analysis (Figure 1).
- Pregnant patients were more likely to have **stage II breast cancer**, **grade 3** tumors, **hormone receptor-negative** tumors or **triple-negative** breast cancer (Table 1).
- With a median follow-up of 66 months, the observed 5-year DFS was 76.9% (73.2% for pregnant and 78.1% for non-pregnant) and 5-year OS was 88.1% (84.2% and 89.2% respectively). **DFS and OS were comparable for pregnant and non-pregnant patients** (Figure 2).
- A **subgroup** analysis of 339 women that received more than 60% of chemotherapy during pregnancy (cut-off at median) revealed a comparable survival compared to non-pregnant women. Proportion of chemotherapy during pregnancy did not impact survival in the pregnant group (Figure 2).

Figure 2: Forest plot with results of multivariable Cox proportional hazard regression of Disease-free (DFS) and Overall Survival (OS) by subgroups of interest

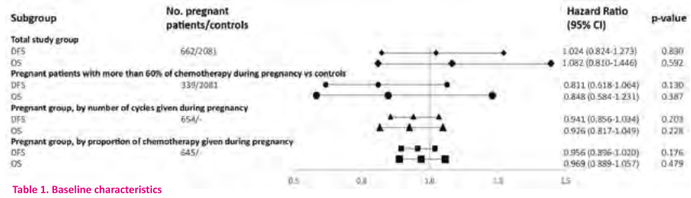


Table 1. Baseline characteristics

Characteristic	Overall No.	Overall %	Pregnant No.	Pregnant %	Non-pregnant No.	Non-pregnant %	p-value
No. of patients	2743		662		2081		
Age (years)							
Median, range	37, 19-47		34, 22-47		38, 19-45		<.001
Stage							
stage I	516	19.8	97	16.1	419	20.9	0.035
stage II	1486	57.0	361	60.1	1125	56.1	
stage III	603	23.1	143	23.8	460	23.0	
missing	*138*		*61*		*77*		
Histological tumor type							
Non-lobular	2581	95.2	634	96.9	1947	94.6	0.016
Lobular invasive	131	4.8	20	3.1	111	5.4	
missing	*31*		*8*		*23*		
Grading, dichotomized							
G1-2	928	35.1	159	26.0	769	37.8	<.001
G3	1718	64.9	453	74.0	1265	62.2	
missing	*97*		*50*		*47*		
HER2 status							
negative	1937	72.6	443	71.5	1494	73.0	0.472
positive	730	27.4	177	28.5	553	27.0	
missing	*76*		*42*		*34*		
Hormone receptor status							
both ER and PgR negative	1014	37.4	310	48.4	704	34.0	<.001
ER and/or PgR positive	1696	62.6	330	51.6	1366	66.0	
missing	*33*		*22*		*11*		
Chemotherapy							
Anthracycline	579	21.1	147	22.2	432	20.8	0.089
Anthracycline + taxane	1916	69.9	469	70.8	1447	69.5	
Non-standard chemotherapy	248	9.0	46	6.9	202	9.7	
missing	*0*		*0*		*0*		

Abbreviations: BC: breast cancer, ER: estrogen receptor, PR: progesterone receptor, HER2: Human Epidermal growth factor Receptor 2

Conclusions

Pregnancy-induced alternations in chemotherapy concentration does not seem to affect maternal prognosis in breast cancer patients. These results support initiation of chemotherapy for BCP where indicated for oncological reasons.

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Baseline menopausal status, Ki-67 and stromal tumor-infiltrating lymphocytes (sTILs) and association with outcome in triple-negative breast cancer (TNBC): exploratory analysis in GeparSixto

#392

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Background

Several trials confirmed a survival benefit from transient menopause during or after chemotherapy for patients with estrogen receptor-negative early breast cancer.[1,2] We investigated the impact of menopause on TNBC outcome after neoadjuvant chemotherapy.

Patients and Methods

This is an exploratory analysis of the TNBC cohort of the phase II GeparSixto study evaluating the addition of carboplatin to an anthracycline-taxane-based neoadjuvant chemotherapy.[3] sTILs and germline (g)*BRCA1* status were centrally assessed. TILs and Ki67 in all patients and according g*BRCA1* status were assessed using the t-test. Association between pathological complete response (pCR, ypT0 ypN0), and menopausal status was analyzed by logistic regression, between menopausal status, age and disease-free survival (DFS) according to pCR by Cox regression. Reported p-values are two-sided, with p≤0.05 considered statistically significant. Hazard ratio (HR) and 95% Confidence Intervals (CI) are provided.

Primary aim was the the impact of baseline menopausal status on Ki-67 and stromal TILs (as continuous variables) assessed in baseline biopsies in all patients, and according to g*BRCA1* status. **Secondary objectives** were the impact of age (≤40 vs >40 years) on baseline Ki-67 and TILs in all patients and according to g*BRCA1* status, the impact of menopausal status at baseline and age on pCR, DFS and distant disease-free survival (DDFS) in patients with pCR compared to non-pCR .

Table 1. Baseline characteristics

	All patients N=315	Pre-menopausal	Post-menopausal		≤40 years	>40 years	
	N (%)*	N (%)*	N (%)*	p-value	N (%)*	N (%)*	p-value
Age (years)							
Median (min-max)	47 (21-78)				n.a.	n.a.	n.a.
≤40	83 (26.3)	83 (43.2)	0 (0)	<0.001			
>40	232 (73.7)	109 (56.8)	123 (100)				
Menopausal status							
Pre-menopausal	192 (61)	n.a.	n.a.	n.a.	83 (100.0)	109 (47.0)	<0.001
Post-menopausal	123 (39)				0 (0.0)	123 (53.0)	
cN stage							
cN0	197 (64.4)	128 (68.8)	69 (57.5)	0.051	58 (70.7)	139 (62.1)	0.179
cN+	109 (35.6)	58 (31.2)	51 (42.5)		24 (29.3)	85 (37.9)	
Histotype							
Ductal invasive	290 (92.1)	174 (90.6)	116 (94.3)	0.223	71 (85.5)	219 (94.4)	0.005
Lobular invasive	6 (1.9)	3 (1.6)	3 (2.4)		1 (1.2)	5 (2.2)	
other	19 (6.0)	15 (7.8)	4 (3.3)		11 (13.3)	8 (3.4)	
LPBC							
No	225 (71.7)	135 (70.3)	90 (73.8)	0.524	55 (66.3)	170 (73.6)	0.205
Yes	89 (28.3)	57 (29.7)	32 (26.2)		28 (33.7)	61 (26.4)	
g*BRCA1* mutation							
No	248 (85.2)	147 (81)	101 (91)	0.040	54 (70.1)	194 (90.7)	<0.001
Yes	43 (14.8)	33 (18)	10 (9)		23 (29.9)	20 (9.3)	

LPBC, lymphocyte-predominant breast cancer; *Valid % are given in the table.

Results

Overall, 315 patients were included in the analysis. Mean Ki-67 was higher in patients ≤40 compared to >40 years (63.9 vs 57.9%, p=0.045) and in pre- compared to postmenopausal patients (63.1 vs 53.9%, t-test p=0.001). Mean TILs did not differ according to age (38.4 vs 33.5%, p=0.126) or menopausal status (35.9 vs 33.0%, p=0.311) (**Figure 1 and Figure 2**). There was no difference in Ki-67 or TILs according to age and menopausal status in g*BRCA1* carriers. pCR rate was higher in women ≤40 years (55.4 vs 41.4%) and premenopausal (50.5 vs 36.6%) (**Figure 3**). In multivariate analysis adjusted for tumor stage, nodal status, tumor grade, Ki-67, TILs and carboplatin use, neither young age nor premenopausal status at baseline predicted for DFS. In non-pCR patients, premenopausal status at baseline but not age ≤40 years was associated with a higher relapse risk (**Figure 4**). Similar results were obtained for DDFS.

Figure 1. Cancer proliferation and stromal TILs according to age and *gBRCA1*

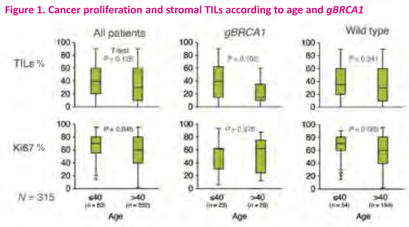


Figure 2. Cancer proliferation and stromal TILs according to menopausal status and *gBRCA1*

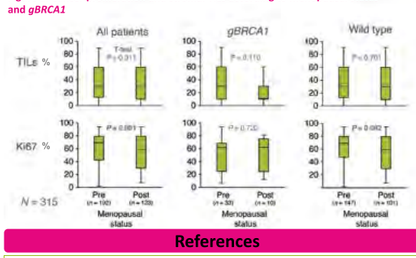


Figure 3: pCR according to menopausal status and age

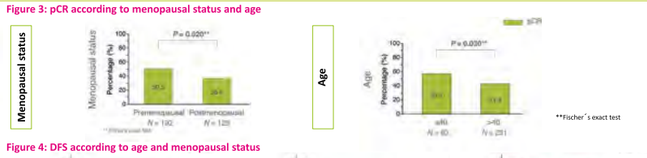
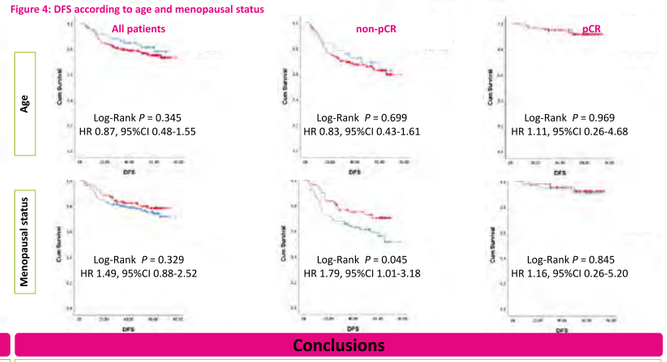


Figure 4: DFS according to age and menopausal status



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Conclusions

In patients with early TNBC, premenopausal as compared to postmenopausal status is associated with a higher cancer cell proliferation at baseline and a higher risk of relapse in case of non-pCR.

Presented at: ESMO Breast Cancer Virtual Congress 2021, 5-8 May

Impact of body mass index (BMI) on prognostic and predictive value of stromal tumor-infiltrating lymphocytes (sTILs) in triple-negative breast cancer (TNBC): a pooled analysis of six neoadjuvant trials.

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Background

The association between obesity and inflammation is complex. Diet-induced obesity is a multifactorial condition, which is associated with a status of low grade chronic inflammation, also defined as metainflammatory state. Obesity induces premature thymic involution, which is associated among all, with alteration of the mechanism regulating T-cell generation, reduction of thymocyte counts, increased apoptosis of developing T-cell populations and reduction in peripheral naïve T-cells.[1] Furthermore, obesity is associated with reduced antitumor immune response.

High level of stromal tumor infiltrating lymphocytes (TILs) have been associated with an increased pathologic complete response (pCR) rate after neoadjuvant chemotherapy.[2,3]

However, in TNBC, high sTILs seem to predict pathologic complete response (pCR) and favorable prognosis only in normal weight patients.[4]

Patients and Methods

TNBC patients, who received anthracycline-taxane-based chemotherapy in the GeparDuo,[5] GeparTrio,[6] GeparQuinto,[7] GeparSixto,[8] GeparSepto,[9] and GeparOcto[10] study, with available Body-mass Index (BMI) and pretreatment sTILs were considered. sTILs were centrally assessed Patients with BMI <18.5 kg/m2 were excluded. Associations between BMI (normal weight, 18.5-<25 vs overweight/obese ≥25 kg/m^2), sTILs (high ≥30% vs low <30) and pCR were assessed using Fisher´s exact test. Association between sTILs (continuous, dichtomized) and pCR (ypT0/is ypN0) according to BMI and interaction BMI*sTILs were analyzes by logistic regression, between sTILs and disease-free survival (DFS) according to BMI and interaction BMI*sTILs by Cox regression.

Objectives

Primary objective was to assess the predictive value of sTILs (as continuous parameter) on pCR according to BMI (normal weight vs overweight/obese)

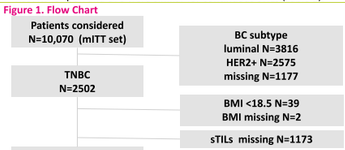
Secondary objectives were:

- the rate of high TILs according to BMI (normal weight vs overweight/obese)
- to assess pCR rate according to BMI (normal weight vs overweight/obese)
- to assess the predictive value of sTILs (as dichotomized parameter) on pCR according to BMI (normal weight vs overweight/obese)
- to assess the predictive value of sTILs (as continuous and dichotomized parameter) on DFS according to BMI (normal weight vs overweight/obese).

Results

- Of 1288 patients, 49.8% were normal weight, 50.2% overweight/obese; median age was 47 [21-78] vs 50 [21-76] years (p<0.001), cT3-4 12.0% vs 16.6% (p=0.021) and N+ 32.7% vs 37.0% (p=0
- Normal weight patients had a higher pCR than overweight/obese patients (47.2% vs 39.9% p=0.009). Median sTILs was 30%, 50.4% of patients had high sTILs (normal weight 50.2% vs ov
predictive for pCR both in normal weight and in overweight/obese patients, Figure 2.
- Median follow-up was 54.7 (53.1-56.3) months. Each 10% increase in sTILs was associated with an 11% reduction in the risk of a DFS event in normal weight and 8% in overweight/obese patie
- Results for pCR and DFS were similar for continuous sTILs (Table 2).

Figure 1. Flow Chart



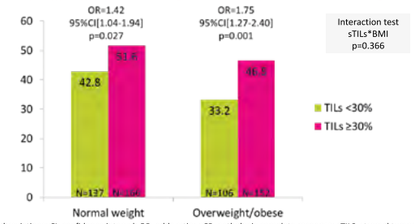
Abbreviations: BC, breast cancer; BMI, body-mass index; mITT, modified-intent to treat; TNBC, triple-negative breast cancer

Table 1. Baseline characteristics

	Category	normal weight n=642 N	valid %	Overweight/obese n=646 N	valid %	p-value
Age	Median [range]	47 [21-78]		50 [21-76]		
	≤40 years	181	28.2	117	18.1	<0.001
	>41-50 years	218	34.0	228	35.3	
	>50 years	243	37.9	301	46.6	
T stage	cT1-cT2	1136	83.5	1134	79.9	<0.001
	cT3-cT4a-c	196	14.4	216	15.2	
	cT4d	28	2.1	70	4.9	
N stage	cN0	794	59.4	797	57.2	0.244
	cN+	543	40.6	597	42.8	
Grading	G1-G2	625	46.1	613	43.7	0.207
	G3	731	53.9	790	56.3	
Histological type	Ductal/ductal-lobular invasive	550	85.8	544	84.2	0.527
	lobular invasive	8	1.2	13	2.0	
	other	83	12.9	89	13.8	
sTILs, %	Median [range]	30 [0.0-100]		30 [0.0-100]		
	<30%	320	49.8	319	49.4	0.868
	≥30%	322	50.2	327	50.6	

Abbreviations: pCR, pathologic complete response; sTILS, stromal tumor infiltrating lymphocytes.

Figure 2. pCR (ypT0 ypN0) in normal weight vs overweight/obese patients according to TILs



Abbreviations: CI, confidence interval; OR, odds ratio; pCR, pathologic complete response; sTILS, stromal tumor infiltrating lymphocytes.

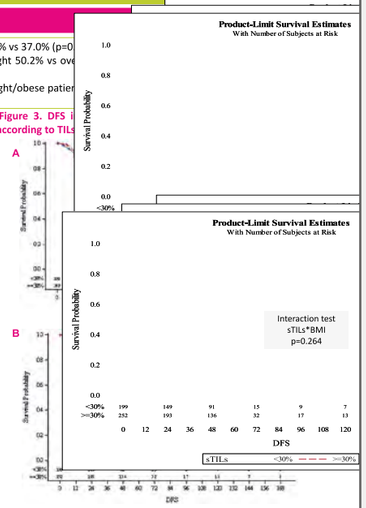
Table 2. pCR and DFS according to BMI and continuous TILs

sTILs Pro 10 unit increase	Normal weight N=441 OR/HR* (95% CI)	p-value	Overweight/obese N=451 OR/HR* (95% CI)	p-value	Interaction test sTILs*BMI p-value
pCR	1.10 (1.03-1.17)	0.0024	1.15 (1.08-1.22)	<0.001	0.302
DFS	0.89 (0.82-0.95)	0.001	0.92 (0.87-0.99)	0.017	0.366

* OR/HR pro 10 unit increase

Abbreviations: CI, Confidence Interval; DFS, disease-free survival; OR, Odds Ratio; HR, Hazard Ratio; sTILS, stromal tumor infiltrating lymphocytes.

Figure 3. DFS i according to TILs



Abbreviations: CI, Confidence Interval; DFS, disease-free survival; HR, Hazard Ratio.

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Conclusions

sTILs were predictive for pCR and DFS in both normal weight and obese/overweight patients.
Our results do not confirm differences in the predictive and prognostic role of sTILs according to BMI in TNBC as described previously.

Presented at: ESMO Breast Cancer Virtual Congress 2021, 5-8 May

EVI1 expression in early-stage breast cancer patients treated with neoadjuvant chemotherapy

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P#401

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Background

Overexpression of the oncogene EVI1 (ecotropic viral integration site 1), a stem cell regulator in hematopoiesis, has been implicated in carcinogenesis, particularly in ovarian[1] and breast carcinoma.[2] However, the prognostic importance of EVI1 overexpression in breast cancer (BC) remains unclear due to low sample sizes of reported outcomes and lack of patient data from controlled clinical trials. The neoadjuvant GeparTrio pilot (NCT00544765)[3] and main (NCT00544765)[4] trials were randomized, controlled phase II and III trials including 2,357 patients with early-stage BC. Patients were treated with anthracycline/taxane based neoadjuvant chemotherapy. The aim of our study was to investigate frequency and clinical relevance of EVI1 expression in newly diagnosed BC treated with neoadjuvant chemotherapy from the GeparTrio trials.

Patients and Methods

EVI1 expression was determined by immunohistochemistry on tissue microarrays of pretherapeutic biopsies of BC patients from GeparTrio trials. EVI1 expression levels were determined using H-score as a cumulative measurement of staining intensity and percentage of positive cells. EVI1 protein expression was analyzed as a continuous variable and categorized into low (≤112.16 H-score) or high (≥112.17 H-score) based on median cut-off. Logistic regression and Cox proportional hazard models were used to correlate EVI1 expression with pathological complete response (pCR=ypT0, ypN0) and survival outcome, respectively. pCR rates were estimated by 2-sided chi-square test. Disease-free survival (DFS) and overall survival (OS) according to EVI1 expression groups were presented by Kaplan-Maier curves and compared with log-rank p-values.

Figure 1: Flow diagram of patients included in the analysis set

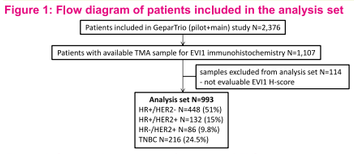


Figure 2: Immunohistochemical images of EVI1 expression

Results

Table 1: Baseline characteristics

Parameter	Category	EVI1 expression Low, N (valid %)	High, N (valid %)	p-value
Overall (N=993)				
Tumor size	cT1-2	321 (65.0%)	368 (74.2%)	**0.002**
	cT3-4a-d	173 (35.0%)	128 (25.8%)	
Nodal status	cN-negative	219 (44.7%)	216 (44.4%)	0.949
	cN-positive	271 (55.3%)	270 (55.6%)	
Tumor grade	G1-2	299 (62.6%)	279 (60.0%)	0.423
	G3	179 (37.4%)	186 (40.0%)	
BC subtype	HR+/HER2-	213 (49.5%)	235 (52.0%)	0.435
	HR+/HER2+	73 (17.0%)	59 (13.1%)	
	HR-/HER2+	42 (9.8%)	44 (9.7%)	
	TNBC	102 (23.7%)	114 (25.2%)	
HR+/HER2- (N=448)				
Tumor size	cT1-2	140 (66.0%)	184 (78.3%)	**0.004**
	cT3-4a-d	72 (34.0%)	51 (21.7%)	
Nodal status	cN-negative	99 (46.9%)	105 (46.1%)	0.924
	cN-positive	112 (53.1%)	123 (53.9%)	
Tumor grade	G1-2	162 (77.5%)	158 (69.6%)	0.066
	G3	47 (22.5%)	69 (30.4%)	
TNBC (N=216)				
Tumor size	cT1-2	65 (63.7%)	83 (72.8%)	0.187
	cT3-4a-d	37 (36.3%)	31 (27.2%)	
Nodal status	cN-negative	47 (47.0%)	56 (49.6%)	0.784
	cN-positive	53 (53.0%)	57 (50.4%)	
Tumor grade	G1-2	33 (34.0%)	44 (41.9%)	0.310
	G3	64 (66.0%)	61 (58.1%)	

Figure 3: Correlation of EVI1 expression with therapy response

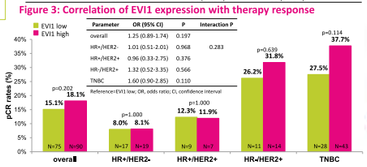
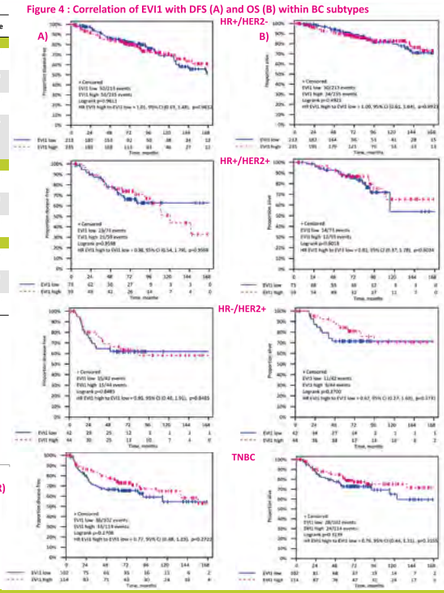


Table 2: EVI1 prognostic value in patients with residual disease (non-pCR)

BC subtype	DFS HR (95% CI)	DFS Log-rank p	OS HR (95% CI)	OS Log-rank p
overall	0.94 (0.73-1.22)	0.660	0.91 (0.67-1.26)	0.585
HR+/HER2-	1.07 (0.73-1.58)	0.731	1.03 (0.63-1.70)	0.895
HR+/HER2+	1.07 (0.57-2.00)	0.833	0.92 (0.41-2.07)	0.833
HR-/HER2+	0.74 (0.34-1.64)	0.456	0.55 (0.21-1.49)	0.234
TNBC	0.85 (0.51-1.42)	0.537	0.93(0.53-1.63)	0.796

Univariate Cox regression, Reference=EVI1 low group; HR, hazard ratio; CI, confidence interval

Figure 4 : Correlation of EVI1 with DFS (A) and OS (B) within BC subtypes



- A total of 993 breast cancer patients with evaluable immunohistochemical EVI1 H-score and available clinical and follow-up data were included in the analysis (Figure 1). Median EVI1 H-score was 112.16 (range 0.5-291.4) in the entire cohort (Figure 2).
- High EVI1 levels were significantly associated with smaller tumor size (cT1-2) in the entire cohort and in HR+/HER2- but not in the TNBC subtypes (Table 1).
- Overall, univariate analysis showed no influence of high EVI1 expression on therapy response. Subgroup analyses stratified by BC subtype included 882 patients with centrally confirmed ER, PR and HER2 status. No significant association with pCR was seen among BC subtypes. However, TNBC patients with high EVI1 expression showed increased pCR rates compared to low group (37.7% vs 27.5%, p=0.114) (Figure 3).
- After a median follow-up of 74.5 (range 0.0-189.5) months, 278 patients had a relapse and 180 died. EVI1 expression neither impacted DFS (HR=0.89 [95%CI 0.71-1.17), log-rank p=0.460) nor OS (HR=0.85 [95%CI 0.62-1.15], log-rank p=0.293) in the entire cohort. Across BC subtypes, TNBC patients with high EVI1 expression showed better but not statistically significant DFS and OS (Figure 4).
- Analysis of the EVI1 prognostic relevance on the 828 patients not achieving pCR showed no significant correlation of high EVI1 expression with DFS or OS in the entire cohort and among BC subtypes (Table 2).

Conclusions

EVI1 did neither influence response to neoadjuvant therapy nor patient survival in the overall cohort. TNBC patients with elevated EVI1 expression showed numerically better pCR and improved survival. Further analyses are needed to verify our findings, especially in the pathological work-up of newly diagnosed TNBC patients.

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Presented at: ESMO Breast 2021, Virtual Meeting, 5-8 May 2021

BACH1 and HIF1α predict response to neoadjuvant nab-paclitaxel (nP) treatment in early breast cancer (BC)

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21P

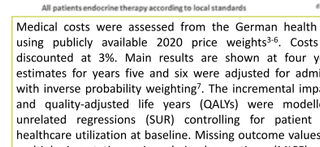
Background

Hypoxia occurs in most solid tumors including BC and plays key role in cancer therapy by regulating the tumor microenvironment. A small hypoxia signature was associated with increased sensitivity to neoadjuvant treatment with bevacizumab in the GeparQuinto trial.[1] HIF1α (hypoxia-inducible factor-1α) functions as a master transcriptional regulator of the adaptive response to hypoxia.[2] BACH1 (BTB domain and CNC homolog 1), a heme-binding transcription factor, acts as a key regulator of mitochondrial metabolism and hypoxia.[3] GeparSepto (NCT01583426) phase III randomized trial showed improved pathological complete response (pCR) and disease-free survival (DFS) in early-stage BC patients treated with neoadjuvant nP compared to solvent-based paclitaxel (P).[4,5] The aim of this study was to investigate the incidence of BACH1 and HIF1α expressions and their correlation with clinical outcomes in HER2-negative BC patients from GeparSepto trial.

Patients and Methods

We correlated tumor BACH1 and HIF1α mRNA expression from available RNA-Seq data of pretherapeutic core biopsies from 279 HER2-negative BC patients with pCR (ypT0, ypN0), DFS and overall survival (OS) in the GeparSepto trial (Figure 1). BACH1 and HIF1α values were analyzed as continuous variables (log transformed values) and categorized as low and high by median cut-off. Logistic regression and Cox proportional hazard models were used to correlate BACH1 and HIF1α expression with pCR and survival outcome, respectively. The interaction between subgroups was assessed by including an interaction term into regression models. DFS and OS in subgroups were presented as Kaplan-Maier curves. Multivariable regression models were adjusted for age (>50 vs ≤50), cT (cT3-4 vs T1-2), and cN (cN+ vs cN0).

Figure 1. GeparSepto study design of HER2-negative setting (N=810)



Results

Figure 2: Patients included in the analysis set

HER2-negative BC patients from GeparSepto trial, N=810 → Patients with sufficient quality sample for whole transcriptome RNAseq, N=279 → **Successfull RNAseq, N=279** HR-negative (=TNBC), N=74 HR-positive, N=205

Figure 3: Correlation between BACH1 and HIF1α

Figure 4: BACH1 and HIF1α expression in HR-positive and TNBC

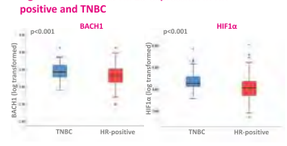


Figure 5: pCR in HR-positive and TNBC according to BACH1 and HIF1α

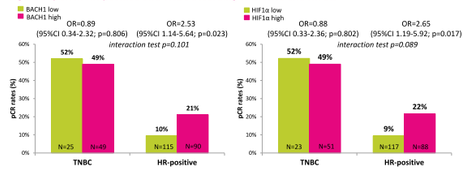


Figure 6: pCR in BACH1 and HIF1α subgroups by treatment arm

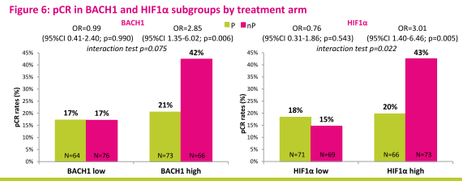


Figure 7: DFS for BACH1 (A) and HIF1α (B) according to treatment arm

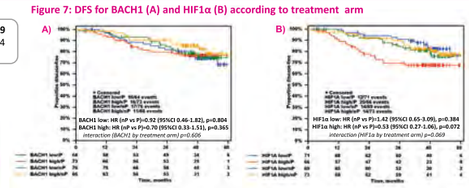


Figure 8: OS for BACH1 (A) and HIF1α (B) according to treatment arm

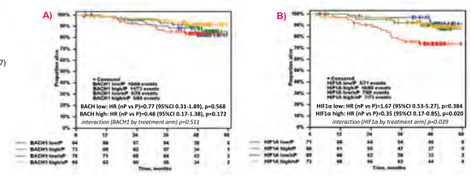


Table 2: Multivariable regression models according to hormone receptor status

Endpoint	BACH1 TNBC OR/HR* (95%CI)	P	BACH1 HR-positive OR/HR* (95%CI)	P	P**	HIF1α TNBC OR/HR* (95%CI)	P	HIF1α HR-positive OR/HR* (95%CI)	P	P**
pCR	1.60 (0.28-9.14)	0.596	3.59 (0.82-15.71)	0.089	0.136	0.77 (0.27-2.25)	0.637	2.90 (1.24-6.75)	0.014	0.115
DFS	0.79 (0.13-4.91)	0.798	1.22 (0.94-3.34)	0.732	0.491	0.63 (0.25-1.61)	0.334	2.24 (1.18-4.26)	0.014	0.045
OS	0.31 (0.02-4.6)	0.387	2.89 (0.70-12.03)	0.145	0.764	0.67 (0.16-2.83)	0.588	4.09 (1.73-9.64)	0.001	0.037

*Reference=low expression ; **Interaction test (gene expression by hormone receptor status); OR, odds ratio; HR, hazard ratio

Table 3: Multivariable regression models within gene expression groups by therapy arm

Endpoint	BACH1 low OR/HR* (95%CI)	P	BACH1 high OR/HR* (95%CI)	P	P**	HIF1α low OR/HR* (95%CI)	P	HIF1α high OR/HR* (95%CI)	P	P**
pCR	0.84 (0.33-2.12)	0.716	2.86 (1.33-6.17)	0.007	0.042	0.67 (0.26-1.70)	0.396	2.91 (1.32-6.42)	0.008	0.018
DFS	0.93 (0.46-1.87)	0.839	0.70 (0.32-1.53)	0.375	0.534	1.58 (0.70-3.55)	0.272	0.62 (0.30-1.26)	0.187	0.096
OS	0.83 (0.33-2.09)	0.686	0.46 (0.16-1.36)	0.159	0.453	2.07 (0.60-7.18)	0.250	0.46 (0.18-1.17)	0.101	0.067

*Reference=P arm; **Interaction test (gene expression by treatment arm); OR, odds ratio; HR, hazard ratio

- A total of 279 patients with available tumor BACH1 and HIF1α mRNA expression were included in the analysis. (Figure 2). Median BACH1 and HIF1α mRNA levels were 3.35 (range 2.20-4.13) and 4.15 (range 2.72-6.04), respectively in the entire cohort. There was a positive correlation between BACH1 and HIF1α expression levels (Figure 3). Elevated BACH1 and HIF1α expression was significantly associated with TNBC (Figure 4). Median follow-up was 49.8 months (range 2.3-62.4).
- Concerning HR-status, BACH1 and HIF1α up-regulation did not impact pCR in TNBC subgroup. In contrast, in HR-positive subgroup, high BACH1 and HIF1α was significantly associated with increased pCR (Figure 5). In multivariate models, only high HIF1α remained a significant independent predictor of pCR and was significantly associated with worse DFS and OS in HR-positive but not in the TNBC patients (Table 2).
- Regarding effects of BACH1 and HIF1α in nP vs P arm, patients with high BACH1 and HIF1α expression benefited from nP treatment (Figure 6). This benefit maintained statistical significance for both BACH1 and HIF1α in the multivariable model with a significant interaction between gene expression and treatment arm (BACH1: p=0.042, HIF1α: p=0.018, Table 3). Patients with induced BACH1 and HIF1α in nP vs P arm were more likely to obtain improved DFS and OS in the uni- and multivariable analyses (Figure 7 and 8; Table 3).

Conclusions

HER2-negative BC with elevated BACH1 and HIF1α expression benefits from nP-based treatment. There was a positive correlation between increased BACH1 and HIF1α levels for predicting pCR. We suggest that high BACH1 and HIF1α expressions enhance the efficacy of nP treatment, perhaps through triggering the hypoxic tumor adaptation.

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Presented at: ESMO Breast 2021, Virtual Meeting, 5-8 May 2021

Whole transcriptome RNAseq was performed by

Health economic properties of *palbociclib* in breast cancer patients with high risk of relapse following neoadjuvant therapy – results from the Penelope-B trial

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132P

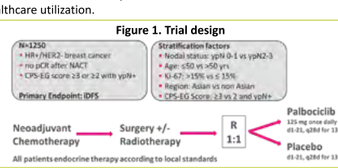
Background

Patients with hormone receptor-positive, HER2-negative breast cancer who have residual invasive disease after neoadjuvant chemotherapy (NACT) are at high risk of relapse. PENELOPE-B was a double-blind, placebo-controlled phase III study that investigated adding *palbociclib* (PAL) to adjuvant endocrine therapy (ET) in these high-risk patients. Clinical results showed no improvement in invasive disease-free survival with ET+PAL compared to ET alone[1]. Of note, PAL use in early breast cancer is not approved. Here we evaluated the cost-effectiveness of ET+PAL in PENELOPE-B.

Patients and Methods

A total of 1250 patients were recruited from 221 centres in 10 countries according to the eligibility criteria shown in Figure 1. Health and medical resource use were assessed before, during, and after treatment for up to 72 months. The EQ-5D instrument was used to score health-related quality of life[2]. Patient diaries and questionnaires were used to collect information on healthcare utilization.

Figure 1. Trial design



Medical costs were assessed from the German health system perspective using publicly available 2020 price weights[3-6]. Costs and effects were discounted at 3%. Main results are shown at four year follow-up (FU), estimates for years five and six were adjusted for administrative censoring with inverse probability weighting[7]. The incremental impacts of PAL on costs and quality-adjusted life years (QALYs) were modelled with seemingly unrelated regressions (SUR) controlling for patient characteristics and healthcare utilization at baseline. Missing outcome values were imputed with multiple imputation using chained equations (MICE) via predictive mean matching (PMM). Scenario and sensitivity analyses explored uncertainty in patient pathways and costs. Subgroup analyses were performed for key prognostic risk factors.

Results

Table 1. Sample characteristics

	ET + PAL N[a]=633 % (N)	ET N=611 % (N)
First diagnosis ≤ age 50 vs > 50	56 (356)	57 (347)
ypN 0-1 vs ypN 2-3	49 (313)	50 (304)
Ki-67 status > 15% vs ≤ 15%	28 (178)	29 (177)
CPS-EG score ≥ 3 vs 2 and ypN+	60 (380)	59 (361)
Tumour grade 1 or 2 vs 3	53 (337)	52 (315)
Hysterectomy (yes/no)	4 (25)	2 (13)
Breast reconstruction surgery (yes/no)	16 (104)	20 (120)
Germany (yes/no)	34 (218)	35 (213)

[a] 3 patients in PAL +ET and 3 patients in ET arm who never started study treatment were excluded.
Key: ET = Endocrine Therapy; PAL = Palbociclib; N = Number of patients; SD = Standard Deviation; CPS-EG = Clinical Pathological Stage-Estrogen Receptor;

- Table 1 shows patient characteristics were balanced between the arms, further details on the sample are available from Loibl et al[1].

Table 2. Clinical events, costs and QALYs

	ET + PAL Mean (SD)	ET Mean (SD)	P-value
Clinical events N = 1244			
FU to event (years)	2.14 (1.27)	1.77 (1.24)	0.009*
Relapse	0.23 (0.42)	0.23 (0.42)	0.891
Number of relapses	1.63 (1.06)	1.69 (1.23)	0.688
Secondary malignancy	0.02 (0.13)	0.02 (0.13)	0.763
Death	0.10 (0.30)	0.11 (0.31)	0.560
Quality of life N = 1104			
FU (years)	3.10 (1.32)	3.06 (1.34)	0.683
Baseline utility	0.90 (0.13)	0.89 (0.14)	0.179
Total QALYs	2.55 (1.13)	2.44 (1.10)	0.099*
Total discounted QALYs	2.39 (1.03)	2.29 (1.00)	0.101
Total cost (Euros, 2020) N = 1145			
FU (years)	3.20 (1.00)	3.16 (1.01)	0.443
Targeted therapy	35519 (8035)	989 (3893)	0***
Total costs	43050 (13383)	7685 (9690)	0***
Total discounted costs	41490 (12606)	7212 (9004)	0***

Key: QALY = Quality-Adjusted Life Years; ET = Endocrine Therapy; PAL = Palbociclib; SD = Standard Deviation; N = Number of patients; FU = Follow-Up; *** - statistically significant at 1%; ** - statistically significant at 5%; * - statistically significant at 10%.

- Table 2 shows no significant differences in clinical events or QALYs.
- Differences in costs between arms were dominated by the cost of PAL.
- Number of patients varied by outcome due to item-missingness, loss to follow-up, and censoring.

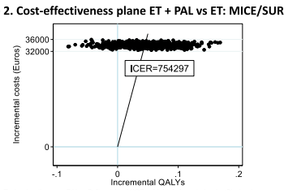
Table 3. Incremental costs, QALYs and ICERs at four years of FU

Adjustment for missing values/ baseline characteristics	None/None N costs = 1145 N QALYs = 1104 Mean (SE)	CC/SUR N = 1007 ß(SE)	MICE/SUR N = 1244 ß (SE)
	I	II	III
Incremental costs	32138 (735)***	34942 (362)***	34114 (695)***
Incremental QALYs	.048 (.065)	-.0136 (.028)	.045 (.055)
ICER	664837	PAL dominated	754297

Key: QALY = Quality-Adjusted Life Years; ICER = Incremental Cost-Effectiveness Ratio; FU = Follow-Up; CC = Complete Case analysis; SUR = Seemingly Unrelated Regressions; MICE = Multiple Imputation by Chained Equations; N = Number of patients; SD = Standard Deviation; SE = Standard Error; ; *** - statistically significant at 1%; ** - statistically significant at 5%; * - statistically significant at 10%.
SUR control for stratification factors, baseline healthcare use, and country; QALY equation also controls for baseline utility

- Table 3 compares raw differences (column I) in costs and effects between the arms to impact estimates adjusted for stratification and baseline characteristics in complete case (CC) analysis (column II) and following imputation of missing values using MICE (column III). Across specifications costs were consistently higher in the ET+PAL arm (by approximately the cost of PAL) while impact on QALYs was highly variable tending toward marginal improvement in patients with relatively worse health status.
- After the first year, differences in costs and QALYs were marginal and increasing over time to favour PAL; however, the absolute magnitude of cost savings was highly uncertain due to the large fraction of administratively censored observations (53% in year five, 84% in year six).
- Bootstrapped (1000 replications) incremental impacts (dots) and the resulting ICER (black line) shown in Figure 2 for MICE/SUR specification highlight that the variation in ICER was driven primarily by the variation in the impact of PAL on QALYs.
- For Germany sub-sample ICER was estimated at 787198 Euros per QALY gained; ICERs were above 600000 Euros in all other scenarios tested.

Figure 2. Cost-effectiveness plane ET + PAL vs ET: MICE/SUR



Key: ET = Endocrine therapy; PAL = Palbociclib; MICE = Multiple Imputation by Chained Equations; SUR = Seemingly Unrelated Regressions; QALY = Quality-Adjusted Life Years; ICER = Incremental Cost-Effectiveness Ratio.

Conclusions

One year of PAL added to ET is not likely to be cost-effective in women with residual invasive disease after NACT. We found limited evidence suggesting PAL enabled additional marginal improvement in health and some cost savings in later years, however, these did not offset the initial cost of PAL therapy through year six. The analysis is subject to self-report bias and limitations of the data collection instruments. Administrative censoring further limited power to estimate impacts beyond year four.

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Immunological markers in patients with breast cancer occurring during pregnancy – results from GBG BCP study

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P4-04-14

Background

Breast cancer is one of the most common malignancies during pregnancy. Breast cancer in pregnancy (BCP) is still a rare event (1 in 3000 to 10000 pregnancies). 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.[1] Pregnancy presents a complex and unique immunological condition. Pregnant women are widely considered to be in a kind of immunosuppressed state, making them more susceptible to infectious diseases.[2]

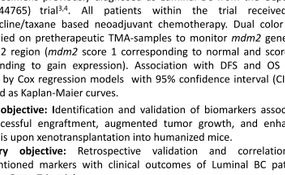
Recent studies have shown similarities between malignancies and the semi-allogenic fetus in terms of immune evasion strategies, for example upregulation of non-classical human leukocyte antigen G (HLA-G). The loss or downregulation of HLA (MHC class I) is also a way to escape anti-tumor immunity.[3] In addition, TIGIT (T cell immunoreceptor with Ig and ITIM domains) as well as PD-1/PD-L1 interactions are crucial in establishing immunotolerance in cancer, healthy adult tissue as well as the fetal-maternal interface.[4,5]

The aim of this study was to investigate the tumor biology and immunology of pregnant breast cancer patients and the impact of pregnancy on the immunological characteristics of the breast cancer.

Patients and Methods

Tissue microarrays (TMAs) of formalin-fixed paraffin embedded core biopsies or surgical specimens from 126 pregnant breast cancer patients treated with neo-(adjuvant) chemotherapy were constructed. TMAs were stained via immunohistochemistry to assess estrogen receptor (ER), progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), Ki-67 (<20% vs ≥20%), and immunomarkers HLA (≤5% vs >5%), HLA-G (≤5% vs >5%), PD-L1 (<1% vs. ≥1%), TIGIT and Nectin-4 as well as hematoxylin-eosin for the prevalence of tumor-infiltrating lymphocytes (TILs, ≤30% vs 31-60% vs >60%). PD-L1 expression using the 22C3 antibody (Abcam) was evaluated in tumour cells, immune cells, and in both tumor and immune cells.

Figure 1. Flow diagram



Results

Table 1. Patient and tumor characteristics

Parameter	Category	Overall N=126 N(%)
Age at diagnosis, years	18-29	14 (11.1)
	30-34	56 (44.4)
	35-39	45 (35.7)
	≥40	11 (8.7)
T stage*	T1	30 (23.8)
	T2	69 (54.8)
	T3	20 (15.9)
	T4	7 (5.6)
N stage*	N0	57 (45.2)
	N1	69 (54.8)
	N2	13 (10.3)
	N3	7 (5.6)
Tumor grading	G1	1 (0.8)
	G2	39 (31.0)
	G3	86 (68.3)
Histological tumor type	ductal or ductal-lobular invasive	111 (89.5)
	lobular invasive	7 (5.6)
	other	6 (4.8)
HR status**	both ER and PgR negative	53 (42.1)
	ER and/or PgR positive	73 (57.9)
HER2 status**	negative	95 (78.5)
	positive	26 (21.5)
M status at diagnosis	M0	99 (83.9)
	M1	5 (4.2)
	MX	14 (11.9)
Biological subtype**	TNBC	42 (34.7)
	HER2+/HR-	7 (5.8)
	HER2+/HR+	19 (15.7)
	HER2-/HR+	53 (43.8)
Ki-67 at diagnosis**	<20%	56 (46.7)
	≥20%	64 (53.3)
TILs*	0-30%	58 (93.5)
	31-60%	3 (4.8)
	>60%	1 (1.6)

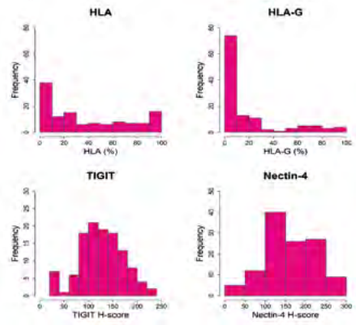
*maximum of cT and pT resp. cN and pN; **assessed from stained TMAs (via immunohistochemistry) by the central pathology, Marburg; Data are N (valid %)

Table 2: PD-L1, HLA-A and HLA-G in the pregnant cohort

Parameter	Category	Overall N=126 N(%)
PD-L1 (immune cells)	negative	91 (76.5)
	positive	28 (23.5)
PD-L1 (tumor cells)	negative	108 (90.8)
	positive	11 (9.2)
PD-L1 (tumor and/or immune cells)	negative	91 (77.8)
	positive	26 (22.2)
HLA	≤5%	26 (21.3)
	>5%	96 (78.7)
HLA-G	≤5%	65 (53.7)
	>5%	56 (46.3)

Data are N (valid %)

Figure 2: Distribution of biomarkers as continuous variables



- Median age of the patients was 34 (range 26-47) years. Among breast cancer subtypes, most patients had either TNBC (34.7%) or HER2-/HR+ (43.8%) tumors. 53.3% of patients had a high expression of Ki-67 (≥20%). TILs were detected in 62 out of 126 (49.2%) analyzed patients, of whom 93.5% (N=58) had a low expression of TILs (≤30%) (Table 1).
- HLA expression (≤5%) was downregulated in 21.3% of patients while 46.3% showed upregulation of HLA-G expression (>5%). Most tumors in our cohort were PD-L1 negative for both tumor cells (90.8%) and immune cells (76.5%) (Table 2).
- Overall, the median H-score was 127 (range 23.8-235) for TIGIT and 156 (range 4.9-288) for Nectin-4 (Figure 2).
- An increased but not significant median expression of HLA-G was observed in patients with T3/4 (N=27) compared to T1/2 (N=99) tumor stage (12.4% vs 3.4%, respectively, p=0.226) whereas the TIGIT median expression was significantly higher in patients with T1/2 compared to those with T3/4 tumor stage (135 vs. 116, respectively, p=0.02). There was no significant difference in the median expression of the other biomarkers HLA, PD-L1 and Nectin-4 in T1/2 vs. T3/4 subgroups. The median expression of all biomarkers did also not significantly differ in N0 vs. N+ subgroups.

Conclusions

- **A heterogeneity of immunomarker expression was detected in the entire cohort of pregnant breast cancer patients.**
- **Subgroup analysis showed a significantly higher expression of TIGIT in patients with T1/2 tumor stage, which might be a sign of the initial anti-tumor response with activation of T- and NK-cells that decreases during tumor progression.**
- **Taken together, these findings suggest a heterogeneity of immunomarkers in tumor tissue, which might be related to the specific immunological situation during pregnancy. These results are hypothesis generating and further analyses are ongoing to evaluate the impact of this heterogeneity on non-pregnant patient cohort.**

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mdm2 gene amplification in estrogen receptor-positive breast cancer cells is associated with enhanced solid tumor growth and pronounced metastatic potential in humanized PDX mice and a poor outcome of luminal breast cancer disease

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PD9-07

Background

Luminal, i.e., estrogen receptor-positive (ER+) breast cancer (BC) is a heterogeneous disease in terms of tumor progression, therapy response, and relapse.[1] Additional biomarkers with a prognostic and predictive impact could facilitate advanced patient stratification and can reveal advanced therapeutic options for individual patients suffering from BC subtype.

Patients and Methods

Generation of NSG based hPDX: CD34+ hematopoietic stem cells (HSC) were isolated from the umbilical cord blood and transplanted into neonatal NOD.Cg-Prkdcscid Il2rytm1Wjl /SzJ (NSG) mice 3 hours post 1 Gy irradiation as previously described[2]. BC samples were transplanted in 7-8 weeks old humanized female NSG mice together with a s.c. 0.18 mg 17ß-estradiol pellet (Innovative Research of America). In addition, 3 previously established, patient-derived xenograft (PDX) models (PT-S2, PT-S3, and PT-S4) provided by Elisabetta Marangoni (Institute Curie, Paris, France), and 2 PDX models (PT-CTC and PT-E2) provided by Andreas Trumpp (HI-Stem, Heidelberg, Germany) were also used. Differences between tumor volume of wild type (*mdm2*^{WT}) and amplified (*mdm2*^{Amp}) hPDX models were assessed by Student´s t-test. For the functional assays *in-vitro*, ZR-75-1 BC cells were treated with the mdm2 inhibitor AMG232. Cell proliferation and apoptosis were analyzed by flow cytometry, a scratch assay was performed to analyze migration cell capacity over time, and Dunnett's multiple comparisons test was applied.

GeparTrio patient cohort for *mdm2* assessment: For this study we selected tissue specimens previously diagnosed as Luminal BC from the GeparTrio (NCT00544765) trial[3,4]. All patients within the trial received an anthracycline/taxane based neoadjuvant chemotherapy. Dual color FISH was applied on pretherapeutic TMA-samples to monitor *mdm2* gene and the cen12 region (*mdm2* score 1 corresponding to normal and score 2-3 corresponding to gain expression). Association with DFS and OS were analyzed by Cox regression models with 95% confidence interval (CI) and presented as Kaplan-Maier curves.

Primary objective: Identification and validation of biomarkers associated with successful engraftment, augmented tumor growth, and enhanced metastasis upon xenotransplantation into humanized mice.

Secondary objective: Retrospective validation and correlation of aforementioned markers with clinical outcomes of Luminal BC patients within the GeparTrio trial.

Results

Figure 1: Patient cohort included in the analysis

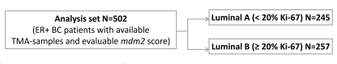
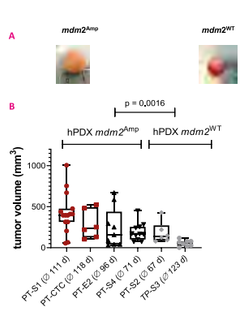


Figure 2: Representative tumor samples (A) and tumor volume (B) from *mdm2*^{Amp} and *mdm2*^{WT} hPDX models



The average days of survival of each model are indicated in brackets.

The tumor volume in all four hPDX-*mdm2*^{Amp} was significantly increased compared to hPDX-*mdm2*^{WT} (Fig. 2A & B; p = 0.012). In addition, the hPDX-*mdm2*^{Amp} showed a significantly enhanced potential to develop lung metastasis compared to hPDX-*mdm2*^{WT} (11/14 vs 1/10, respectively, p = 0.0028; data not shown).

Figure 3: Functional assays: apoptosis (A), proliferation (B) and migration (C) on ZR-75-1 BC cells treated with the mdm2 inhibitor AMG232

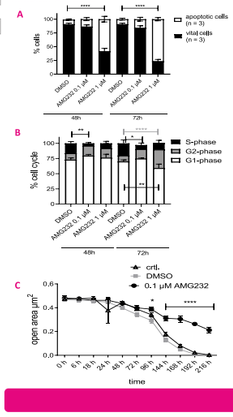
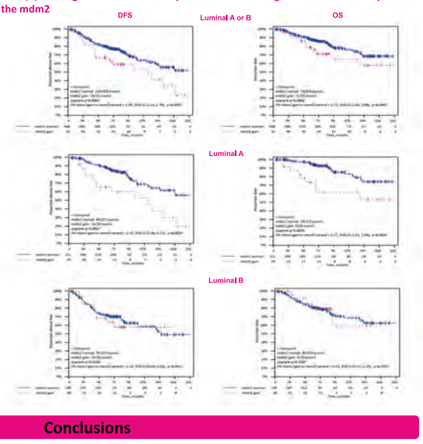


Figure 4: DFS and OS in patients with mdm2 gain versus normal expression



mdm2 targeting with 1 µM AMG232 induced a significant fraction of apoptotic cells (p < 0.0001) (Fig. 3A). In addition, AMG232 treatment caused a reduced S-phase fraction (48h: p = 0.008, 72h: p = 0.049), a reduced G1-phase after 72h (p = 0.0027) and an elevated fraction of G2 (p < 0.0001) (Fig.3B). Finally, cells exposed to *mdm2* targeting (AMG232) showed a delayed scratch overgrowth in the wound-healing assay (Fig. 3C).

Patients with *mdm2* gain showed a statistically significantly worse DFS (HR = 1.80 [95%CI 1.16-2.79], log rank p = 0.008) and OS (HR = 1.75 [95%CI 1.00-3.05, log-rank p = 0.047) compared to those without *mdm2* alteration in the entire Luminal BC cohort. Similar results were observed in patients with Luminal-A (DFS: HR = 2.56 [95%CI 1.40-4.71], p = 0.002; OS: HR = 3.27 [95%CI 1.51-7.09], log-rank p = 0.002) but not with the Luminal-B subcohort (DFS: HR = 1.16 [95%CI 0.60-2.26], log-rank p = 0.653; OS: HR = 0.95 [95%CI 0.41-2.23], log-rank p = 0.911) (Fig. 4).

Conclusions

- **An *mdm2* gene amplification propels growth and progression of ER+ BC in a preclinical humanized xenograft NSG mouse model.**
- **mdm2 inhibition of ER+ BC cells *in-vitro* reduces cell proliferation and migration and induces tumor cell apoptosis.**
- **An unfavorable impact of an *mdm2* gain on survival outcome of Luminal BC patients is mainly caused within the Luminal-A BC sub-cohort.**
- **Prospective studies are required to verify the suitability of *mdm2* for advanced Luminal BC stratification and therapeutic targeting of ER+ BC.**

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Germline *BRCA*1/2 and other predisposition genes in high-risk early-stage HR+/HER2- breast cancer (BC) patients treated with endocrine therapy (ET) with or without palbociclib: A secondary analysis from the PENELOPE-B study

P5-13-36

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Background

The PENELOPE-B trial (**Figure 1**) did not show an improved invasive disease-free survival (iDFS) by adding palbociclib to ET in high-risk HR+/HER2- BC.[1] In a HR+/HER2- patient population germline (g) *BRCA*1/2 mutations were observed in approximately 14% and *BRCA*1/2 plus other BC predisposition gene mutations in 20%.[2] In metastatic BC CDK4/6 inhibitors may have greater activity in patients with a *BRCA* mutation detected in ctDNA.[3] Here, we aimed to investigate the incidence of mutations in g*BRCA1/2* and other BC disposition genes (expected to be 10% and 13%, GBG data on file) and their impact on patient outcome in PENELOPE-B.

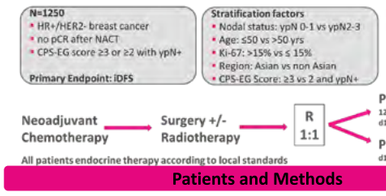


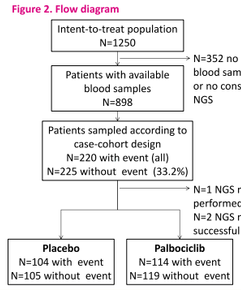
Figure 1: PENELOPE-B study design

Patients and Methods

Blood samples from 898 of the 1250 PENELOPE-B patients were available. 445 patients were sampled following a case-cohort design[4] (all 220 cases defined as patients with any event during follow-up and 225 randomly selected patients without any event) and analyzed by targeted next generation sequencing (NGS) for germline variants in *BRCA1/2* and 16 non-*BRCA1/2* cancer predisposition genes: *ATM*, *BARD1*, *BRIP1*, *CDH1*, *CHEK2*, *FANCM*, *MRE11A*, *NBN*, *PALB2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, *STK11*, *TP53*, *XRCC2*.

The primary definition of mutational status was the prevalence of a pathogenic mutation (mt) in one or more analyzed BC predisposition genes. Statistical analyses were based on inverse probability weighting. For time-to-event endpoints (iDFS, distant disease-free survival [DDFS], and overall survival [OS]) weighted Cox proportional hazard models and weighted Kaplan-Meier estimates were used. Confidence intervals (CI) for 3-year survival rates and hazard ratios as well as interaction p-values were created by resampling.

Figure 2. Flow diagram



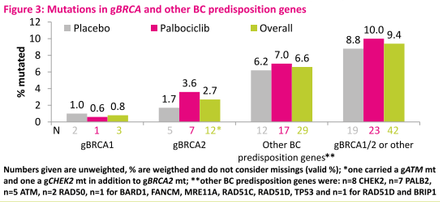
Results

Table 1. Baseline patient and tumor characteristics

Parameter	Category	Placebo N (%)*	Palbociclib N (%)*	Overall N (%)*
Age at diagnosis, years	≤50	120 (59.2)	133 (57.1)	253 (58.1)
	>50	89 (40.8)	100 (42.9)	189 (41.9)
Menopausal status	premenopausal	102 (50.1)	120 (51.0)	222 (50.6)
	postmenopausal	107 (49.9)	113 (49.0)	220 (49.4)
Global region	Non-Asian	195 (92.8)	215 (91.9)	410 (92.4)
	Asian	14 (7.2)	18 (8.1)	32 (7.6)
cT at first diagnosis	cT1/2	105 (52.4)	117 (52.4)	222 (52.4)
	cT3/4	103 (47.6)	116 (47.6)	219 (47.6)
cN at first diagnosis	negative	19 (9.3)	23 (11.3)	42 (10.3)
	positive	190 (90.7)	210 (88.7)	400 (89.7)
Ki67 % at randomization	≤15%	149 (77.6)	164 (76.0)	313 (76.8)
	>15%	60 (22.4)	69 (24.0)	129 (23.2)
Histological lymph node status at randomization	ypN 0-1	100 (49.2)	115 (49.5)	215 (49.3)
	ypN 2-3	109 (50.8)	118 (50.5)	227 (50.7)
Risk status at randomization	CPS-EG Score 2 and ypN+	77 (40.8)	88 (41.2)	165 (41.0)
	CPS-EG Score ≥3	132 (59.2)	145 (58.8)	277 (59.0)
ypT	ypT0/is/1/2	155 (75.8)	178 (79.0)	333 (77.5)
	ypT3/4	53 (24.2)	55 (21.0)	108 (22.5)
Grading	grade 1/2	119 (58.9)	139 (60.1)	258 (59.6)
	grade 3	86 (41.1)	91 (39.9)	177 (40.4)

*numbers given are unweighted, % are weigthed and do not consider missings (valid %);

Figure 3: Mutations in *gBRCA* and other BC predisposition genes



Numbers given are unweighted, % are weighted and do not consider missings (valid %); *one carried a g*ATM* mt and one a g*CHEK2* mt in addition to g*BRCA2* mt; **other BC predisposition genes were: n=8 CHEK2, n=7 PALB2, n=5 ATM, n=2 RAD50, n=1 for BARD1, FANCM, MRE11A, RAD51C, RAD51D, TP53 and n=1 for RAD51D and BRIP1

442 of 445 patients were successfully analyzed for mutational status (**Figure 2**). Baseline characteristics were well balanced between arms and are presented in **Table 1**. Mutations in g*BRCA* and other BC predisposition genes are summarized in **Figure 3**. The clinical baseline variables did not differ between patients with versus without mutation with respect to all genes analyzed. With regard to g*BRCA1* and g*BRCA2* genes only, age was different between patients with versus without mutation but not other clinical variables: All 15 (100%) g*BRCA*mt carriers were younger than 50 years compared to 238 (56%) wildtype (wt) patients.

After a median follow-up of 42.9 months, mutational status (mt vs. wt) based on all genes analyzed was not prognostic in terms of iDFS (**Figure 4**). Similar results were obtained for DDFS (hazard ratio 0.970, 95%CI 0.521-1.758) and OS (0.768, 95%CI 0.274-1.615). Neither mutated patients nor the wildtype patients had a benefit from palbociclib treatment (**Figure 5**); interaction tests for treatment arm/mutational status for all time-to-event endpoints were not statistically significant. Analysis by g*BRCA1/2* showed similar results but had less statistical power.

Figure 4. iDFS by mutation status (any mutation)

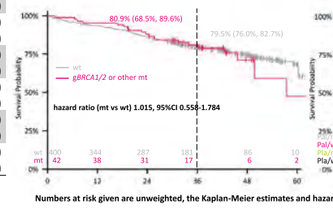
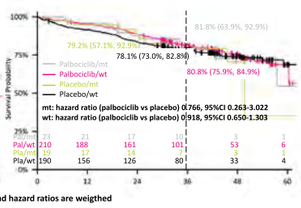


Figure 5. iDFS by treatment arm and mutation status



Numbers at risk given are unweighted, the Kaplan-Meier estimates and hazard ratios are weigthed

Conclusions

This case-cohort analysis of 442 patients enrolled in the PENELOPE-B trial is the largest investigation that analyzed BC predisposition genes in HR+ patients. The detection of BC predisposition genes was lower than expected.
In this subset of patients from the PENELOPE-B trial, patients with g*BRCA1/2* or other BC disposition genes had a comparable outcome to non-carriers overall and irrespective of treatment.

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The trial was financially supported by Pfizer Inc. We thank all patients, participating sites and collaborating study groups: ANZBCTG, ABCSG, BC Cancer, Unicancer, ICORG, JBCRG, KCSG, GEICAM, I-Spy, ICR-CTSU

Molecular plasticity of luminal breast cancer and response to CDK 4/6 inhibition – the biomarker program of the PENELOPE-B trial investigating post-neoadjuvant Palbociclib

PD-02-04

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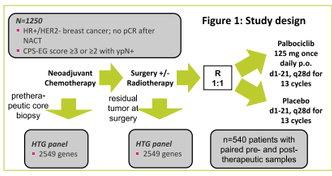
Background

Molecular plasticity of breast cancer can contribute to the development of therapy-resistant disease. In this investigation, we studied changes in molecular signatures between pretherapeutic (pre-Tx) and post-therapeutic (post-NACT) tumor samples from patients included in the PENELOPE-B (NCT01864746) trial (**Figure 1**). After completion of NACT, PENELOPE-B patients were randomized to palbociclib versus placebo in addition to standard endocrine therapy. The PENELOPE-B study did not show a significant benefit from palbociclib in women with HR+, HER2- primary breast cancer without a pathological complete response after taxane-containing neoadjuvant chemotherapy (NACT) and at high-risk of relapse (CPS-EG score ≥3 or 2 and ypN+)[1]. However, the first translational investigations showed that some patients with a luminal-B tumor subtype, based on absolute intrinsic molecular subtyping (AIMS)[2] subtyping after NACT, had a numerical benefit from post-NACT palbociclib. We have therefore extended the analysis and included a cohort of paired pre-Tx and post-NACT samples.

Methods

We investigated gene expression in pre-Tx (n=540) tumor tissue samples using the HTG EdgeSeq Oncology Biomarker Panel including 2549 genes (HTG Molecular Diagnostics Inc.); for the same patients the same panel on post-NACT residual tumor samples were available. Based on 91 genes of this panel, the AIMS subtype was calculated. In addition, we performed exploratory biomarker analyses to identify genes with prognostic and predictive relevance.

Figure 1: Study design



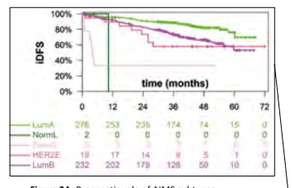


Figure 2A: Prognostic role of AIMS subtypes determined in pre-therapeutic core biopsies

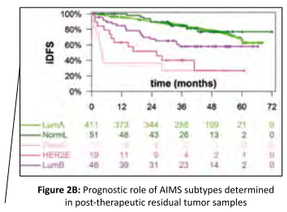


Figure 2B: Prognostic role of AIMS subtypes determined in post-therapeutic residual tumor samples

Table 1: Pre-therapeutic and post-therapeutic AIMS subtypes (LumB/BasalL/HER2E vs LumA/NormL) are independent prognostic parameters for iDFS

model	AIMS subtype		
	HR (95% CI)	HR (95% CI)	p
Bivariable n=540	pre-therapeutic	1,86 (1,26-2,73)	0,002
	post-therapeutic	2,83 (1,90-4,20)	<0,001
multivariable* n=532	pre-therapeutic	1,90 (1,26-2,86)	0,002
	post-therapeutic	2,66 (1,68-4,20)	<0,001

*covariables: age, region, cT, ypT, ypN, Ki-67, grade, and risk status

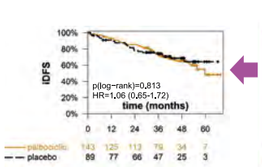


Figure 4A: LumB pre-therapeutic – no differences between therapy arms

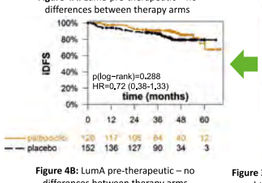


Figure 4B: LumA pre-therapeutic – no differences between therapy arms

Figure 3: Molecular plasticity – changes in AIMS subtypes in pre-and post-therapy samples

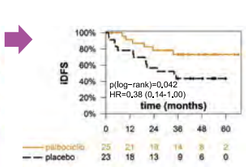


Figure 5A: LumB post-Tx: small group of patients with significant differences between therapy arms

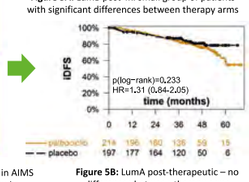


Figure 5B: LumA post-therapeutic – no differences between therapy arms

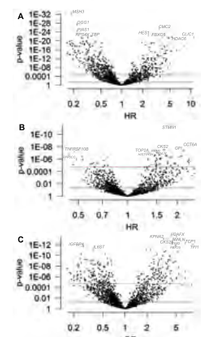


Figure 6: Differential gene expression (n=540). A: pre-therapeutic genes for iDFS, B: post-therapeutic genes for iDFS, C: Subtype switch: pre-therapeutic genes for prediction of post-therapeutic AIMS subtype (LumB/BasalL/HER2E vs LumA/NormL). Blue line: significance level p=0.05; red line: significance after Bonferroni correction.

Results

AIMS subtypes were prognostic in pre-therapeutic biopsies (**Figure 2A**) and post-therapeutic tumors (**Figure 2B**). The prevalence of AIMS subtypes, in particular LumA vs LumB, changed from pre-Tx to post-NACT tumors (**Figure 3**). In the pre-Tx samples, 278 (51%) and 232 (43%) of tumors had LumA and LumB subtypes, respectively, as expected from a high-risk cohort. However, in the post-NACT samples, LumA tumors were predominant (n=411, 76%) over LumB (n=48, 9%). 159 (29%) and 8 (1%) tumors switched their subtype from LumB to LumA and LumA to LumB, respectively.

We compared the groups of low proliferating (LumA and NormL) and high proliferating subtypes (LumB, BasalL and HER2E). In bivariable Cox regression analysis, the grouped pre-Tx and post-NACT AIMS subtypes were independent prognostic factors for iDFS (**Table 1.**). These and further Cox models investigating interaction effects show that patients with tumors changing from high (pre-Tx) to low proliferation (post-NACT) had a worse iDFS risk compared to stable low proliferating tumors, but an improved iDFS risk compared to stable high proliferating tumors.

A benefit from palbociclib was observed in post-therapeutic lumB tumors (**Figure 5A**), but not in any of the pre-Tx AIMS subgroups (**Figure 4A,B**) or the post-Tx lumA subtype (**Figure 5B**). Based on the results of the AIMS subtyping, we extended the exploratory analysis to identify genes that might be involved in the prognostic effects as well as genes driving the subtype switch (**Figure 6A,B,C**).

Conclusions

Our findings show that the switch from high-risk molecular subtypes (in particular LumB) to low-risk subtypes (in particular LumA) 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 the results suggest that molecular defined tumor subtypes might not be as stable as originally thought.

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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

SASCIA

OT1-02-01

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GBG GERMAN BREAST GROUP | AGO-B BREAST STUDY GROUP

Background

Patients with triple-negative breast cancer (TNBC) without a pathologic complete response[1,2,3] as well as hormone receptor (HR)-positive/HER2-negative patients with a CPS+EG (clinical, pathologic stage + estrogen receptor status and grade) score ≥3 or 2 with ypN+[4] have a high risk of recurrence. In high-risk patients, post-neoadjuvant therapy can significantly improve survival.[5,6,7,8] Sacituzumab govitecan (SG) has shown high activity in heavily pretreated patients with metastatic TNBC[9] and HR-positive/HER2-negative BC,[10,11] even after prior immune-checkpoint inhibitors or CDK4/6 and mTOR inhibitors. Efficacy in TNBC was confirmed in the phase III ASCENT trial,[12] irrespective of Trop-2 expression or *gBRCA1/2* status.[13] A phase III trial in a HR-positive cohort is ongoing.[14]
Based on these studies, SG might be an ideal therapy against the resistant residual disease after standard neoadjuvant chemotherapy (NACT) regardless of HR status.

Study Overview

SASCIA (NCT04595565) is a phase III, prospective, multi-center, randomized, open label, parallel group study in patients with HER2-negative BC with residual disease after NACT at high risk of recurrence with 1:1 allocation to SG or treatment of physician's choice (TPC). In patients with HR-positive BC, endocrine-based therapy will be administered according to local guidelines. SASCIA will randomize 1200 patients with centrally confirmed HER2-negative, HR-positive (≥1% positive stained cells) or HR-negative BC assessed preferably on tumor tissue from post-neoadjuvant residual invasive disease.

Objectives and Endpoints

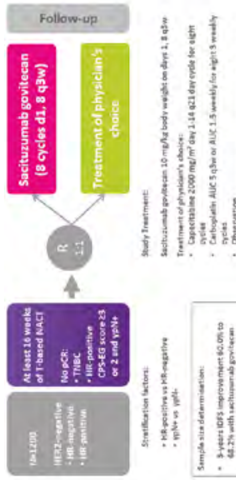
Primary objective:
To compare invasive disease-free survival (iDFS) between patients treated with SG vs. TPC
Secondary objectives (selection):
- To compare overall survival (key secondary objective) and distant DFS between groups.
- To compare safety, compliance, patient reported outcome and quality of life.
- To explore the predictive value of markers (including immune markers) for SG.
- To explore ctDNA dynamics as early predictors of response.

Figure 1: Biomaterial collection

	Screening Phase	Treatment Phase				Follow-up Phase
	Prior to Rando	prior to start of therapy (pre-treatment)	day1 cycle 3 pre-dose	day1 cycle 6 pre-dose	at EOT	Recurrence (at 1st relapse)
FFPE tumor tissue*	x*					x
Plasma ctDNA		x			x	x
Serum		x	x	x	x	x
Whole Blood		x	x	x		

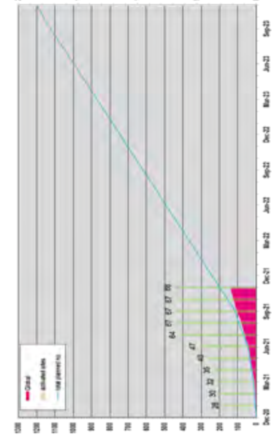
*FFPE from pre-neoadjuvant core biopsy (breast) and FFPE post-neoadjuvant surgically removed tissue from breast for central pathology) or post-neoadjuvant surgically removed tissue from involved lymph node if no residual tumor from breast is available, in case of bilateral BC blocks from both sides are obligatory. Abbreviations: ctDNA, circulating tumor DNA; EOT, End of Treatment; FFPE, Formalin-Fixed Paraffin-Embedded;

Study Design



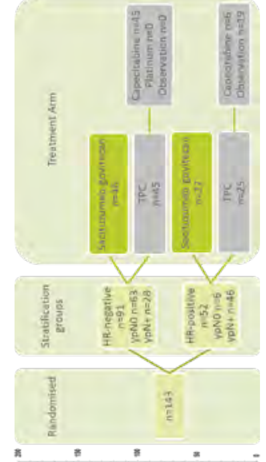
Abbreviations: CPS+EG, clinical, pathological stage + estrogen receptor status and grade) score; HR, hormone receptor; NACT, neoadjuvant chemotherapy; pCR, pathologic complete response; TNBC, triple-negative breast cancer.

Recruitment



*Cut-off 10. October 2021

Recruitment Overview



*Cut-off 10. October 2021
Abbreviations: TPC, Treatment of physician's choice

Key Inclusion Criteria

- Patients with residual invasive disease after NACT at high risk of recurrence defined by either:
  – HR-negative: any residual invasive disease > ypT1mi
  – HR-positive: CPS+EG score ≥ 3 or CPS+EG score 2 and ypN+ using local ER and grade assessed on core biopsies taken before NACT.
- Patients must have received taxane-based NACT for 16 weeks (anthracyclines are permitted):
  – This period must include 6 weeks of a taxane-containing NACT
  – For patients with progressive disease that occurred after at least 6 weeks of taxane-containing NACT, a total treatment period of less than 16 weeks is also eligible.
- An interval of less than 16 weeks since the date of final surgery or less than 10 weeks from completing radiotherapy (whichever occurs last) and the date of randomization is required.
- Immune checkpoint inhibitor / immunotherapy during NACT is allowed.
- Radiotherapy should be delivered before the start of study treatment.

Key Exclusion Criteria

- Patients with definitive clinical or radiologic evidence of stage IV cancer (metastatic disease) are not eligible.
- Patients with a history of any malignancy are ineligible with the following exceptions:
  – Patient has been disease-free for at least 5 years and is at low risk for recurrence of that malignancy.
  – CIS of the cervix, basal cell and squamous cell carcinomas of the skin.
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study, including Gilbert's disease, Crigler-Najjar-Syndrom, known hepatitis B, hepatitis C, known HIV positivity or known autoimmune disease (other than diabetes, vitiligo, or stable thyroid disease).
- Any condition that interferes with the safe administration of the treatment of physician's choice (in TPC arm).
- Receipt of live attenuated vaccines within 30 days prior to study entry or within 30 days of receiving chemotherapy.
- Known or suspected congestive heart failure (>NYHA I) and/or coronary heart disease.
- History of idiopathic pulmonary fibrosis, organizing pneumonia, drug-induced pneumonitis, idiopathic pneumonitis or active pneumonitis on chest CT scan.
- Known allergic reactions to irinotecan.

Conclusions

SASCIA is a phase III study investigating the efficacy and safety of SG compared to TPC in patients with HER2-negative BC with residual disease after NACT at high risk of recurrence. Recruitment has started in December 2020 and will take an estimated 36 months (42 patients per month). As of 10th October 2021, 143/1200 patients have been randomized in Germany. International study groups will join soon.

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Presented at SABCS, December 7-10, 2021.

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DESTINY

120

Trastuzumab-Deruxtecan (T-DXd; DS-8201) vs trastuzumab emtansine (T-DM1) in high-risk patients with HER2-positive, residual invasive early breast cancer (BC) after neoadjuvant therapy (NAT): a randomized, phase 3 trial (DESTINY-Breast05)

Michael Untch[1], Charles E Geyer, Jr[2], Aleix Prat[3], Priya Rastogi[4], Naoki Niikura[5], Elton Mathias[6], Lee Anne McLean[6], Yibin Wang[6], Sibylle Loibl[7]

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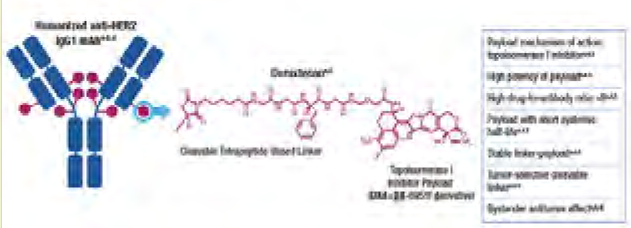
NSABP | GBG GERMAN BREAST GROUP | SOLTI | AGO-B

Background

- NAT in combination with trastuzumab ± pertuzumab is the standard of care for patients with human epidermal growth factor receptor 2 (HER2)–positive high risk or locally advanced breast cancer.[1] Patients who have residual invasive disease at surgery after standard of care chemotherapy plus anti-HER2 therapy are at higher risk for disease recurrence or death than those who have a pathological complete response.[2] Adjuvant T-DM1 improves outcomes in these high-risk patients.[3]
- T-DXd is an antibody-drug conjugate composed of a humanized immunoglobulin G1 monoclonal antibody specifically targeting HER2, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor payload (**Figure 1**).[4,5,6]
- The phase 2 DESTINY-Breast01 trial showed that treatment with T-DXd resulted in an objective response rate of 61.4% (113/184 patients), median progression-free survival of 19.4 months, and median response duration of 20.8 months in patients with HER2-positive (immunohistochemistry 3+ or in situ hybridization positive) unresectable or metastatic breast cancer previously treated with T-DM1.[7]
- Here we describe a randomized phase 3 trial evaluating T-DXd vs T-DM1 as an adjuvant treatment for high-risk patients with HER2-positive primary breast cancer who have residual invasive disease after NAT or who are inoperable at primary diagnosis or have positive pathological node status after NAT (DESTINY-Breast05; NSABP B-60; GBG-103; SOLTI-2001; AGO-B-050) (NCT04622319) (**Figure 2**).

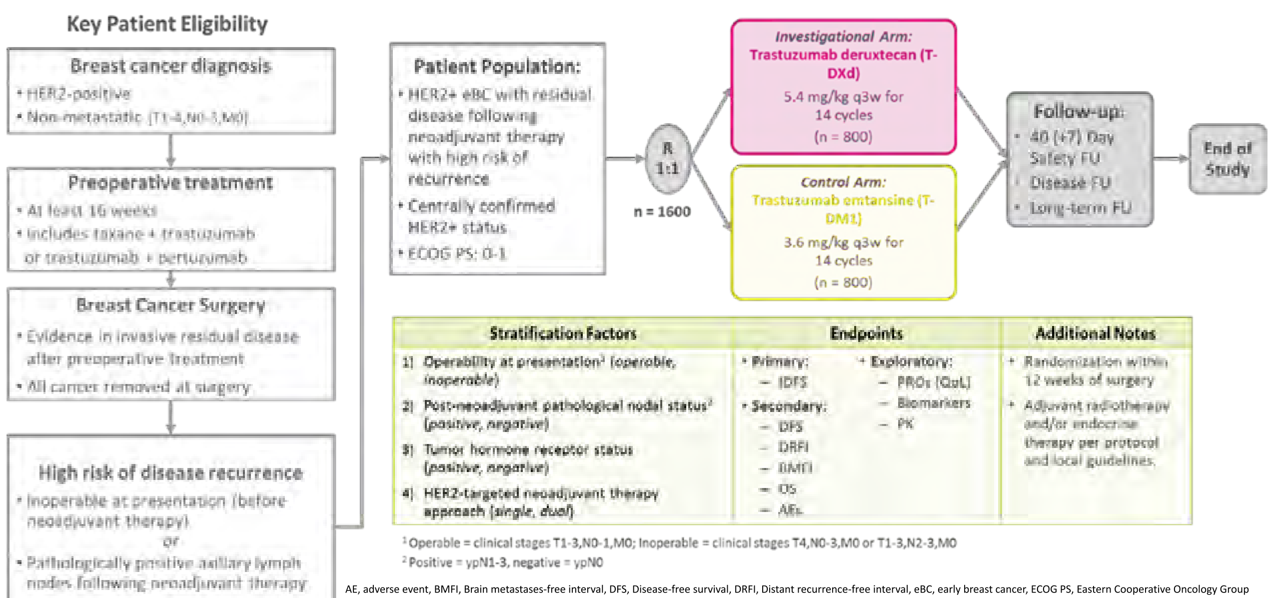
Figure 1: Structure and 7 Key Attributes of T-DXd



Abbreviations: HER2, human epidermal growth factor receptor 2; IgG1, immunoglobulin G1; mAb, monoclonal antibody; T-DXd, trastuzumab deruxtecan.
[a] The clinical relevance of these features is under investigation.

Patients and Methods

Figure 2: Study Design and Population



[1] Operable = clinical stages T1-3,N0-1,M0; Inoperable = clinical stages T4,N0-3,M0 or T1-3,N2-3,M0
[2] Positive = ypN1-3, negative = ypN0

AE, adverse event, BMFI, Brain metastases-free interval, DFS, Disease-free survival, DRFI, Distant recurrence-free interval, eBC, early breast cancer, ECOG PS, Eastern Cooperative Oncology Group performance status, FU, follow-up, HER2, Human epidermal growth factor receptor 2, IDFS, Invasive disease-free survival, OS, Overall survival, PK, pharmacokinetics, PRO, patient reported outcome, QoL, quality of life, R, randomization

Inclusion criteria

- Aged 18 years (20 years in Japan)
- HER2-positive breast cancer (immunohistochemistry 3+ or in situ hybridization+ as confirmed by a central laboratory[a]) histologically confirmed as invasive and stage T1-4, N0-3, M0 at disease presentation prior to NAT
- Completion of NAT and HER2-directed treatment
  – at least 6 cycles of chemotherapy with a total duration of 16 weeks
  – including minimum 9 weeks of trastuzumab (± pertuzumab) and 9 weeks of taxane-based chemotherapy (± anthracycline)
- Pathological evidence of invasive residual disease in patients meeting one of the following criteria for high risk:
  – Inoperable breast cancer at presentation (clinical stages T4, N0-3, M0 or T1-3, N2-3, M0)
  – Operable breast cancer at presentation (clinical stages T1-3, N0-1, M0) with axillary node–positive (ypN1-3) disease after NAT
- Adequate excision: surgical removal of all clinically evident disease in the breast and lymph nodes
- ≤12 weeks between last surgery and randomization
- Left ventricular ejection fraction ≥50%
- Protocol-defined adequate organ and bone marrow function

Exclusion criteria

- Stage IV breast cancer
- Prior ipsi- or contralateral breast cancer, except for lobular carcinoma in situ
- Clinically evident gross residual or recurrent disease after NAT and surgery
- Progressive disease on preoperative systemic therapy
- Prior anti-HER2 antibody-drug conjugate
- History of cumulative exposure to doxorubicin >240 mg/m², epirubicin or liposomal doxorubicin hydrochloride >480 mg/m², or other anthracyclines with exposure equivalent to doxorubicin >240 mg/m²
- History of (noninfectious) interstitial lung disease/pneumonitis that required steroids or has interstitial lung disease/pneumonitis noted on computed tomography scan of the chest at screening (asymptomatic interstitial changes confined to recent radiation therapy fields are not excluded)
- Pulmonary compromise from intercurrent pulmonary illness
- Uncontrolled infection requiring IV antibiotics, antivirals, or antifungals
- Myocardial infarction within 6 months before randomization or symptomatic congestive heart failure
- QTcF prolongation >470 ms (women) or >450 ms (men)

[a] Pretreatment biopsy to be used. If material is insufficient, residual tumor tissue taken at definitive surgery can be used instead.

Figure 3: Countries With Participating Study Sites

Conclusions

DESTINY-Breast05 is a multicenter, open-label, randomized phase 3 trial comparing the efficacy and safety of T-DXd vs T-DM1 in high-risk patients with HER2-positive, residual, invasive breast cancer after NAT. The study is currently recruiting patients and will include approximately 400 sites globally. Recruitment has started in December 2020 and will take an estimated 42 months. As of 12th May 2021, 19 patients have been randomized globally. Recruitment in Germany will start shortly.

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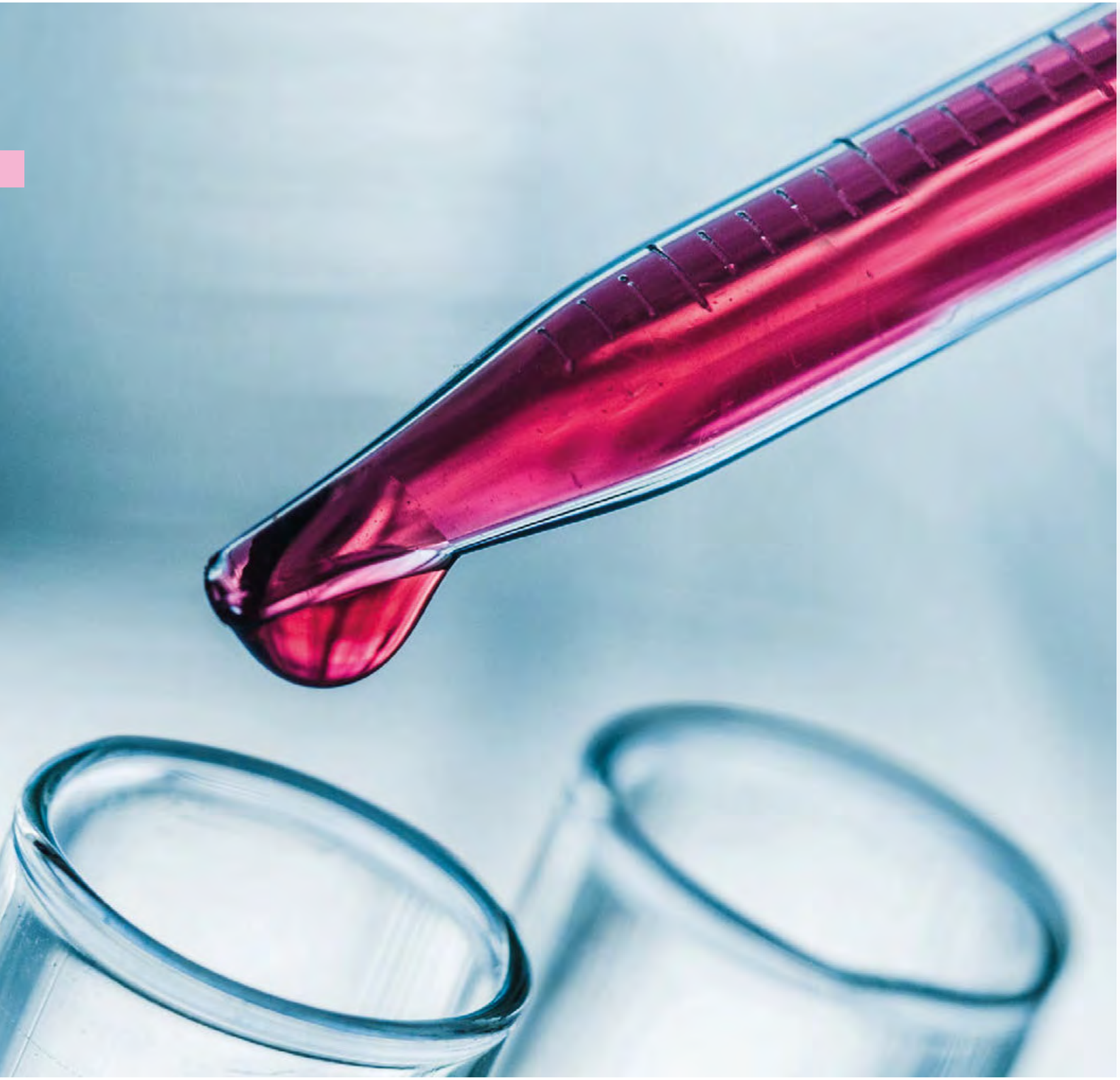
Presented at: 40. Jahrestagung der Deutschen Gesellschaft für Senologie e.V. 17-19 June 2021, Virtual Meeting

This study is sponsored by Daiichi Sankyo, Inc. In March 2019, AstraZeneca entered into a global development and commercialization collaboration agreement with Daiichi Sankyo for trastuzumab deruxtecan (T-DXd; DS-8201).



New Study Concepts and Methodologies

Interview with Prof. Dr. Sibylle Loibl, coordinating investigator of the ETERNITY^{B} registry

Registry for long-term follow-up of safety and efficacy parameters of GBG study participants

Prof. Dr. Sibylle Loibl
German Breast Group

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.

Primary objective: to evaluate long-term-survival endpoints

1. What was the rationale for setting up ETERNITY^{B}?

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 register study ETERNITY^{B} (B = breast) to collect a similar data set as in GBG 71 focused on long-term outcome.

2. Which patients can be enrolled in ETERNITY^{B}?

Patients will be eligible for ETERNITY^{B} if they have participated and received treatment in a GBG clinical trial for early breast cancer. Inclusion in ETERNITY^{B} requires a signed informed consent. Data collection and documentation of follow-up will start after the regular end of the respective GBG trial or with the start of the post study follow-up period as defined in the respective study protocol.
The first study that offers ETERNITY^{B} enrollment to former study patients is the PENELOPE^{B} study, further studies such as SASCIA or GeparPiPPa will follow.

3. Many study patients come to the study centers mainly for the key study procedures. Standard treatment and follow-up often take place at another hospital or private practice, especially after the study has ended. How is this issue addressed in ETERNITY^{B}?

Survival status, relapse and safety assessments will be regularly performed for all patients included in ETERNITY^{B}. The collection of this data can happen via the study investigator on site. However, telephone contact or written contact with the patient directly, the treating physician or relatives (in case of death) is also acceptable. Data should be documented at least once a year in the registry.

4. How much documentation is required? Are there monitor visits planned for ETERNITY^{B}?

In contrast to our PSRO registry, the study centers collect and document the relevant long-term data for ETERNITY^{B}. Most of the documentation can be done by the non-physician study staff and the study centers receive adequate compensation. Information on long-term outcome (recurrence, secondary malignancies, and death), pregnancies after study participation and their respective outcome, further anti-cancer therapies, as well as long-term side-effects of the respective study treatments will be collected.
In addition, two content-related questions on quality of life and the degree of impairment caused by side effects are used to assess the quality of life of the patients. There are no additional questionnaires. Since patients do not receive any study treatment in ETERNITY^{B}, no safety reporting is foreseen. There is no monitoring at all for ETERNITY^{B}.

5. Do you also plan to collect biomaterial?
Guidelines recommend confirming the diagnosis of disease recurrence by histological examination. We therefore ask patients to voluntarily provide some remaining samples of tumor tissue taken by the treating physician at the time of recurrence. However, participation in ETERNITY^{B} is not linked to the provision of biomaterials. Shipment will be managed and paid by GBG as known from other GBG studies.

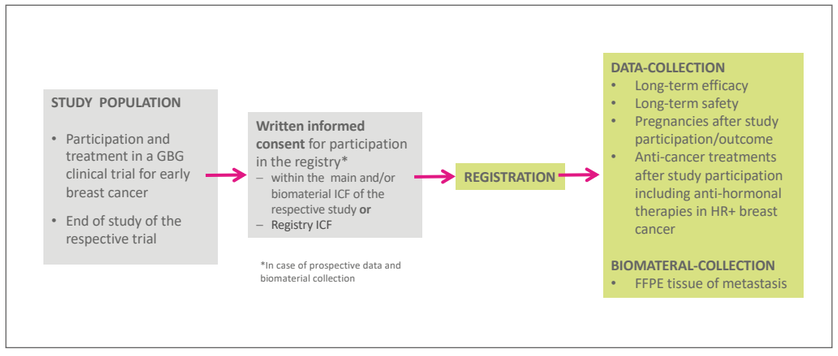


Figure 1: Study design of the FU-Registry

Interview with Dr. Mattea Reinisch, coordinating investigator of the GeparPiPPa trial

A phase II study of neoadjuvant PI3K-inhibitor administration in PIK3CA-mutant triple-positive breast cancer

Dr. Mattea Reinisch
KEM | Evang. Kliniken Essen-Mitte

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, hormone-receptor (HR)-positive; PIK3CA mutant early breast cancer

Primary objective: to compare pathological complete response rates between patients treated with inavolisib concurrently given to endocrine therapy, pertuzumab and trastuzumab versus endocrine therapy, pertuzumab and trastuzumab alone.

1. GeparPiPPa will evaluate neoadjuvant systemic therapy with the investigational PI3K-inhibitor inavolisib in combination with endocrine therapy and anti-HER2 therapy. What is the rationale for this PI3K-targeting strategy in the era of neoadjuvant chemotherapy in HR+/HER2+ early breast cancer?

PIK3CA mutations can be found in about 20%-30% of HER2+ breast cancer patients and are associated with a poor response to chemotherapy and anti-HER2 therapy, especially in HR+ breast cancer. However, due to a crosstalk between the estrogen receptor, PI3K and HER2 pathways, inhibition of PI3K signaling results in activation of HER2 and the sensitivity towards anti-HER2 agents is expected to rise. Currently available preclinical and clinical evidence justifies further development and investigation of a chemotherapy-free therapy regimen combining dual anti-HER2 blockade in combination with a PIK3 inhibitor in the neoadjuvant setting.

2. Can you tell us about the planned study design of GeparPiPPa? Which patients qualify for the study?

Inavolisib is an oral pure selective PI3K alpha inhibitor. Within the GeparPiPPa trial, we investigate whether the addition of inavolisib to a chemotherapy-free treatment consisting of standard anti-HER2 therapy and endocrine therapy will increase the pathological complete response rate compared to the inavolisib-free arm. 170 patients 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) either with inavolisib (6 cycles) or without inavolisib.
Endocrine therapy consists of either tamoxifen 20 mg or an aromatase inhibitor +/- GnRH analogue for premenopausal women and men.
Patients ≥18 years with a confirmed HER2 positive, HR positive and PIK3CA mutated breast cancer with a palpable size of ≥ 2 cm or a sonographical size of ≥ 1 cm in maximum diameter (cT1c – cT3) are eligible for the GeparPiPPa study. The HR+/HER2+ and PIK3CA status needs to be centrally confirmed. Eligible patients need to have adequate organ functions and laboratory values within the normal ranges.

3. PI3K-inhibitors are known to be associated with several toxicities which may have an impact on patients' quality of life. Could you explain these class-specific adverse events? What are the advantages of inavolisib?

Reported side effects of PI3K-Inhibitors are skin toxicity, increase in blood sugar, diarrhea or other adverse events affecting the gastrointestinal tract. So far, the most evaluated drug in breast cancer of this class is alpelisib, which has recently been approved for the treatment of HR-positive, HER2-negative metastatic breast cancer based on the Solar-1 study. In Solar-1 it has been shown that the above mentioned side effects of apelisib were in general well manageable.
Due to the selective mode of action of inavolisib, side effects are expected to be similar or less as compared to other PI3K inhibitors.
In addition, patients do not receive chemotherapy within the study avoiding chemotherapy-associated long-term side effects like polyneuropathy, cardiac-toxicity and secondary malignancies. Nevertheless, the benefit-risk ratio of inavolisib in combination with dual anti-HER2 targeting and endocrine therapy is unknown and therefore we will thoroughly collect information about the adverse events and treatment compliance in the study.

4. Could you describe the effort to identify resistance mechanisms and predictors of therapeutic response within the GeparPiPPa trial?

The GeparPiPPa trial has implemented a comprehensive translational research program. Translational research is a highly important part of clinical research. Within GeparPiPPa we collect blood and tumor tissue to perform analyses helping us to gain a deeper insight into the tumors' behavior.
We examine and compare pre-specified molecular markers such as Ki-67, tumor infiltrating lymphocytes, and other pathway markers, for example AKT and PTEN on core biopsies and residual disease and aim to assess the predictive and prognostic effect of different PIK3CA hot spot mutations. The collection of plasma ctDNA and germline DNA will allow to explore potential new biomarkers of response and resistance to administration of inavolisib.

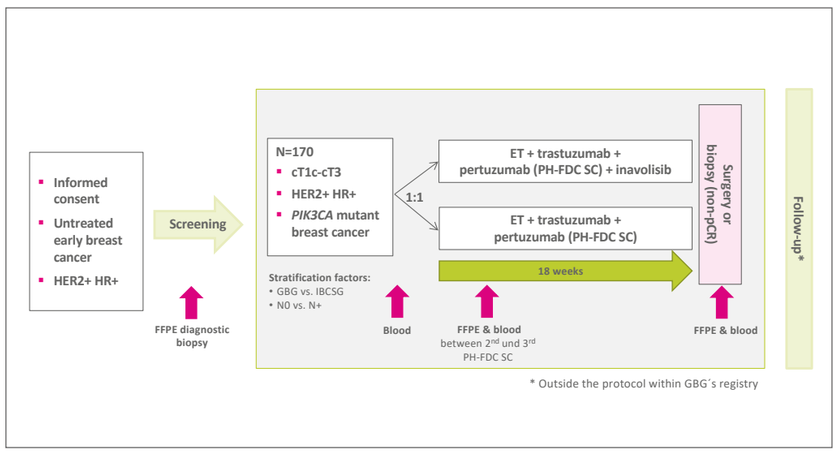


Figure 1: Study design of GeparPippa

Interview with Prof. Dr. Carsten Denkert, member of the Molecular Tumor Board

Establishment of a Molecular Screening Program at GBG

Prof. Dr. Carsten Denkert
Institute of Pathology,
Philipps University Marburg
and Marburg University Hospital
(UKGM), Marburg

The Molecular Screening Program is an add-on offer of tailored breast cancer tumor tissue panel sequencing for GBG study participants with locally advanced and metastatic disease.

1. GBG has implemented a Molecular Screening Program which is running at your facility in Marburg. Could you give a short description of the program?

Next-generation sequencing (NGS) allows for simultaneous sequencing of multiple cancer susceptibility genes per tumor sample. For this purpose, we have designed a custom-tailored NGS panel to detect variants in 25 genes known for their impact on breast cancer development, including BRCA1/2, PIK3CA as well as ESR2, HER2 and other genes. The aim was to have one gene panel that would allow the detection of all clinically relevant genes in breast cancer. Formalin-fixed paraffin-embedded (FFPE) tumor samples are subjected to NGS and subsequent variant analysis to identify clinically relevant targetable genomic alterations.

2. How will the GBG network benefit from this program?

Based on national and international guidelines, mutation analysis on breast cancer is recommended in different clinical situations. However, up to now, a comprehensive screening for molecular aberrations in tumor tissue from breast cancer patients is not part of clinical routine in many centers. It is important for the GBG network to implement NGS-based sequencing as a part of current and future central pathology activities. For several alterations, e. g. PIK3CA and BRCA1/2 there is already clinically validated evidence from large phase 3 trials, while clinical validations for other targets are still ongoing. Therefore, it is important to include patients with locally advanced and metastatic breast cancer in molecular screening programs to identify suitable trials testing targeted therapies matched to the identified genomic alterations.

3. The newly established Molecular Tumor Board at GBG (GBG-MTB) reviews the specific molecular features of the analyzed tumor tissues. Please explain how the process works.

We have decided to work together with Molecular Health, a biotechnological company from Heidelberg, for the GBG-MTB. We use the MHguide software approach for annotation and clinical interpretation of the NGS sequencing results. This has the advantage that a standardized knowledge-base as well as a well-established software platform can be used to focus the clinical discussions in the GBG-MTB on the most interesting and relevant alterations.
Treatment recommendations are made by the clinical experts in the GBG-MTB, taking into account the standardized information of the MHguide as well as their clinical expertise.

4. About 30 patients have already been included in the screening program. What are the lessons learned from the first results?

We have sequenced hormone receptor-positive, HER2-negative tumors from patients included in the AMICA and the PADMA trial. The evaluation is still ongoing, but it was a remarkable result that actionable alterations were detected in approximately 30% of patients in this luminal cohort.

5. What prospects do you see for the future?

The sequencing technology is now fully established at the Institute of Pathology in Marburg, and the MHguide software approach is linked to the GBG-MTB. It is planned to use the NGS-based approach in the GeparPiPPa trial that will start in 2022, and to extend the sequencing activities to the analysis of liquid biopsies. NGS-sequencing will become an integrated part of the GBG central pathology activities.

Recruiting Studies

GBG 103: TruDy / DESTINY-Breast05

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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-positive 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=0.54), 83.0% for node-positive patients (46.2% of T-DM1 patients; hazard ratio=0.52) and 82.1% for hormone receptor (HR)-negative patients (28.1% of T-DM1 patients; hazard ratio=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 corresponding to the node-negative disease are excluded.

It is recognized that patients who do not achieve pCR after appropriate NACT are at 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 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 (hazard ratio=0.28) in patients with HER2-positive metastatic BC previously treated with trastuzumab and taxane (Cortés et al. Ann Oncol. 2021; 32 (suppl_5)).

Based on the differentiating features of T-DXd and the anticancer activity in metastatic BC patients after failure of T-DM1, the 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-positive 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-positive 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 1600 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; 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 2021, there are 7 patients enrolled in the study (global 205 patients). Global enrollment is targeted to be completed in 42 months and the end of study (i.e. last visit of the last patient randomized) is estimated for 2031.

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

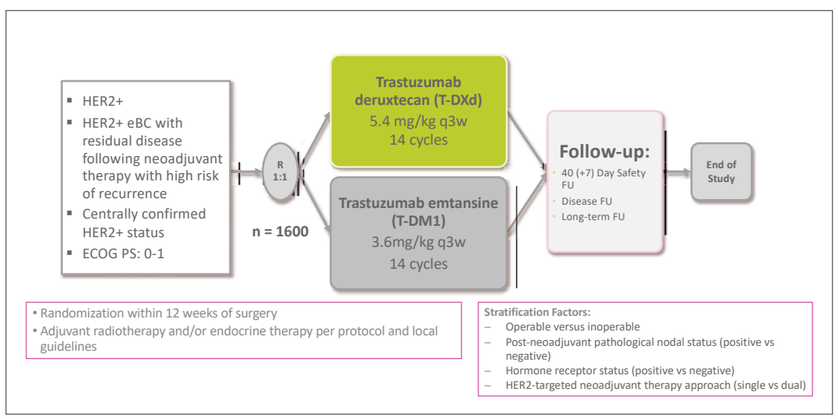

Figure 1: Study design of TruDy/DESTINY-Breast05

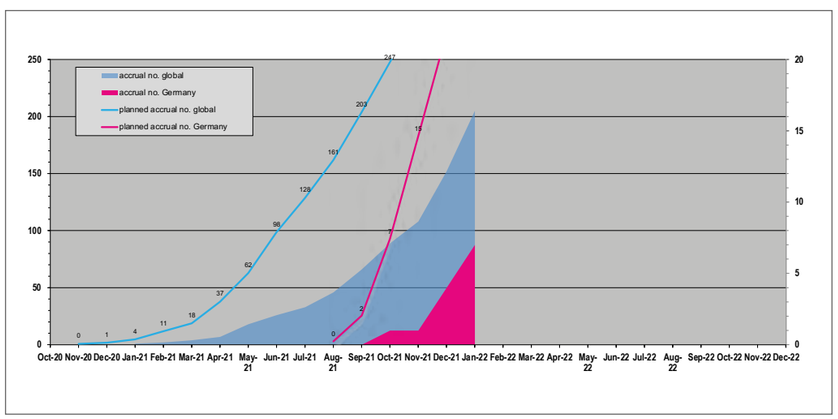

Figure 2: TruDy/DESTINY-Breast05 recruitment as of 1st January 2022

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

AGO-B BREAST STUDY GROUP

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SPONSOR:
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National Center for Tumor Diseases, Erlangen

GBG 102: SASCIA

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Phase III post-neoadjuvant 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 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, 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, sacituzumab govitecan can kill tumor cells expressing Trop-2, but also 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 (10 mg/kg, days 1, 8 of 21-day) in patients with advanced or metastatic TNBC who have received ≥ 2 prior 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.

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

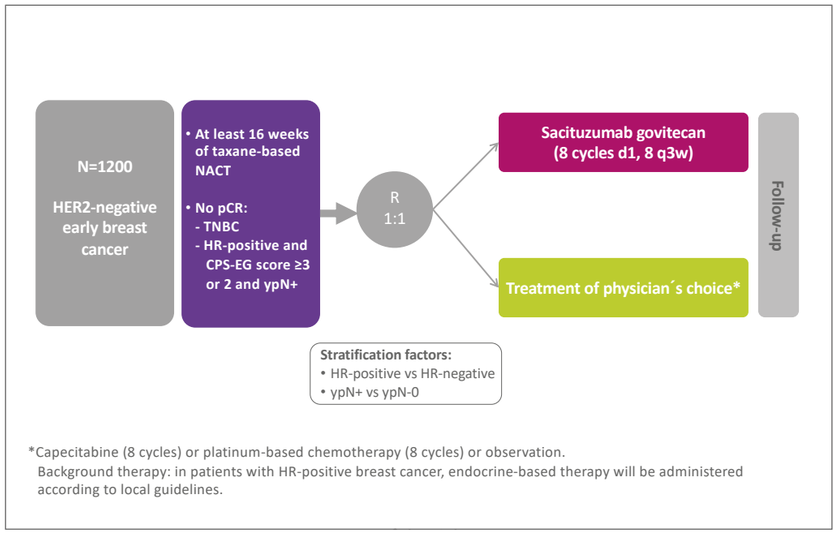

Figure 1: Study design of the SASCIA study

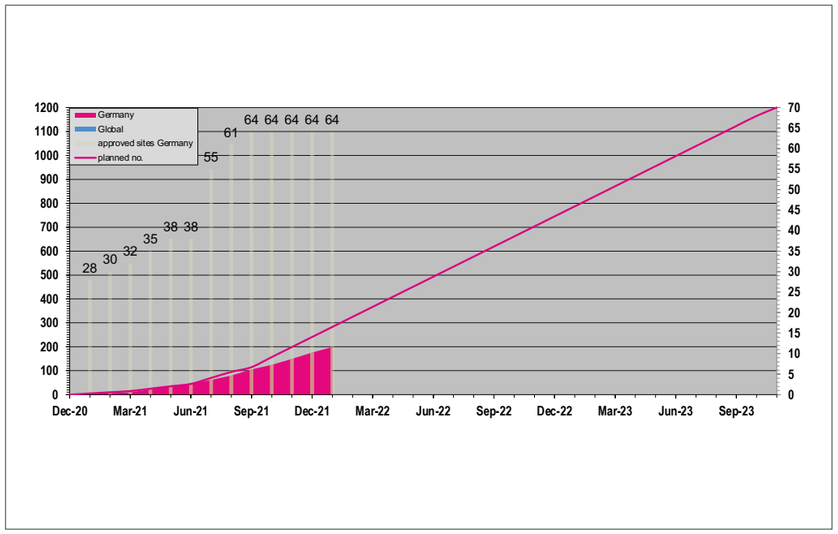

Figure 2: SASCIA recruitment as of 31st December 2021

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; control arm). 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. 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 outcome and quality of life. The SASCIA study will also address translational research questions such as to explore circulating tumor DNA (ctDNA) dynamics as early predictors of ctDNA clearance in ctDNA-positive patients; to explore the predictive value of markers (including genetic and immune markers) for sacituzumab govitecan.
One interim analysis for overwhelming efficacy will be performed when 256 events (2/3 of the total events) have occurred.

Study report
SASCIA recruitment started on November 10, 2020 in Germany. As of 31st December 2021, there are 199 patients enrolled in the study. The recruitment in other European countries is planned to start in Q1 2022. The expected study duration is approximately 36 months.

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

COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

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

GBG 100: APPALACHES

A Phase II study of Adjuvant PALbociclib as an Alternative to CHemotherapy in Elderly patientS with high-risk ER+/HER2-early breast cancer (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 decide treatment of patients with cancer, and ageing is a continuous process making it difficult to set a unique threshold to define older patients. However, many recent studies used 70 years to define older patients, recognizing that patient vulnerability or frailty should also be taken into account (Wildiers, et al. 2007). In older patients with estrogen receptor (ER)+/HER2- early breast cancer, historical data about recurrence rate and the benefit of adjuvant chemotherapy is sparse. In general, the chemotherapy-induced benefit is lower and toxicity is higher than in younger women, and there are competing risks for morbidity and mortality. Several randomized studies in older patients have reported on disease free survival (DFS, including local recurrence as well) and 3-year overall survival (OS, including death from other causes). The 3-year DFS and OS were 85% and 95% in ICE-2 study (unpublished data), 78% and 90% in ELDA study (Perrone, et al. 2015), and 86% and 93% in CALGB49907 study (Muss, et al. 2009). Less toxic adjuvant treatment with comparable efficacy might improve the benefit-toxicity balance of the overall treatment strategy.

Study design and objectives
Women or men aged ≥ 70 years with stage II or stage III, early invasive breast cancer fulfilling all inclusion criteria will be centrally registered at EORTC after written informed consent has been obtained. Randomization will be stratified by country, pathological TNM stage (stage II versus stage III) and potential clinical frailty as defined by the G8 geriatric assessment score (> 14 versus ≤ 14). Patients will be randomized with a 2:1 allocation rate to receive either 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 an adjuvant chemotherapy, followed by standard adjuvant endocrine therapy for a duration of at least 5 years (control chemotherapy arm).
In the experimental arm palbociclib 125 mg will be administered once a day, orally, for 21 days followed by 7 days off treatment in the 28-day cycle with an objective of 2-years total duration of study medication, in combination with standard adjuvant endocrine therapy for a duration of at least 5 years. Longer duration can be proposed to patients according to investigators and patients. In patients for whom adjuvant radiation therapy is indicated, radiation therapy will be administered before the start of palbociclib. Patients in the control treatment arm will be treated with adjuvant chemotherapy as initial adjuvant systemic treatment. The investigator needs to select for each patient one out of the 4 following schemes: 1) 4 cycles docetaxel 75 mg/m2 / cyclophosphamide 600 mg/m2 q3w; 2) 4 cycles doxorubicin 60 mg/m2 / cyclophosphamide 600 mg/m2 q3w; 3) 4 cycles epirubicin 90 mg/m2 / cyclophosphamide 600 mg/m2 q3w; 4) 4 cycles weekly paclitaxel 80 mg/m2 D1, D8, and D15 q3w. The chemotherapy can start after sufficient wound healing is achieved according to the investigator, but in any case, ≤ 13 weeks after last surgery. Prophylactic use of G-CSF is recommended after each cycle of the 3-weekly regimens), with type and length decided per local institutional guidelines. In patients for whom radiation therapy is indicated, radiation therapy will be administered after the last dose of chemotherapy.
Primary objective of APPALACHES trial is to assess the efficacy of the combination of at least 5 year-endocrine therapy and 2 year-palbociclib as adjuvant systemic treatment instead of adjuvant chemotherapy followed by endocrine

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

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

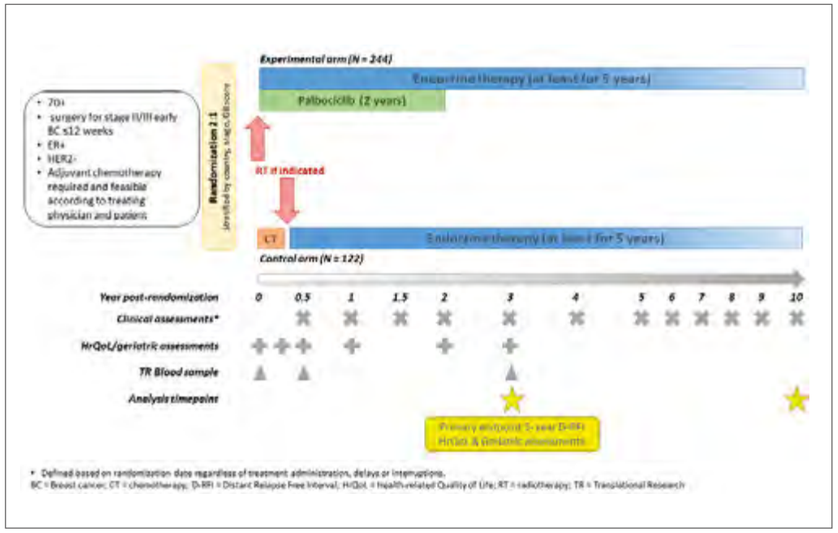

Figure 1: APPALACHES study design

Study report

APPALACHES recruitment started in March 2020. As of 31st December 2021, there are 23 patients enrolled in the study. The expected study duration is approximately 84 months.

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

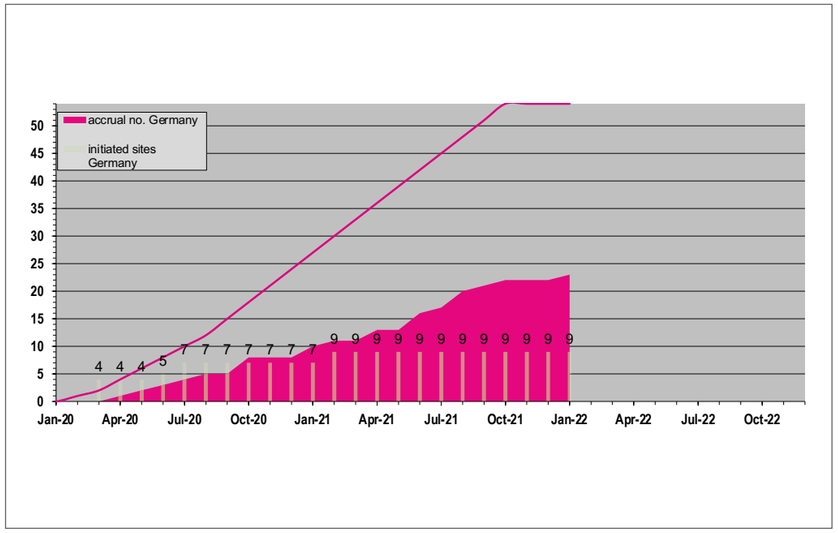

Figure 2: APPALACHES recruitment as of 31st December 2021

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

EORTC The future of cancer research

SPONSOR:
EORTC

STUDY CHAIR:
Dr. Mattea Reinisch
Kliniken Essen-Mitte

GBG 98: ALEXANDRA/IMpassion030

CONTACT:
Dr. Ioannis Gkantiragas
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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 TNBCs exhibit a poor clinical outcome, generally with rapid progression and a shorter time to local and distant relapse (Dent R et al. Clin Cancer Res 2007). Three-year invasive disease-free survival (iDFS) rates of 81% have been reported for patients with TNBC who have received adjuvant anthracycline/taxane therapy (Sparano JA et al. J Clin Oncol 2015). Upon systemic relapse, patients with metastatic TNBC have poor outcomes, with rapid progression and decreased overall survival (OS) (Kassam F et al. Clin Breast Cancer 2009).
Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in an improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). TNBC may be more immunogenic compared to other breast cancer subtypes and promising clinical activity has been reported with atezolizumab in phase I/Ib metastatic TNBC trials (Adams S et al JAMA Oncol 2019). Furthermore, the results of the randomized phase III IMpassion130 study demonstrated enhanced anti-tumor activity when atezolizumab was co-administered with chemotherapy in the first line metastatic setting, with benefit mainly observed in PD-L-positive cohort.
Atezolizumab has been generally well tolerated. Atezolizumab in combination with taxanes (including paclitaxel and nab-paclitaxel) has shown toxicities similar to those experienced with paclitaxel or nab-paclitaxel alone and have generally been manageable. The benefit-risk ratio for atezolizumab in combination with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide is expected to be acceptable in this setting.

Study design and objectives
ALEXANDRA/IMpassion030 primarily aims to evaluate the efficacy, safety, and pharmacokinetic profile of adjuvant atezolizumab plus standard chemotherapy versus chemotherapy alone in early TNBC. Patients with operable stage II or III TNBC, confirmed by central pathology review, will be randomized to receive either adjuvant atezolizumab in combination with paclitaxel followed by atezolizumab, dose-dense doxorubicin or epirubicin (investigator's choice), and cyclophosphamide (atezolizumab+T-AC/EC) or paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator's choice) and cyclophosphamide alone (T-AC/EC). Patients are stratified by type of surgery, nodal status, and centrally assessed PD-L1 status. Adjuvant treatment will consist of weekly paclitaxel 80 mg/m2 for 12 weeks followed by dose dense anthracycline (epirubicin 90 mg/m2 or doxorubicin 60 mg/m2) and cyclophosphamide 600 mg/m2 for 4 doses every 2 weeks or the same chemotherapy regimen (T-AC/EC) given concomitantly with atezolizumab 840 mg every 2 weeks followed by maintenance atezolizumab 1200 mg every 3 weeks until completion of 1 year of atezolizumab. The primary endpoint is to evaluate iDFS of adjuvant atezolizumab+T-AC/EC compared with T-AC/EC alone in patients with TNBC. Secondary endpoints include iDFS by PD-L1 and lymph node status, overall survival, safety, patient functioning and health related quality of life (HRQoL). Furthermore, tumor tissue and blood samples will be collected for biomarker research.

Study report
ALEXANDRA/IMpassion030 worldwide recruitment started in July 2018 and in Germany in June 2019, respectively. As of 31st December 2021 there are 48 patients enrolled in the study. Enrollment is targeted to be completed in QII 2022.

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

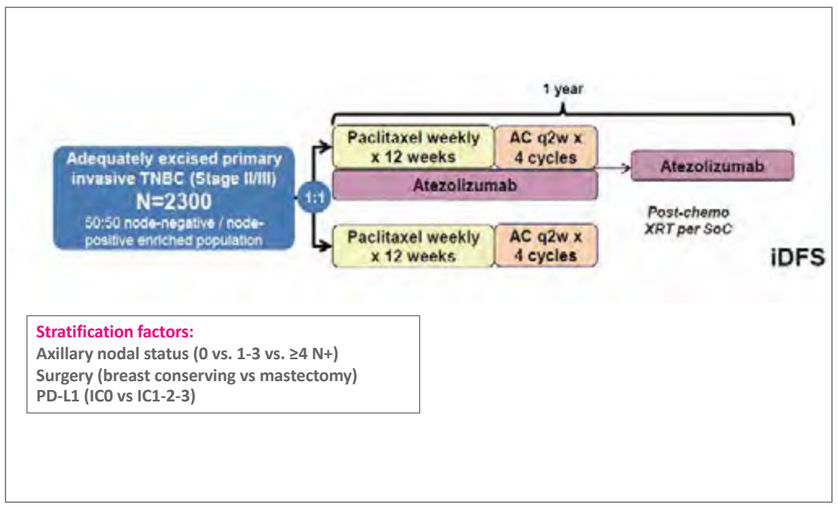

Figure 1: Study design of the ALEXANDRA/IMpassion030 study

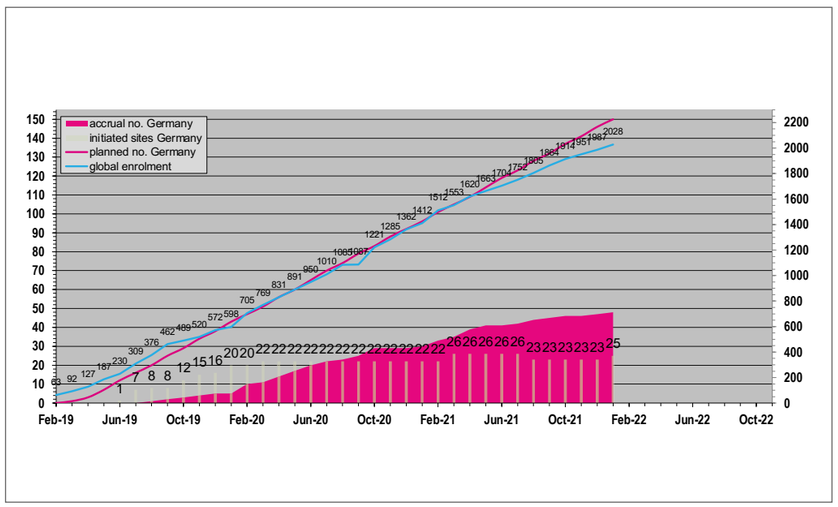

Figure 2: ALEXANDRA/IMpassion030 recruitment as of 31st December 2021

COLLABORATING STUDY GROUPS:
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BIG Breast International Group
frontier science
ALLIANCE
INSTITUT JULES BORDET

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

GBG 93: PADMA

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)

CONTACT:
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Clinical Project Management
padma@GBG.de

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 within approximately 36 months.

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 which strategy would benefit patients most. In real-world, most patients with MBC receive CT to obtain a quick response, although it has not been proven that a achieving a quick response will have an impact on patient benefit. Since palbociclib in combination with ET is superior to ET alone, PADMA is investigating if palbociclib + ET is superior to mono-chemotherapy with or without ET maintenance. Many clinical studies have rigid inclusion and exclusion criteria, predefine study treatment, and strictly define patient monitoring intervals which does 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 questionaire, 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, or withdrawal of consent of the patient or change of initial treatment plan (either approximately six chemotherapy cycles followed by maintenance endocrine therapy or chemotherapy until disease progression).

PADMA primarily aims to compare the 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; 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, p16 expression) which might predict the response to CDK inhibition in MBC as well as evaluation of circulating tumor DNA (ctDNA) at various time points to monitor tumor progression.

The main changes of the first protocol amendment were a reduction of the number of planned patients, and the removal of an initially planned interim analysis and of an activity tracker monitoring sleep and activity levels, respectively. With amendment 2 of the study protocol the number of planned patients was reduced again and study duration prolonged. In addition, a molecular screening is offered to all patients included in the study to identify molecular changes of therapeutic relevance within the context of precision medicine.

Study report

The PADMA recruitment started in March 2018 in Germany. As of 31st December 2021, there are 88 patients enrolled in the study. The end of the study (i.e. last visit of the last patient randomized) is estimated for 2023 earliest.

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

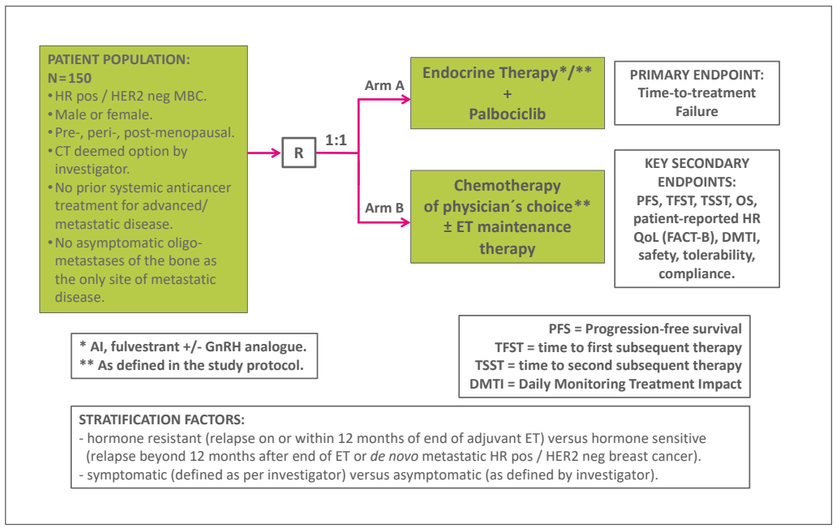

Figure 1: PADMA study design

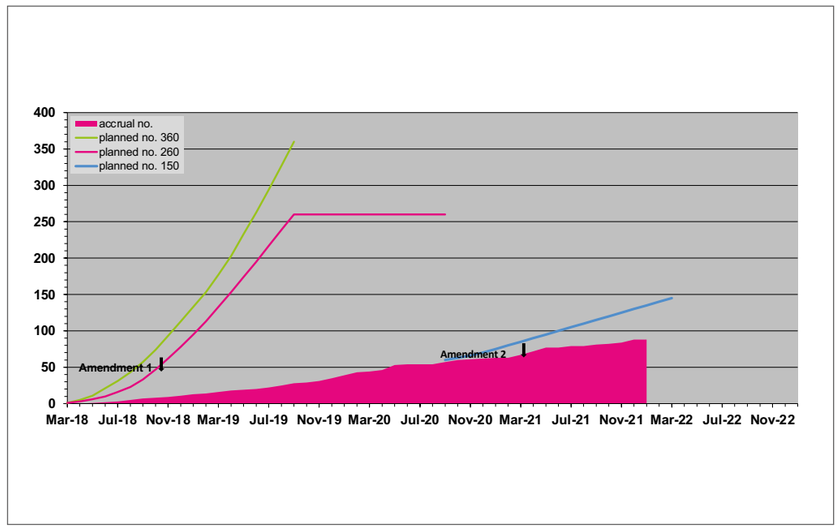

Figure 2: PADMA recruitment as of 31st December 2021

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

CONTACT:
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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

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 post-surgical threatment strategy should be rather baseds 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 of ≥ 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 and 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.

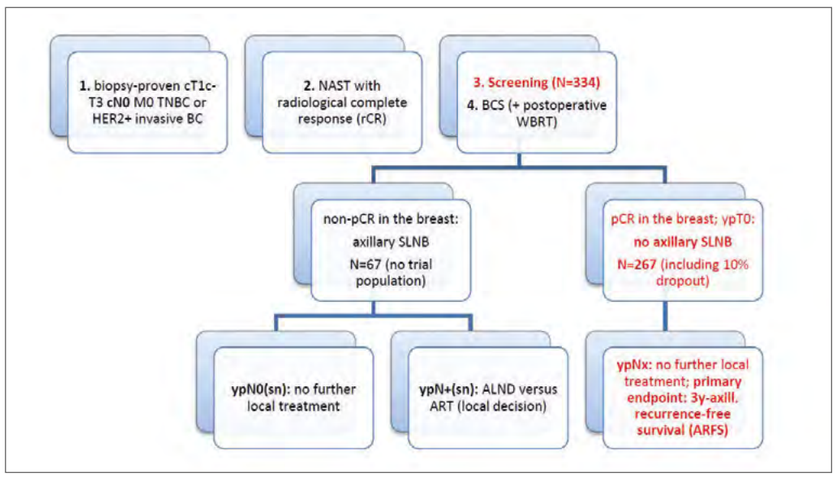

Figure 1: EUBREAST-01 flowchart

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, loco-regional 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.

Study report

EUBREAST-01 global recruitment started in January 2021 with first-patient-in on 15th January 2021 in Germany. As of 31st December 2021, there are 78 patients enrolled in the study. The expected study duration for recruitment is approximately 2 years [1].

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

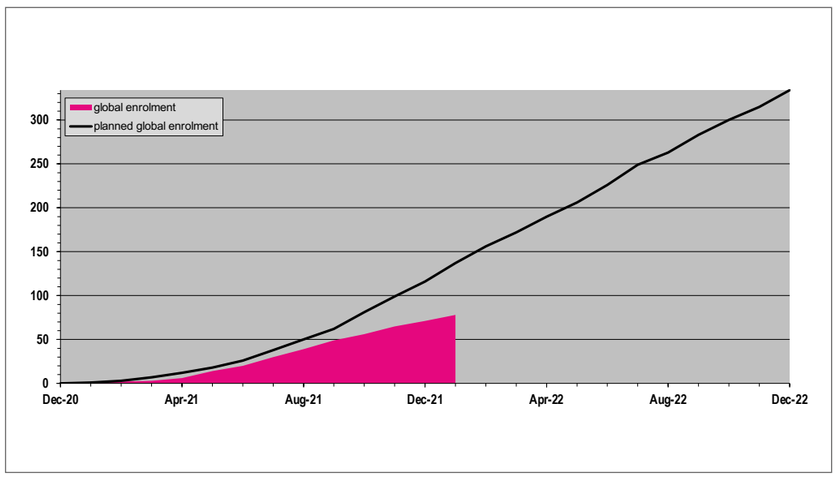

Figure 2: EUBREAST-01 recruitment as of 31st December 2021

COLLABORATING STUDY GROUPS:

SPONSOR:
University Medicine Rostock (UMR)

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

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

GBG 79: Brain Metastases in Breast Cancer (BMBC)

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

Background

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

Due to the analysis of small and heterogeneous patient cohorts, risk factors for the development of brain metastases and the impact of early detection of brain metastases have been analyzed insufficiently. Improved treatment strategies are required as the incidence of patients with brain metastases will increase over the next years due to 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 as long as the data is captured anonymously.

The registry study is conducted in collaboration with Prof. Dr. Volkmar Müller, Priv. Doz. Dr. Isabell Witzel, and Dr. Elena Laakmann 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 tumor.

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

Study report

The study was opened for documentation in April 2014 with more than 50 participating centers. As of 31st of December 2021, 3,492 patients have been registered and 530 tissue samples have been received. Registration of patients is ongoing.

A retrospective analysis including 882 patients from the BMBC registry with available data of three Graded Prognostic Assessment (GPA)-scores that estimate the prognosis of patients with brain metastases by objective criteria (original-GPA, breast-GPA and updated breast-GPA scores) was recently published. Several clinical parameters and all GPA-scores were significantly associated with overall survival. However, all GPA-scores showed only a moderate diagnostic accuracy in predicting overall survival in the analyzed cohort [1].

Another project using data from the BMBC registry was presented at the ESMO Breast Cancer Congress 2021. This retrospective analysis involved a total of 2,948 patients, including 1,311 patients with HER2+ disease and identified factors associated with prognosis of HER2+ patients with brain metastases. A significantly longer overall survival was observed for the hormone receptor-positive subcohort and this finding warrants further research [2].

Publications

1. Riecke K, Müller V, Weide R, et al. Predicting Prognosis of Breast Cancer Patients with Brain Metastases in the BMBC Registry-Comparison of Three Different GPA Prognostic Scores. Cancers (Basel) 2021; 13(4):844.

2. 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.

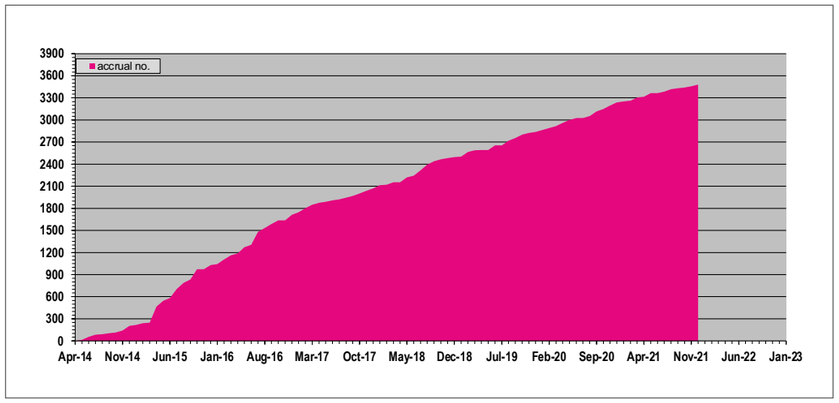

Figure 1: BMBC recruitment as of 31st December 2021

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

COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

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

PSRO

CONTACT:
Jan Steffen
Clinical Project Management
follow.up@GBG.de

GBG 71: Patient Self-Reporting Outcome Registry

PSRO (Patient Self-Reporting Outcome) is a multicenter registry designed to capture long-term follow-up 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 has read out. However, collection of data over a long time period is often not feasible due to the logistical and financial burden for study sites and sponsors.
To address this issue, we have set up a registry in 2010 where patients are contacted consensually in writing and send back information about their health status.

Method

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

Study report

We accept participants from most GBG trials for early breast cancer. Currently, over 12,000 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 already have entered patients into the registry and have contributed to this important project so far.

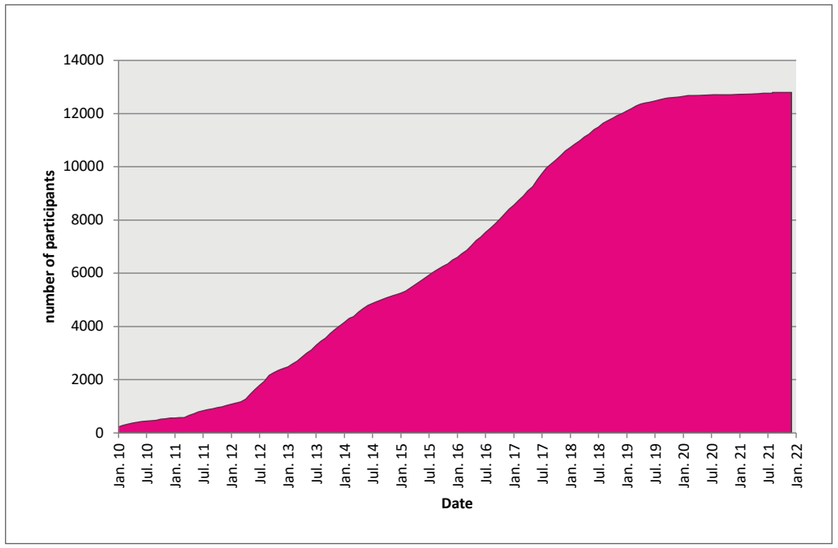

Figure 1: Recruitment into PSRO-registry as of 30th November 2021

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

ZKS Köln ZENTRUM FÜR KLINISCHE STUDIEN

SPONSOR:
GBG Forschungs GmbH

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

GBG 29: Breast Cancer in Pregnancy (BCP)

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

Prospective and Retrospective Registry Study of the German Breast Group (GBG) for Diagnosis and Treatment of Breast Cancer in Pregnancy compared to Young Non-Pregnant Women

NCT00196833

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

Background

Breast cancer in pregnancy is regarded as a rare coincidence. However, about 7% of the women diagnosed with breast cancer are younger than 40 years with a small increase in the incidence in the last years (Eisemann N. et al. Geburtshilfe Frauenheilkd. 2013; DeSantis C et al. CA Cancer J Clin. 2011). The median age of first pregnancy in Germany is 30 years (according to the federal statistical office). Since the incidence of breast cancer under the age of 40 is rising and women tend to delay pregnancy into later reproductive years the coincidence of pregnancy and breast cancer is increasing. Little is known about the incidence of breast cancer in pregnancy in Germany and Western Europe.
Therefore, in 2003 the German Breast Group launched a registry which was extended throughout Europe and worldwide (Breast International Group), to systematically investigate breast cancer during pregnancy and to increase the evidence for treatment options.
With an amendment of the original study protocol, it is now possible to also include a non-pregnant control cohort of women diagnosed with breast cancer at or below the age of 40 years. Those can be matched to the pregnant breast cancer patients as controls treated in everyday clinical practice.
All patients with histologically confirmed breast cancer who are pregnant, as well as patients of 40 years or younger with histologically confirmed breast cancer who are not pregnant and have given informed consent for data collection and biomaterial collection can be entered into the registry. Retrospective participants can be entered without an informed consent as long as the data are captured anonymously.

Study objectives

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

Study report

As of 31st December 2021, a total of 3,086 patients have been registered, 2,711 in Germany (674 pregnant and 2,037 non pregnant women).

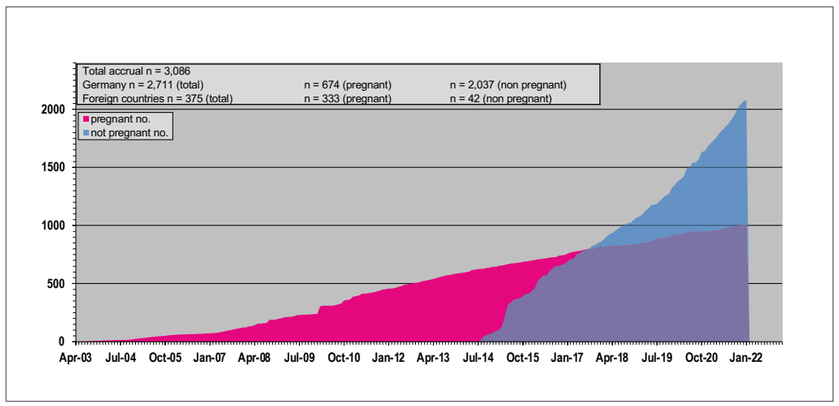

Figure 1: BCP recruitment as of 31st December 2021

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 alternations 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]. A translational research project developed from the BCP registry aimed to investigate the tumor biology and immunology of pregnant breast cancer patients and the impact of pregnancy on the immunological characteristics of the breast cancer. Results were recently presented at the SABCS 2021. Heterogeneity of immunomarker expression was detected in the entire cohort of pregnant breast cancer patients which might be related to the specific immunological situation during pregnancy. Subgroup analyses showed a significantly higher expression of TIGIT, a specific T cell immunoreceptor, in patients with T1/2 compared to those with T3/4 tumor stage, which might be a sign of the initial anti-tumor response with activation of T- and NK-cells that decreases during tumor progression. These preliminary results are hypothesis generating and warrant further research to evaluate the impact of the described heterogeneity in a matched non-pregnant patient cohort [2].

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.

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. Galas K, Gleitsmann M, Rey J, et al. Immunological markers in patients with breast cancer occurring during pregnancy – results from GBG BCP study. Cancer Res. 2021; abstract 767.

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 2021

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 has read out. However, collection of data over a long time period is often not feasible due to the logistical and financial burden for study sites and sponsors

Patient Self-Reported Outcome (PSRO)

To improve follow-up and reduce the workload for the trial sites, we developed a concept to use 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 68.

General Follow-up Database and eCRF

Follow-up documentation across different studies and 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-033	GAIN	2,994	1,012	65%
GBG-066	GeparSixto	588	338	66%
GBG-068	GAIN-2	2,857	2,280	75%
GBG-069	GeparSepto	1,203	792	72%
GBG-070	Dafne	65	52	63%
GBG-074	Genevieve	333	205	58%
GBG-075	Insema	5,194	2,865	75%
GBG-084	GeparOcto	945	732	74%
GBG-088	GeparX	768	585	66%
GBG-089	GeparNuevo	174	133	77%
GBG-090	GeparOla	106	64	57%

Table 1: Status of the GBG trials in follow-up as of December 2021 (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 1,550 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-3-week carboplatin followed by neoadjuvant administration of atezolizumab/placebo with epirubicin or doxorubicin/cyclophosphamide (EC/AC). After surgery patients will reinitiate 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 receiving adjuvant therapy or are in the follow-up period. The first interim analysis of event-free survival (EFS) is expected at end of 2022.

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

GeparOLA (GBG 90, NCT 02789332)

is a multicenter, prospective, randomized open-label phase II study that has recruited 107 patients.

The study evaluated the efficacy of paclitaxel and olaparib in comparison to paclitaxel and carboplatin followed by epirubicin/cyclophosphamide as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and homologous recombination deficiency (HRD) patients with deleterious *BRCA*1/2 tumor or germline mutation and/or HRD score high. The addition of olaparib to paclitaxel was well tolerated and resulted in a pCR rate of 55.1% (90%CI 44.5%-65.3%). However, this was not sufficient to exclude the predefined pCR rate of 55% in the olaparib + paclitaxel arm. Subgroup analyses revealed higher pCR rates in the olaparib group compared to the carboplatin group with regards to hormone receptor-positive tumors, patients younger than 40 years and patients with HRD score high, *BRCA*1/2 wildtype (Fasching et al. Ann Oncol 2020).

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

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 of 2 different nab-paclitaxel regimens (weekly x 12 vs d1, d8 qw3 x 4). 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 given d1,8 q22 (45% vs 39%, respectively, p=0.062, to the significance level of α=0.1) in early breast cancer. Weekly nab-paclitaxel resulted in higher rates of serious adverse events and treatment discontinuations mainly due to adverse events (Blohmer et al. Cancer Res 2020). Among predefined subgroups, particularly patients receiving epirubicin/cyclophosphamide every two weeks and

patients receiving denosumab benefitted from the weekly nab-paclitaxel schedule. A high RANK expression was associated with significantly higher pCR rates, an effect that was pronounced in patients with luminal breast cancer. However, a clinical benefit of denosumab in relation to RANK expression could not be shown (Link et al. Ann Oncol 2020).

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

BRIGHTNESS (GBG 81, NCT 02032277)

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

The study compared paclitaxel plus carboplatin plus Poly(ADP-ribose) polymerase (PARP) inhibitor veliparib with paclitaxel plus carboplatin and with paclitaxel alone, each followed by standard neoadjuvant chemotherapy with doxorubicin/cyclophosphamide in triple-negative breast cancer (TNBC) patients. Overall, an addition of veliparib to neoadjuvant chemotherapy did not increase the pCR rate in the breast and lymph nodes in TNBC patients. In contrast, the addition of carboplatin to paclitaxel resulted in a significant improvement in pCR rates compared to paclitaxel alone. The increased toxicity of carboplatin with or without veliparib did not impact the delivery of neoadjuvant chemotherapy (Loibl et al. Lancet Oncol. 2018). Long-term results after a median follow-up of 4.5 years confirmed that only the addition of carboplatin to paclitaxel has an impact on pCR and event-free survival (EFS). Stratified analysis of OS demonstrated no statistically significant benefit of carboplatin (Loibl et al. Ann Oncol. 2021).
A prespecified secondary analysis on TNBC subtyping in the BRIGHTNESS trial revealed high pCR rates in basal-like and immunomodulatory subsets. The benefit of carboplatin regarding pCR was seen across all molecular subtypes (Filho OM et al JAMA Oncol. 2021). A recent matched cohort study of patients with germline *BRCA* (g*BRCA*) mutated TNBC demonstrated no significant difference in pCR between g*BRCA* and non-g*BRCA* patients when carboplatin with or without veliparib was added to the neoadjuvant chemotherapy (Filho OM et al. NPJ Breast Cancer. 2021).

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

KATHERINE (GBG 77, NCT 01772472)

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

The trial investigated whether adjuvant T-DM1 was more effective than trastuzumab in patients with HER2-positive primary breast cancer who received neoadjuvant chemotherapy including trastuzumab and had residual invasive disease after surgery.
Interim analyses showed a significantly improved invasive disease-free survival (iDFS) with adjuvant T-DM1 compared to trastuzumab. Safety data were consistent with the known safety profile of T-DM1, with more adverse events associated with T-DM1 than with trastuzumab alone (von Minckwitz et al. N Engl J Med 2019).
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 invasive disease-free survival 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 does not increase the overall risk of CNS recurrence. Neoadjuvant chemotherapy had a minimal impact on safety (Mamounas et al. Ann Oncol. 2021).

Further analyses are to follow in 2022 for this important study and we therefore encourage all participating sites to provide follow-up data for their patients.

Post-neoadjuvant studies

Penelope[B] (GBG 78, NCT 01864746)

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

The study evaluated the addition of the CDK4/6 inhibitor palbociclib as postneoadjuvant treatment for HER2-/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).
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 g*BRCA*1/2 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 g*BRCA*1/2 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).

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.

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 analyzed by the sponsor IKP. Publication of the results is planned for 2022.

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

PALLAS (GBG 87, NCT 02513394)

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

The trial was designed to determine if the addition of two years of palbociclib to adjuvant endocrine therapy improves invasive disease-free survival (iDFS) over endocrine therapy alone in patients with HR+/HER2- early-stage breast cancer. At the 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 2021). Results on 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, resuming that 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 taken on this important trial. The follow-up of patients will continue for at least 10 years from trial entry and we encourage all participating sites to provide follow-up data for their patients.

OLYMPIA (GBG 82, NCT 02032823)

is a multicenter, double-blind, parallel group, placebo-controlled, randomized phase III trial that has recruited 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 *BRCA*1/2 mutations and high-risk HER2-negative 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 survival 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 recently 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).

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

APHINITY (GBG 67, NCT 01358877)

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

The study compared safety and efficacy of a combination therapy with two anti-HER2 agents (trastuzumab and pertuzumab) in addition to chemotherapy in the adjuvant setting, compared to chemotherapy and trastuzumab alone. Addition of pertuzumab significantly improved the rates of invasive disease-free survival (iDFS) when it was added to trastuzumab and chemotherapy. Diarrhea was more common with pertuzumab than with placebo (von Minckwitz et al. N Engl J Med 2017). 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-positive early breast cancer while a modest OS benefit did not reach statistical significance (Piccart et al J Clin Oncol 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 recently 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 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 (until 10 years after the randomization of the last patient, which is around September 2023), and we would like to remind participating sites to provide regular follow-up data to avoid later delays in the study analysis.

Metastatic studies

AMICA (GBG 97, NCT03555877)

is a multicenter, prospective, open-label, phase II study that has recruited 56 patients in Germany.

AMICA primarily aimed to estimate the median progression-free survival (PFS) with 95% confidence interval (CI) of an anti-hormonal maintenance therapy with ribociclib after 1st line chemotherapy at the discretion of the investigator (e.g. taxanes, capecitabine, vinorelbine, anthracycline). Secondary objectives were to determine the median overall survival with 95% CI, to describe safety, treatment compliance and clinical benefit rate and to evaluate patient reported outcomes. Biomarkers predictive for response to treatment will be analyzed.
The study was amended (after recruitment of 37 patients) from a randomized into a one-armed

trial due to slow accrual, thereby reducing the initially planned sample size of 150 to 95. AMICA has stopped recruitment at the end of 2021 due to poor accrual as recommended by the Independent Data Monitoring Committee (IDMC) with 56 of the planned 95 patients recruited.

We are thanking all participating centers for their commitment and efforts so far. For timely analysis of the primary endpoint, which is planed in 2022, we would like to encourage all participating sites to continue to support the AMICA study by providing the follow-up data and remaining biomaterial for their patients.

PATINA
A COLLABORATIVE STUDY SPONSORED BY ALLIANCE FOUNDATION TRIALS, LLC

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 plus anti-HER2 therapy plus endocrine therapy versus anti-HER2 therapy plus 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 plus endocrine therapy is superior to anti-HER2-based therapy plus 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 for April 2026. The study is now in 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

AURORA (GBG 85, NCT02102165)

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

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, and to ultimately identify the right therapy for each individual patient. At the same time, patients with genetic aberrations that are being targeted by new drugs in development will be offered the possibility to participate in clinical trials, when approved and available in their countries.
Recruitment was set on hold 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 recently published. 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 are thanking all participating centers for their commitment and efforts so far.

Surgical studies

Universitätsspital Basel

TAXIS (GBG101, OPBC-03, 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 that has recruited 32 patients.

The trial was designed to show that tailored axillary surgery (TAS) and axillary radiotherapy are 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. Secondary objectives include assessment of quality of life, overall survival, breast cancer-specific survival, time to local recurrence, time to regional recurrence, time to distant recurrence, reported morbidity outcomes (lymphedema and decreased range of shoulder motion), adverse events, late radiotherapy-related adverse events, and surgical site infections.
TAXIS recruitment started in August 2019 in Germany. Recruitment was temporarily stopped at the end of 2020, and it is planned to re-open the trial for recruitment in Germany in QI 2022.
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 was able to show that TAS selectively reduced the tumor load in the axilla and remained much less radical than ALND (Weber et al. Breast 2021).

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

INSEMA

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 the SABCS 2021. 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 60% at all time points. There were significant differences for breast and arm symptom scores favoring the no SLNB group in all post-baseline assessments. Patients in the SLNB group had improved arm symptoms and functioning compared to those receiving cALND (Gerber et al. Cancer Res 2022).

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

Completed Studies

GBG 89: GeparNuevo

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

NCT02685059

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

Background

Chemotherapy remains standard of care for primary triple-negative breast cancer (TNBC). Immunotherapy seems very attractive for TNBC given the rather high pre-existing immunogenicity reflected by stromal tumor infiltrating lymphocytes (sTILS) that are predictive and prognostic in this breast cancer subtype (Adams et al. Oncoimmunology 2015, Adams et al. JAMA Oncol 2018, Denkert et al. Lancet Oncol 2018). Checkpoint inhibitors prolonged survival in melanoma, lung cancer and in PD-L1-positive metastatic TNBC (Chae et al. J Immunother Cancer 2018, Schmid et al. N Engl J Med 2018). Recent data from the randomized, phase III KEYNOTE-522 trial showed that treatment with neoadjuvant pembrolizumab plus chemotherapy versus placebo plus chemotherapy, followed by adjuvant pembrolizumab versus placebo significantly improved pathological complete response (pCR) rate and event-free survival with manageable toxicities in patients with early-stage TNBC (Schmid et al. N Engl J Med 2020, Schmid et al. Cancer Res 2021, Abstract GS1-01). A phase I study showed an increased clinical response and suggested a correlation with PD-L1 expression (Emens et al. JAMA Oncol 2019). Furthermore, the PD-L1 inhibitor durvalumab has demonstrated efficacy in bladder and lung cancer (Powles et al. JAMA Oncol 2017, Antonia et al. N Engl J Med 2017). The GeparNuevo study aimed to investigate in a proof of concept study whether the addition of durvalumab increases the pCR rate and whether TILs or PD-L1 expression predict response to durvalumab.

Study design and objectives

GeparNuevo primarily aimed to compare the pCR (ypT0 ypN0) rates of neoadjuvant treatment of sequential, nab-paclitaxel followed by epirubicin and cyclophosphamide (EC) +/- the PD-L1 antibody durvalumab in patients with early TNBC.

Secondary objectives included assessment of pCR rates per arm separately for the stratified subpopulations and according to other pCR definitions, breast conservation rates, toxicity and compliance, time-to-event outcomes such as invasive disease-free survival (iDFS), and overall survival (OS) in both arms, and quality of life. Moreover, a broad translational program was included to examine and compare pre-specified molecular markers and gene expression signatures such as tumor infiltrating lymphocytes, PD-1, PD-L1, and Ki-67 on core biopsies before chemotherapy, after the window phase and on surgical tissue after the end of chemotherapy.

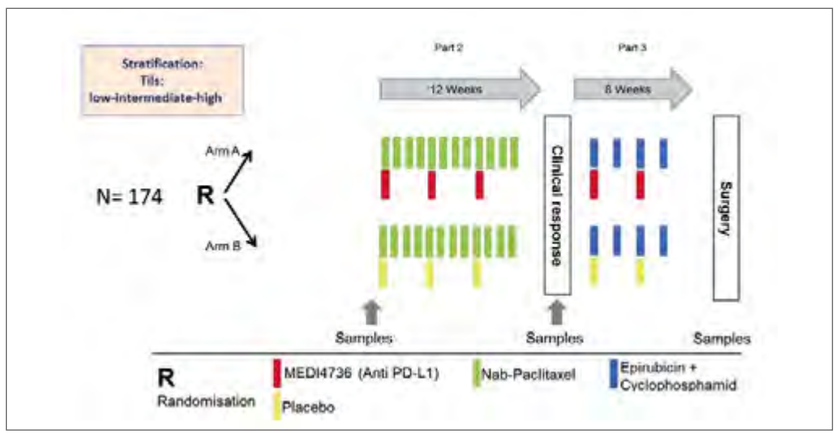

Figure 1: GeparNuevo study design

Study report

GeparNuevo randomized a total of 174 patients between June 2016 and September 2017 from 28 sites in Germany. A total of 117 patients participated in the monotherapeutic window phase which was terminated based on the IDMC (Independent Data Monitoring Committee) consideration indicating an average of 49 days from diagnosis to the start of the 1st chemotherapy as a delay to start of definitive treatment. All randomized patients completed treatment.

The addition of durvalumab to anthracycline/taxane based chemotherapy led to a moderate increase in pCR rate by absolute 9%. A durvalumab effect was seen only in the window cohort (pCR 61.0% vs 41.4%, OR=2.22 [95%CI 1.06-4.64], p=0.035; interaction p=0.048). More patients in the durvalumab arm experienced thyroid dysfunctions compared with the placebo arm. Other immune-related effects were rare and observed in both arms. One patient developed a hypophysitis on durvalumab. No patient died during the study [1]. Long-term results after a median follow-up of 43.7 months demonstrated that durvalumab added to neoadjuvant chemotherapy in TNBC significantly improved survival (3-year iDFS: 85.6% with durvalumab vs 77.2% with placebo, HR=0.48 [95%CI 0.24-0.97], stratified log-rank p=0.036) despite a modest pCR increase, suggesting an activation of anti-tumor immunity. No new serious safety findings were reported [2]. Within the translational biomarker program, mRNA signatures were evaluated to predict response to neoadjuvant PD-L1 inhibition in combination with chemotherapy in early TNBC. A total of 162 patients with available formalin- fixed, paraffin-embedded tissue samples were included in the analysis. The immune-associated signatures identified were associated with better pCR after chemotherapy, but they might be of limited use for the prediction of response to additional immune checkpoint blockade [3].

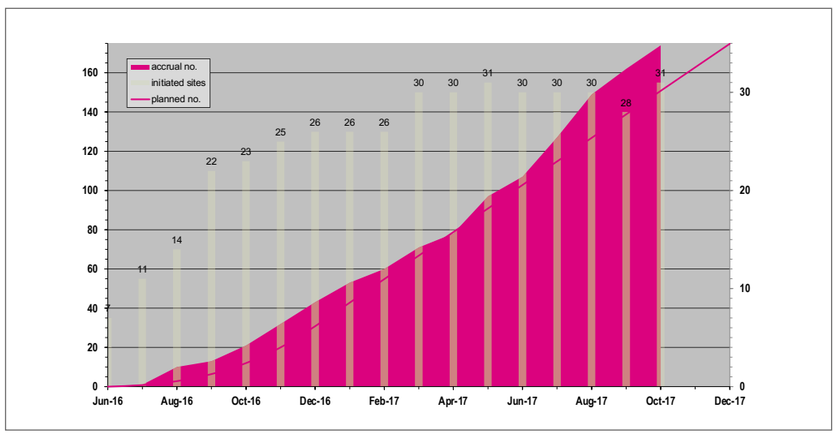

Figure 2: GeparNuevo final recruitment as of 1st October 2017

Publications

1. Loibl S, Untch M, Burchardi N, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol. 2019 Aug 1;30(8):1279-1288.

2. Loibl S, Schneeweiss A, Huober J, et al. Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neoadjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC). J Clin Oncol 2021; 39.15_suppl.506.

3. Sinn BV, Loibl S, Hanusch CA, et al. Immune-related Gene Expression Predicts Response to Neoadjuvant Chemotherapy but not Additional Benefit from PD-L1 Inhibition in Women with Early Triple-negative Breast Cancer. Clin Cancer Res. 2021;27:2584-2591.

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

COLLABORATING STUDY GROUPS:

SPONSOR:
GBG Forschungs GmbH

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GBG 86: DESIREE

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

NCT 02387099

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DESIREE is a multicenter, double-blind, randomized phase II trial that has recruited 160 patients from 29 sites in Germany.

Background

The BOLERO-2 study demonstrated a clinical meaningful benefit for patients who received everolimus in addition to exemestane and who progressed during/after a non-steroidal aromatase inhibitor (NSAI) (Baselga N Engl J Med 2012) and led to approval of everolimus in this indication. However, experience from routine use as well as from the BOLERO-2 and other studies have shown a high rate of everolimus induced stomatitis especially during the first 12 weeks of treatment. Especially outside the clinical trial setting this is a leading cause for treatment discontinuation not related to tumor progression.
In the non-responder part (setting III) of the neoadjuvant GeparQuinto study, everolimus was given as salvage treatment in combination with paclitaxel for patients without response to 4 cycles epirubicin/cyclophosphamide +/- bevacizumab. A dose-escalation schema was implemented successfully to improve the tolerability of everolimus when given in combination with cytotoxic agents (von Minckwitz Ann Oncol 2011; von Minckwitz Ann Oncol 2014).
The DESIREE study compared the cumulative rate of stomatitis episodes grade ≥ 2 (WHO's oral toxicity scale (OTS)) at 12 weeks after start of treatment using a conventional (EVE 10 mg) and a dose escalation schema (EVE esc) of everolimus in combination with exemestane in patients with HR+/HER2- metastatic breast cancer and progression or relapse after NSAI.

Study design and objectives

DESIREE primarily aimed to compare the rate of stomatitis episodes grade ≥ 2 at 12 weeks after treatment start using a conventional or a dose escalation schedule of everolimus in combination with exemestane. Secondary objectives included the cumulative rate of stomatitis episodes grade ≥ 2 at 24 weeks after treatment start, incidence of any grade stomatitis episodes at 12 and 24 weeks after treatment start, rate of patients on 10 mg of everolimus daily at 12 and 24 weeks, clinical benefit rate (CBR) at 24 weeks, safety with regard to other organ signs and symptoms, time to onset of stomatitis grade ≥ 2, relative total dose intensity (RTDI) for everolimus and quality of life (QoL) using the FACT-B questionnaire. Potential biomarkers predicting safety and compliance will be determined at a later time.

Study report

Between June 2015 and October 2020, 160 patients were randomized and 156 started therapy (EVE esc: 80 patients, EVE 10 mg: 76 patients) in the DESIREE study. The study met its primary endpoint: the dose escalation schema of everolimus over three weeks can be successfully implemented in postmenopausal patients with HR-positive/HER2-negative metastatic breast cancer to reduce the incidence of high-grade stomatitis in the first 12 weeks of treatment. Within 24 weeks of treatment, the incidence of stomatitis episodes grade ≥ 2 was numerically lower in the EVE esc arm, but there was not significant difference between the two arms anymore [1]. It is important to note that there was a numerical (not statistically significant) difference of -7.8% in the CBR and 14.1% more patients with progressive diseases in the EVE esc arm at 24 weeks, favouring the standard everolimus administration schedule. Differences in the patient characteristics might have influenced this, however we cannot completely rule out if the EVE esc schedule has impaired the efficacy vs the standard administration without dose escalation. Toxicity reported in the DESIREE study was in line with the known safety profile of everolimus and exemestane, without new safety concerns. The use of a dose escalation regimen did not lead to significant differences in dose reductions, interruptions and discontinuations, resulting in a similar median RTDI between arms. QoL was comparable between the two treatment arms.

Publications

1. Loibl S, Schmidt M, Lübbe K, et al. A multicenter, randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer (mBC) (DESIREE). Ann Oncol 2021; 32 (suppl_5): S1283-S1346.

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

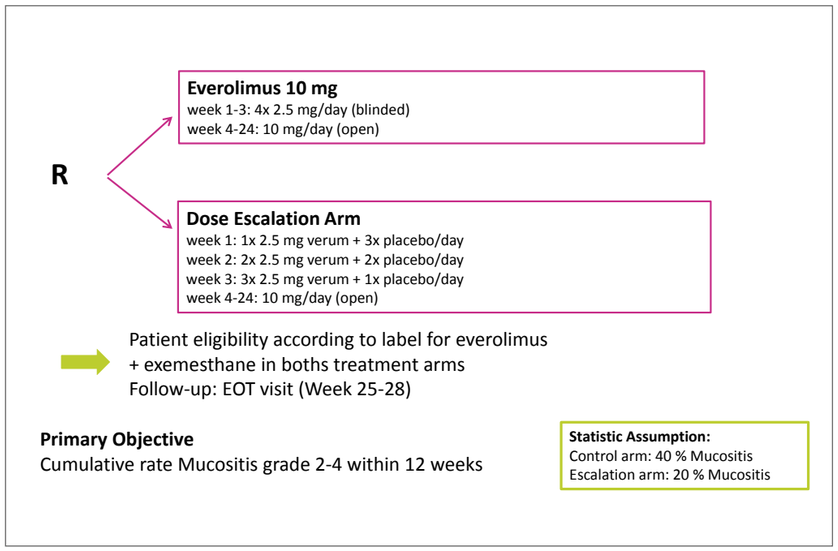

Figure 1: DESIREE study design

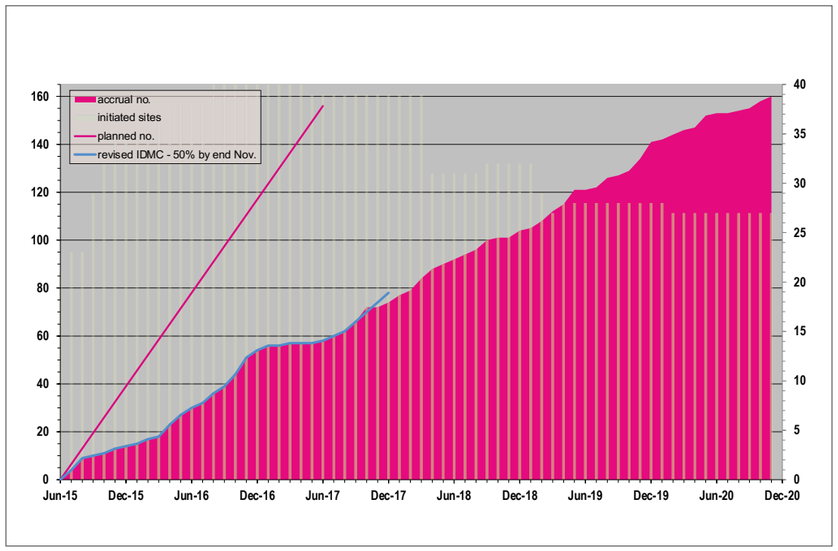

Figure 2: DESIREE final recruitment as of 27th October 2020

COLLABORATING STUDY GROUPS:

GBG GERMAN BREAST GROUP

SPONSOR:
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STUDY CHAIR:
Prof. Dr. Sibylle Loibl
German Breast Group,
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Translational Research & Biobanking

Translational Research & Biobanking

Central Pathology and GBG Tumor Bank

The Institute of Pathology at the University of Marburg has expanded its digital slide repository and image analysis infrastructure in 2021. Currently, over 70,000 whole slide images (WSIs) from tissues stained with hematoxylin and eosin (H&E) and breast cancer biomarkers (e. g. ER, PgR, HER2, Ki67) are available from former central pathology assessments and current translational research projects. WSIs and digitalized tissue microarrays (TMAs) are used for quantitative tissue-based biomarker analysis, which is performed semi-automatically with different software solutions, using machine learning and cell segmentation approaches.

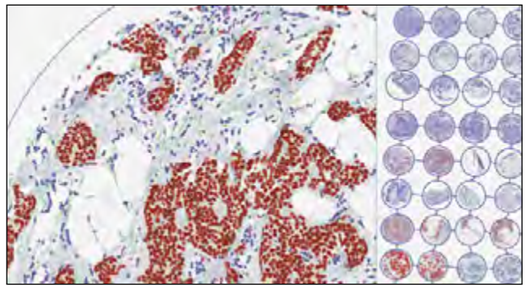

Figure 1: Biomarker analysis on TMA.
Detection of different cell types and positive biomarker staining was performed semi-automatically.

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 intratumor 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 (SP1 to SP9) 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 SP7 (Clinical Translation) will be responsible for the implementation of the clinical translation and GBG will participate with their longstanding expertise on clinical study protocols, biomaterial collection and biomarker validation.

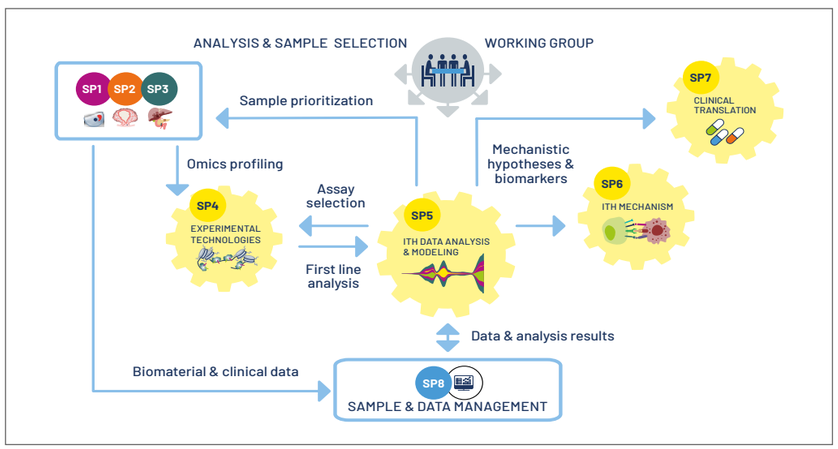

Figure 2: Saturn³ flowchart

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

ONCOBIOME, a project within EU framework "Horizon 2020"

Horizon 2020 (H2020) is the biggest EU research and innovation program with funding available over 7 years. The proposal "ONCOBIOME" from Prof. Laurence Zitvogel (Institute Gustave Roussy, Paris) has been positively evaluated and GBG is one of the 16 participating partners throughout the EU. The aim of the 5-year running project is to determine the relationship between intestinal microbial signatures and the prognosis and treatment resistance in four common cancer entities (breast, colon, lung and melanoma).

The GBG participates with sample collections (tumor tissue and stool sample) as well as expertise in clinical translational research. Starting with amendment 1, the stool sample collection was introduced in the study protocol of GeparDouze. Before start of therapy, stool samples are collected in a special conservation medium and stored frozen at -20°C. 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).

RAD51 predict, a project within the ERA PerMed consortium

This project aims to clinically validate a RAD51 predict test, designed by the experimental therapeutics research group of VHIO (Val d'Hebron, Barcelona), led by Dr. Violeta Serra. RAD51 is a biomarker indicating DNA repair functionality of the tumor. The test aims to identify patients with genetic alterations leading to homologous repair deficiency (HRD), who can benefit from therapies with PARP-inhibitors. GBG supports the project by providing the well-characterized clinical cohorts of GeparSixto and GeparOla, thus making a significant contribution to the clinical validation of the test. First results were recently published. Tissue microarrays (TMAs) of pre-therapeutic core biopsies from 133 triple-negative breast cancer (TNBC) patients from GeparSixto study were measured by immunofluorescence to evaluate the RAD51-, BRCA1 and γH2AX-scores. In primary TNBC, the RAD51 test is highly concordant with tBRCA mutation and genomic HRD score. Furthermore, RAD51 independently predicts clinical benefit (pCR) from adding carboplatin to NACT in TNBC (Llop-Guevara et al. Ann Oncol 2021).

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

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GBG Study Finder 2022*

Early Breast Cancer

Operative Studies (M0)

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

Operable triple-negative breast cancer: • Stage II-III • Pathological tumor size ≥ 2 cm if pN0	**ALEXANDRA** Arm A: Adjuvant chemotherapy with 12x paclitaxel weekly followed by EC/AC q2w **+ atezolizumab q2w followed by atezolizumab monotherapy q3w** (total duration of atezolizumab will be one year) Arm B: Chemotherapy alone
Operable HR-positive / HER2-negative breast cancer: • Age ≥ 70 years; Stage II-III • Adjuvant chemotherapy required and feasible	**APPALACHES** Arm A: **Palbociclib** 2 years + standard adjuvant endocrine therapy ≥ 5 years Arm B: Adjuvant chemotherapy followed by standard adjuvant endocrine therapy ≥ 5 years
HER2-negative breast cancer, non-pCR after neoadjuvant chemotherapy (NACT) • HR-negative (TNBC) or • HR-positive with CPS-EG score ≥ 3 or 2 and ypN+ • At least 16 weeks of taxane-based chemotherapy	**SASCIA** Arm A: **Sacituzumab govitecan** 8 cycles d1,8 q3w Arm B: Treatment of physician's choice (8 cycles capecitabine or platinum-based chemotherapy or observation) In patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.
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	**TruDy/DESTINY-B05** Arm A: **Trastuzumab deruxtecan** 14 cycles d1 q3w Arm B: Trastuzumab emtansine (T-DM1) 14 cycles d1 q3w
HER2-positive, HR-positive breast cancer • cT1c-T3 prior to neoadjuvant treatment • Centrally confirmed *PIK3CA* mutation (tumor) • BMI ≤ 30	**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)

Metastatic Breast Cancer

All subtypes

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

HER2-negative Breast Cancer

HER2-negative and HR-positive metastatic breast cancer : • 1st systemic therapy for the treatment of metastatic breast cancer • Patients with only asymptomatic oligometastases of the bone as the only site of metastatic disease are excluded	**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	**Breast Cancer in Pregnancy (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 *BRCA*1 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	**BRCA-P**** Study to determine the preventive effect of denosumab on breast cancer in women carrying a *BRCA*1 germline mutation: **Denosumab 120 mg** 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	**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 other countries	**ETERNITY[8]** 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 by study site.

* Further studies are currently in planning. Please refer to www.gbg.de
** Planned start of recruitment QI-II/2022

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