GBG

GERMAN
BREAST
GROUP

Leading in Breast Cancer Research

# ANNUAL SCIENTIFIC REPORT **2023**

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# Editorial

Twenty years ago, the GBG Forschungs GmbH was founded with the aim of advancing breast cancer research in Germany and improving patient care. Over two decades, enormous progress has been made in treating patients with breast cancer, and we are proud to have contributed to improving patients' survival.

We are excited to announce that several new studies are planned to commence in 2024, such as CAMBRIA-1, ELEMENT, LOBSTER, NeoRad, PREcoopERA, among others. We are also happy to share featured interviews with Dr. Kristina Lübbe for ELEMENT as well as Prof. Dr. Jens-Uwe Blohmer for LOBSTER under "New Study Concepts and Methodologies".

**In March 2023, we celebrated the 20th anniversary of GBG with all our colleagues and collaborators in presence in Frankfurt/Main.**

Our accomplishments in 2023 have been visible, as with every year, in international conferences such as ASCO, ESMO Breast, German Society for Senology, as well as the San Antonio Breast Cancer Symposium (SABCS). You can find our conference contributions in the section "Congress Contribution".

Moreover, our impact factor for 2023 was 1,291 with a total of 35 papers published in peer-reviewed journals. Section "Publications" lists all papers published in 2023.

We also continue to meet, as closely as ever, with our key opinion leaders and researchers in our regular Subboard meetings, and we continue to build a rich network of national and international study groups. Our close and ongoing work with the Gynecologic Oncology Working Group (Arbeitsgemeinschaft Gynäkologie Onkologie -Breast Study Group, AGO-B) remains a vital connection for our shared mission to promote science and research in the field of breast cancer.

We are also happy to announce the recommencement of our Scientific Board, with the aim of more intensive and comprehensive planning of clinical studies as well as promoting young investigators.

You can find all recruiting and follow-up studies in the respective sections. Furthermore, "Translational Research & Biobanking" provides a glimpse into our translational research projects. Finally, you will find our GBG Study Finder 2023 from page **78**.

We would like to thank you for your continued collaboration and support. As we reflect on the accomplishments of GBG in 2023, we also look forward to 2024 with more achievements to come, as we continue to follow our mission of healing through innovation, competence, and partnership in the field of breast cancer therapy.

Yours
Prof. Dr. Sibylle Loibl
on behalf of the GBG Team and the Subboards

# About the German Breast Group

The German Breast Group's (GBG) Annual Scientific Report features a fresh look that aligns with our newly redesigned website. For sure, GBG's core values of innovation, expertise, and collaboration remain constant. Continuously committed to breast cancer research in Germany, we manage clinical trials across the entire therapeutic spectrum of breast cancer – ranging from prevention to neoadjuvant, adjuvant, local and palliative treatment situations. Our focus on investigator-initiated trials that are academically driven, emphases our commitment to address critical clinical and research questions to challenge and optimize breast cancer treatment strategies. Furthermore, our commitment to adhering to the highest standards of the International Conference on Harmonization of Good Clinical Practice (ICH-GCP 1998) and regulatory requirements underscores our unwavering dedication to scientific values.

## OUR EXPERTISE

Within the realm of breast cancer research, GBG stands out in providing a comprehensive range of services. From initial stages of idea generation and study design creation in our subboards of breast cancer experts to clinical project management, monitoring, data management, biometrics, statistics, and international publication of the trial results we harbor all neccessary skills and expertise required for our pursuit of improving breast cancer treatments. Our scope includes translational research, biobanking, pathological central laboratory support, continuous medical education, and stringent quality control measures.

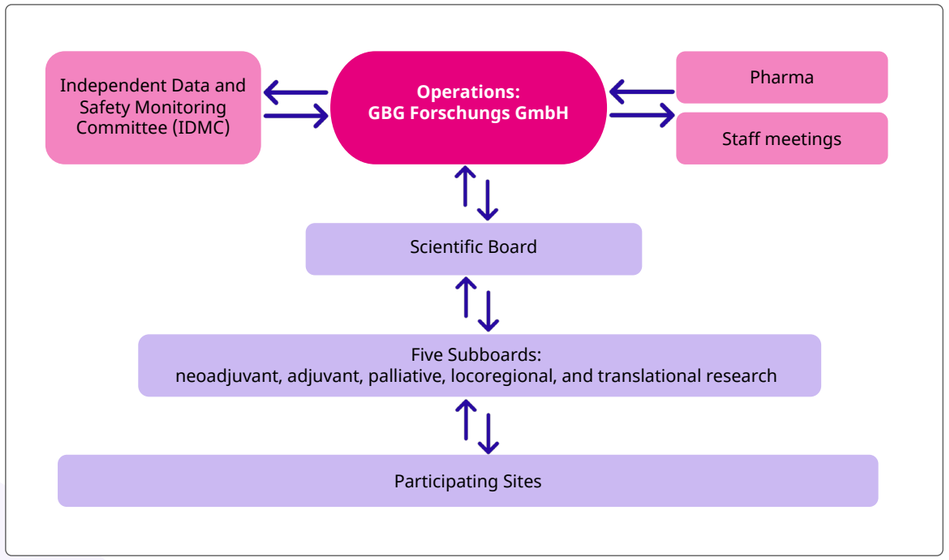



Figure 1: Structure of the German Breast Group

## OUR INFRASTRUCTURE

The core of GBG is a comprehensive infrastructure that links scientific concepts developed in our routine GBG study group subboard gatherings to the collaborating trial sites across numerous medical facilities, utilizing GBG's specialized departments. While an official membership is not mandatory, physicians actively engaged in our trials become integral members of the study group. Our investigators, predominantly located in gynecological institutions, including university clinics, general hospitals, specialist practices, and general practices provide invaluable insights to the research conducted.

## PATIENT RECRUITMENT AND IMPACT

The impact of our work is evident in a multitude of publications covering breast cancer treatment over the past decades. Our goal is the continuous improvement of breast cancer treatment strategies and clinical guidelines, leading to a decrease in mortality over the years. The cumulative patient recruitment reflects the growing influence of GBG and the trust placed in our studies by both physicians and patients alike.

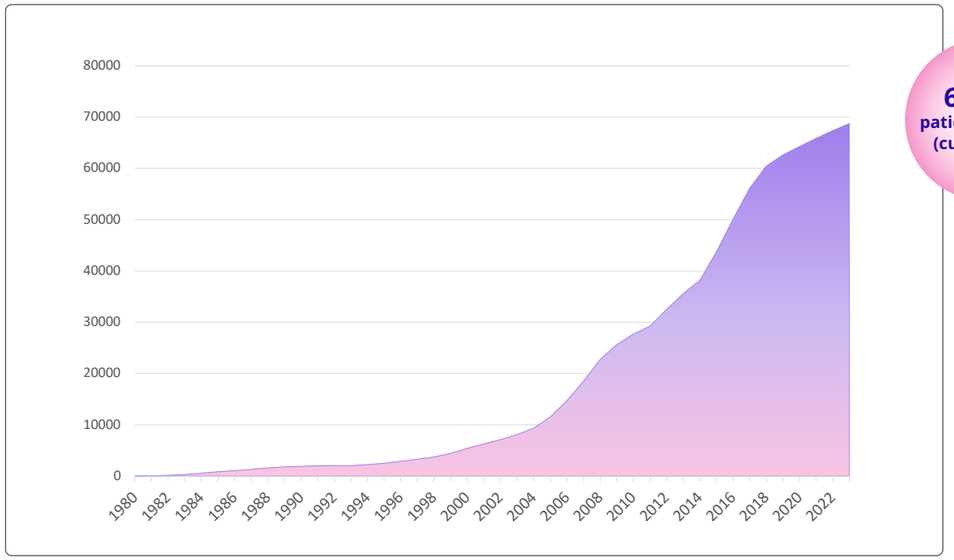



Figure 2: Cumulative patient recruitment

## THE INDEPENDENT DATA AND SAFETY MONITORING COMMITTEE (IDMC)

Since its inception in 2003 GBG has been committed to maintaining the highest standards of safety and efficacy in clinical trials. At the forefront of this dedication is the Independent Data and Safety Monitoring Committee (IDMC), which is a pivotal component in the continual enhancement of working processes related to in-house observation, monitoring, and consultation.

The IDMC plays a crucial role in safeguarding the integrity of GBG-sponsored trials. Its responsibilities encompass a comprehensive review of ongoing trials, focusing on key aspects such as:

- **Objectives and Scientific Impact: Rigorous examination of trial objectives, the scientific impact of findings, and a meticulous analysis of adverse events (AE), serious adverse events (SAE).**
- **Protocol Modifications: Thorough assessment of all major modifications to the trial protocol, including accrual goals, guarantees that adjustments align with the study's original objectives.**
- **Efficacy Analysis: The IDMC is actively involved in the interim and final efficacy analyses of trials, stepping in when the protocol-specified number of recruited patients or events has been achieved. This ensures a robust evaluation of the trial's effectiveness.**

## CONTINUOUS IMPROVEMENT AND PROACTIVE OVERSIGHT

By establishing the IDMC, GBG demonstrates its commitment to proactive and vigilant oversight, fostering an environment of continuous improvement in clinical trial practices. This dedicated committee meets the evolving challenges of the dynamic scientific landscape and contributes significantly to the reliability and credibility of GBG-sponsored research.

As we maneuver through the complex landscape of breast cancer research, the IDMC is the evidence of our commitment to guarantee the safety, quality, and scientific rigor of every trial conducted under the auspices of GBG.

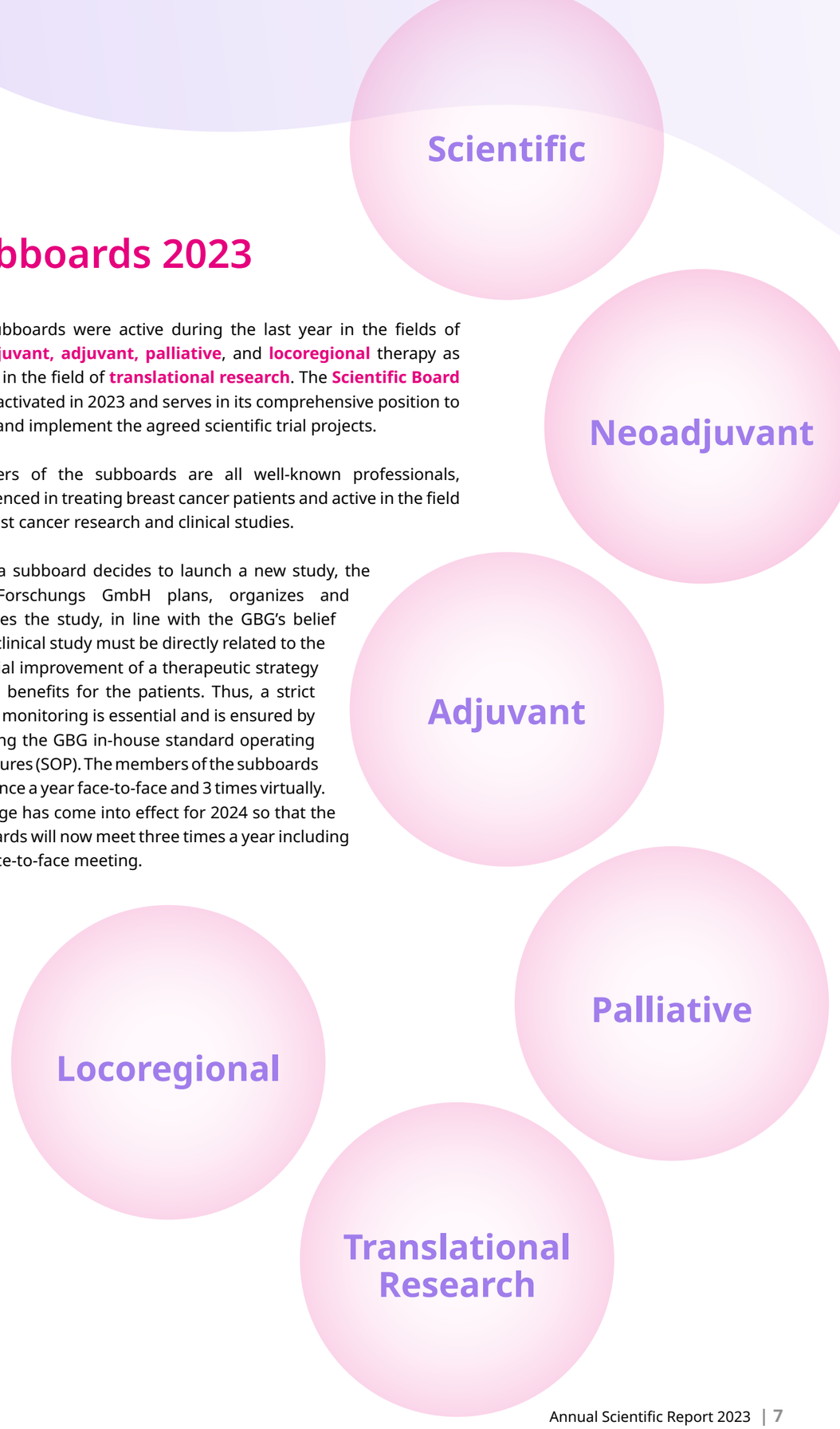


# Subboards 2023

Five subboards were active during the last year in the fields of **neoadjuvant, adjuvant, palliative**, and **locoregional** therapy as well as in the field of **translational research**. The **Scientific Board** was reactivated in 2023 and serves in its comprehensive position to refine and implement the agreed scientific trial projects.

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 patients. 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. A change has come into effect for 2024 so that the subboards will now meet three times a year including one face-to-face meeting.



# Subboards 2023

## Scientific


Dr. V. Nekljudova, Neu-Isenburg


Prof. Dr. F. Marmé, Mannheim


PD Dr. D. Krug, Kiel


Dr. J. Holtschmidt, Neu-Isenburg


Dr. T. Link, Dresden


PD Dr. M. Reinisch, Essen


Prof. Dr. S. Loibl, Neu-Isenburg


Prof. Dr. K. Rhiem, Köln


Prof. Dr. C. Denkert, Marburg


PD Dr. L. Michel, Heidelberg


PD. Dr. M. van Mackelenbergh, Kiel

## Neoadjuvant


Prof. Dr. A. Schneeweiss, Heidelberg


Prof. Dr. V. Bjelic-Radisic, Wuppertal


Prof. Dr. C. Solbach, Frankfurt am Main


Prof. Dr. J. U. Blohmer, Berlin


Prof. Dr. C. Denkert, Marburg


Prof. Dr. P. Fasching, Erlangen


Prof. Dr. M. Untch, Berlin


Dr. T. Link, Dresden


Dr. C. Hanusch, München


PD Dr. M. Reinisch, Essen


Prof. Dr. A. Hartkopf, Ulm


Prof. Dr. S. Loibl, Neu-Isenburg

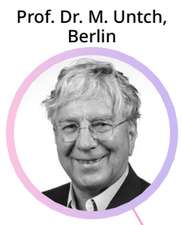

Prof. Dr. C. Jackisch, Essen


Prof. Dr. K. Rhiem, Köln


Prof. Dr. J. Huober, St. Gallen

# Subboards 2023

## Adjuvant


Prof. Dr. M. Untch, Berlin


Prof. Dr. C. Denkert, Marburg


Prof. Dr. W. Janni, Ulm


Prof. Dr. E. Stickeler, Aachen


Prof. Dr. S. Loibl, Neu-Isenburg


PD Dr. B. Sinn, Berlin


Prof. Dr. F. Marmé, Mannheim


Prof. Dr. M. Schmidt, Mainz


PD Dr. L. Michel, Heidelberg


PD Dr. M. Reinisch, Essen


Dr. S. Schmatloch, Kassel


Prof. Dr. T. Reimer, Rostock

## Palliative


Prof. Dr. M. Thill, Frankfurt am Main


Prof. Dr. T. Decker, Ravensburg


Prof. Dr. C. Denkert, Marburg


Prof. Dr. M. Schmidt, Mainz


Prof. Dr. S. Loibl, Neu-Isenburg


Prof. Dr. V. Müller, Hamburg

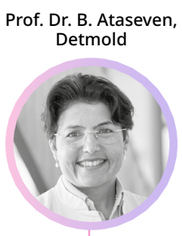
Prof. Dr. C. Mundhenke, Bayreuth


Dr. K. Lübbe, Hannover

# Subboards 2023

## Locoregional


Prof. Dr. S. Loibl,
Neu-Isenburg


Prof. Dr. B. Ataseven,
Detmold


PD Dr. I. Bekes,
St. Gallen


Prof. Dr. T. Kühn,
Esslingen


Prof. Dr. C. Denkert,
Marburg


PD Dr. D. Krug,
Kiel


Prof. Dr. B. Gerber,
Rostock

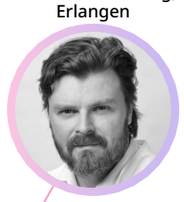

Dr. J. Holtschmidt,
Neu-Isenburg


Prof. Dr. J. Heil,
Heidelberg


Prof. Dr. M. Golatta,
Heidelberg

## Translational Research


PD Dr. M. van Mackelenbergh,
Kiel


Prof. Dr. P. Fasching,
Erlangen


Prof. Dr. C. Denkert,
Marburg


Prof. Dr. E. Stickeler,
Aachen


Prof. Dr. T. Fehm,
Düsseldorf


PD Dr. B. Sinn,
Berlin


Prof. Dr. T. Karn,
Frankfurt am Main


Prof. Dr. C. Schem,
Hamburg


Prof. Dr. S. Loibl,
Neu-Isenburg

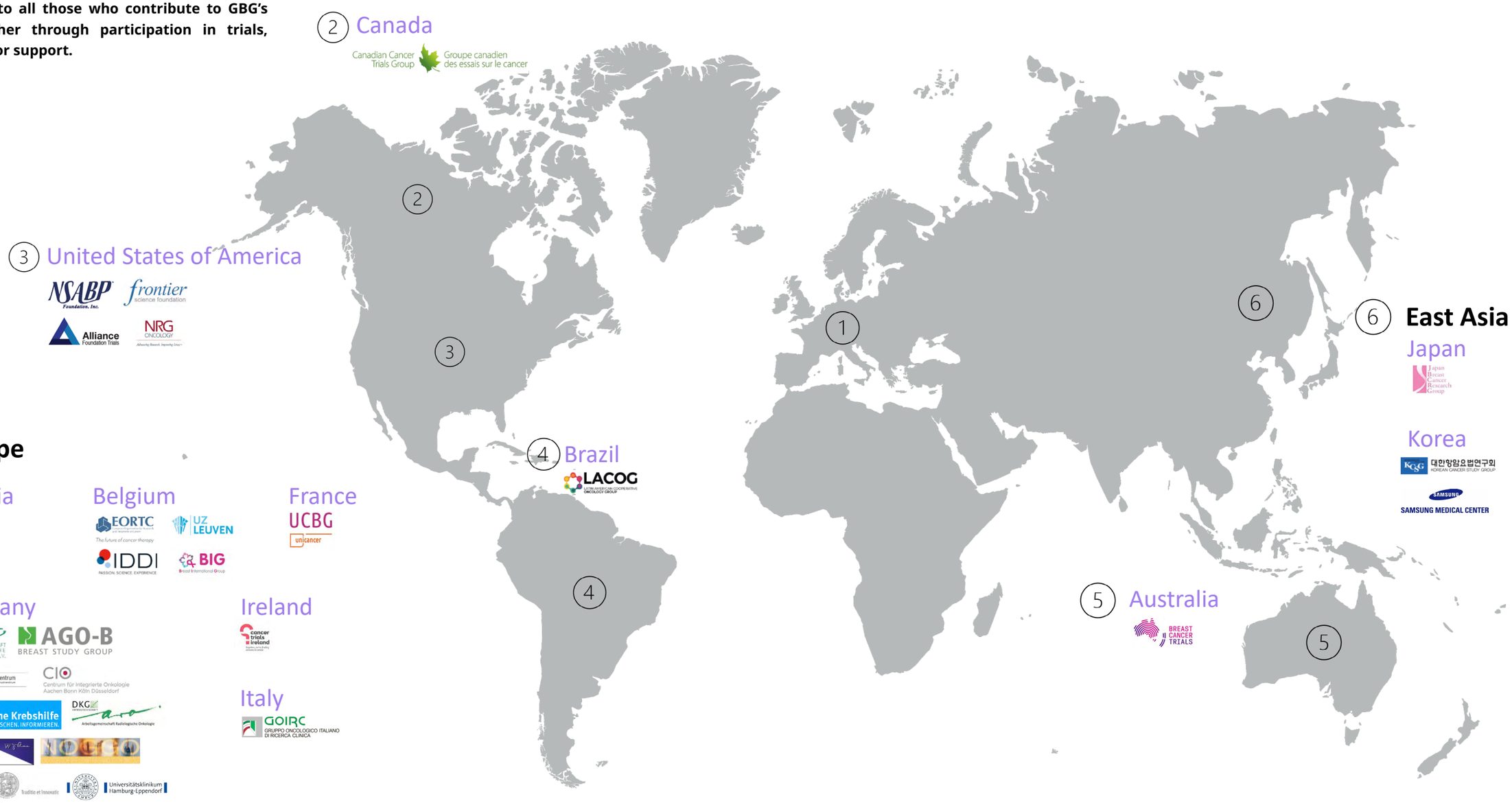
Prof. Dr. A. Noske,
Zürich


Prof. Dr. V. Müller,
Hamburg


Prof. Dr. F. Marmé,
Mannheim

# Cooperations with other study groups

**As we embark on another year of research, we express our gratitude to all those who contribute to GBG's success, whether through participation in trials, collaboration, or support.**



## 1 Europe

### Austria

### Belgium

### France

### Germany

### Ireland

### Italy

### Netherlands

### United Kingdom

## 2 Canada

## 3 United States of America

## 4 Brazil

## 5 Australia

## 6 East Asia

### Japan

### Korea

### Spain

### Switzerland

### Sweden

# Peer-reviewed articles in 2023

Cui, W., K. A. Phillips and L. A. Keogh. "Selection of Endpoints in Breast Cancer Clinical Trials: A Qualitative Study of Key Trial Stakeholders." Am J Cancer Res 12, no. 12 (2022): 5599-612.

Click here for more info

IF 5.94

Curigliano, G., H. J. Burstein and Panelists St Gallen Consensus Conference. "Understanding Breast Cancer Complexity to Improve Patient Outcomes: The St Gallen International Consensus Conference for the Primary Therapy of Individuals with Early Breast Cancer 2023." Ann Oncol 34, no. 11 (Nov 2023): 970-86.

Click here for more info

IF 51.77

Curigliano, G., V. Mueller and E. Winer. "Corrigendum to "Tucatinib Versus Placebo Added to Trastuzumab and Capecitabine for Patients with Pretreated Her2d Metastatic Breast Cancer with and without Brain Metastases (Her2climb): Final Overall Survival Analysis": [Annals of Oncology 33 (2022) 321-329]." Ann Oncol 34, no. 7 (Jul 2023): 630.

Click here for more info

IF 51.77

Cuzick, J., K. Chu and M. Dowsett. "Effect of Baseline Oestradiol Serum Concentration on the Efficacy of Anastrozole for Preventing Breast Cancer in Postmenopausal Women at High Risk: A Case-Control Study of the Ibis-Ii Prevention Trial." Lancet Oncol 25, no. 1 (Jan 2024): 108-16.

Click here for more info

IF 51.1

de Azambuja, E., E. Agostinetto and Investigators. "Cardiac Safety of Dual Anti-Her2 Blockade with Pertuzumab Plus Trastuzumab in Early Her2-Positive Breast Cancer in the Aphinity Trial." ESMO Open 8, no. 1 (Feb 2023): 100772.

Click here for more info

IF 6.88

Decker, T., K. Ludtke-Heckenkamp and S. Loibl. "Anti-Hormonal Maintenance Treatment with the Cdk4/6 Inhibitor Ribociclib after 1st Line Chemotherapy in Hormone Receptor Positive / Her2 Negative Metastatic Breast Cancer: A Phase Ii Trial (Amica)." Breast 72 (Dec 2023): 103575.

Click here for more info

IF 10

Denkert, C., C. Lambertini and M. Basik. "Biomarker Data from the Phase Iii Katherine Study of Adjuvant T-Dm1 Versus Trastuzumab for Residual Invasive Disease after Neoadjuvant Therapy for Her2-Positive Breast Cancer." Clin Cancer Res 29, no. 8 (Apr 14 2023): 1569-81.

Click here for more info

IF 13.8

Fasching, P. A., C. Szeto and S. Loibl. "Inferred Immune-Cell Activity Is an Independent Predictor of Her2-Negative Breast Cancer Prognosis and Response to Paclitaxel-Based Therapy in the Geparsepto Trial." Clin Cancer Res 29, no. 13 (Jul 5 2023): 2456-65.

Click here for more info

IF 13.8

Francis, P. A., G. F. Fleming and Group the International Breast Cancer Study. "Adjuvant Endocrine Therapy in Premenopausal Breast Cancer: 12-Year Results from Soft." J Clin Oncol 41, no. 7 (Mar 1 2023): 1370-75.

Click here for more info

IF 50.72

Garcia-Saenz, J. A., F. Marme and H. S. Rugo. "Patient-Reported Outcomes in High-Risk Hr+ /Her2- Early Breast Cancer Patients Treated with Endocrine Therapy with or without Palbociclib within the Randomized Penelope[B] Study." Eur J Cancer 196 (Jan 2024): 113420.

Click here for more info

IF 10

Goncalves, J. P. L., C. Bollwein and K. Schwamborn. "Characterization of Hormone Receptor and Her2 Status in Breast Cancer Using Mass Spectrometry Imaging." Int J Mol Sci 24, no. 3 (Feb 2 2023).

Click here for more info

IF 6.21

Hamy, A. S., J. Abecassis and F. Reyal. "Evolution of Synchronous Female Bilateral Breast Cancers and Response to Treatment." Nat Med 29, no. 3 (Mar 2023): 646-55.

Click here for more info

IF 87.24

Holmes, F. A., B. Moy and N. E. T. Study Group Exte. "Overall Survival with Neratinib after Trastuzumab-Based Adjuvant Therapy in Her2-Positive Breast Cancer (Extenet): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial." Eur J Cancer 184 (May 2023): 48-59.

Click here for more info

IF 10

Huober, J., M. van Mackelenbergh and M. Untch. "Identifying Breast Cancer Patients at Risk of Relapse Despite Pathological Complete Response after Neoadjuvant Therapy." NPJ Breast Cancer 9, no. 1 (Apr 7 2023): 23.

Click here for more info

IF 7.52

Link, T., J. U. Blohmer and C. Denkert. "Rank Expression as an Independent Predictor for Response to Neoadjuvant Chemotherapy in Luminal-Like Breast Cancer: A Translational Insight from the Geparx Trial." Clin Cancer Res 29, no. 22 (Nov 14 2023): 4606-12.

Click here for more info

IF 13.8

Loibl, S., F. Andre and ESMO Guidelines Committee. "Early Breast Cancer: ESMO Clinical Practice Guideline for Diagnosis, Treatment and Follow-up(Dagger)." Ann Oncol (Dec 8 2023).

Click here for more info

IF 51.77

Loibl, S., H. A. Azim and F. Amant. "ESMO Expert Consensus Statements on the Management of Breast Cancer During Pregnancy (Prbc)." Ann Oncol 34, no. 10 (Oct 2023): 849-66.

Click here for more info

IF 51.77

Loibl, S., and J. Holtschmidt. "Sacituzumab Govitecan in Hr+ and Her2- Metastatic Breast Cancer: For All or for Some?", Lancet 402, no. 10411 (Oct 21 2023): 1394-95.

Click here for more info

IF 168.9

Mackelenbergh, M. T. van, S. Loibl and on behalf of the CTNeoBC project. "Pathologic Complete Response and Individual Patient Prognosis after Neoadjuvant Chemotherapy Plus Anti–Human Epidermal Growth Factor Receptor 2 Therapy of Human Epidermal Growth Factor Receptor 2–Positive Early Breast Cancer." Journal of Clinical Oncology 41, no. 16 (2023): 2998-3008.

Click here for more info

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Marmé, F., E. Krieghoff-Henning and T. J. Brinker. "Deep Learning to Predict Breast Cancer Sentinel Lymph Node Status on Insema Histological Images." Eur J Cancer 195 (Dec 2023): 113390.

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IF 10

Page, D. B., G. Broeckx and E. Specht Stovgaard. "Spatial Analyses of Immune Cell Infiltration in Cancer: Current Methods and Future Directions: A Report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer." J Pathol 260, no. 5 (Aug 2023): 514-32.

Click here for more info

IF 9.88

Riecke, K., V. Muller and I. Witzel. "Long-Term Survival of Breast Cancer Patients with Brain Metastases: Subanalysis of the Bmbc Registry." ESMO Open 8, no. 3 (Jun 2023): 101213.

Click here for more info

IF 6.88

Schmidt, M., U. Nitz and Noggo W. S. G. study groups Gbg/Ago-B. "Adjuvant Capecitabine Versus Nihil in Older Patients with Node-Positive/High-Risk Node-Negative Early Breast Cancer Receiving Ibandronate - the Ice Randomized Clinical Trial." Eur J Cancer 194 (Nov 2023): 113324.

Click here for more info

IF 10

Schmidt, M., C. Denkert and Sibylle Loibl. "Personalisierte Medizin – von der Translation zur Klinik." Die Gynäkologie 56 (2023): 341-46.

Click here for more info

IF 0.12

Squifflet, P., E. D. Saad and C. TNeoBC Project. "Re-Evaluation of Pathologic Complete Response as a Surrogate for Event-Free and Overall Survival in Human Epidermal Growth Factor Receptor 2-Positive, Early Breast Cancer Treated with Neoadjuvant Therapy Including Anti-Human Epidermal Growth Factor Receptor 2 Therapy." J Clin Oncol 41, no. 16 (Jun 1 2023): 2988-97.

Click here for more info

IF 50.72

Tarantino, P., G. Viale and G. Curigliano. "ESMO Expert Consensus Statements (Ecs) on the Definition, Diagnosis, and Management of Her2-Low Breast Cancer." Ann Oncol 34, no. 8 (Aug 2023): 645-59.

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IF 51.77

Tausch, C., K. Daster and W. P. Weber. "Trends in Use of Neoadjuvant Systemic Therapy in Patients with Clinically Node-Positive Breast Cancer in Europe: Prospective Taxis Study (Opbc-03, Sakk 23/16, Ibcsg 57-18, Abcsg-53, Gbg 101)." Breast Cancer Res Treat 201, no. 2 (Sep 2023): 215-25.

Click here for more info

IF 4.62

Thagaard, J., G. Broeckx and E. Specht Stovgaard. "Pitfalls in Machine Learning-Based Assessment of Tumor-Infiltrating Lymphocytes in Breast Cancer: A Report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer." J Pathol 260, no. 5 (Aug 2023): 498-513.

Click here for more info

IF 5.94

Thomssen, C., M. Vetter and Nnbc Europe Study Group. "Adjuvant Docetaxel in Node-Negative Breast Cancer Patients: A Randomized Trial of Ago-Breast Study Group, German Breast Group, and Eortc-Pathobiology Group." Cancers (Basel) 15, no. 5 (Mar 3 2023).

Click here for more info

IF 5.2

Turner, N. C., M. Oliveira and C. APItello-291 Study Group. "Capivasertib in Hormone Receptor-Positive Advanced Breast Cancer." N Engl J Med 388, no. 22 (Jun 1 2023): 2058-70.

Click here for more info

IF 176.08

Virassamy, B., F. Caramia and S. Loi. "Intratumoral Cd8(+) T Cells with a Tissue-Resident Memory Phenotype Mediate Local Immunity and Immune Checkpoint Responses in Breast Cancer." Cancer Cell 41, no. 3 (Mar 13 2023): 585-601 e8.

Click here for more info

IF 38.59

Weber, W. P., Z. Matrai and P. Markellou. "Association of Axillary Dissection with Systemic Therapy in Patients with Clinically Node-Positive Breast Cancer." JAMA Surg 158, no. 10 (Oct 1 2023): 1013-21.

Click here for more info

IF 16.9

Williams, T. M., A. Schneeweiss and S. Loibl. "Caveolin Gene Expression Predicts Clinical Outcomes for Early-Stage Her2-Negative Breast Cancer Treated with Paclitaxel-Based Chemotherapy in the Geparsepto Trial." Clin Cancer Res 29, no. 17 (Sep 1 2023): 3384-94.

Click here for more info

IF 13.8

Wimberger, P., J. U. Blohmer and S. Loibl. "The Effect of Denosumab on Disseminated Tumor Cells (Dtcs) of Breast Cancer Patients with Neoadjuvant Treatment: A Geparx Translational Substudy." Breast Cancer Res 25, no. 1 (Mar 28 2023): 32.

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IF 8.41

# Peer-reviewed reviews in 2023

Page, D. B., G. Broeckx and E. Specht Stovgaard. „Spatial Analyses of Immune Cell Infiltration in Cancer: Current Methods and Future Directions: A Report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer." J Pathol 260, no. 5 (Aug 2023): 514-32.

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IF 9.88

Thagaard, J., G. Broeckx and E. Specht Stovgaard. „Pitfalls in Machine Learning-Based Assessment of Tumor-Infiltrating Lymphocytes in Breast Cancer: A Report of the International Immuno-Oncology Biomarker Working Group on Breast Cancer." J Pathol 260, no. 5 (Aug 2023): 498-513.

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IF 5.94

## GBG-PUBLICATIONS GRADING SYSTEM

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

- 7 GBG points for publication 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.

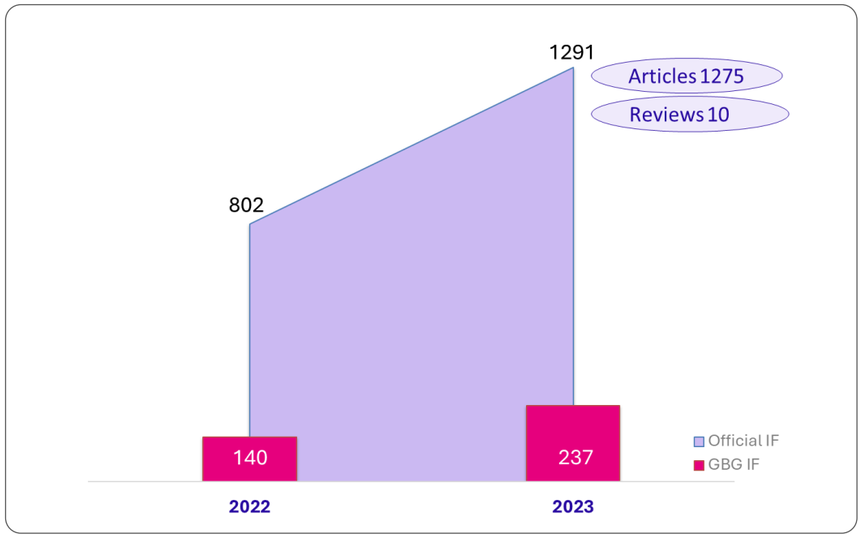


Figure 3: GBG and official Impact Factor (IF) in 2022 and 2023

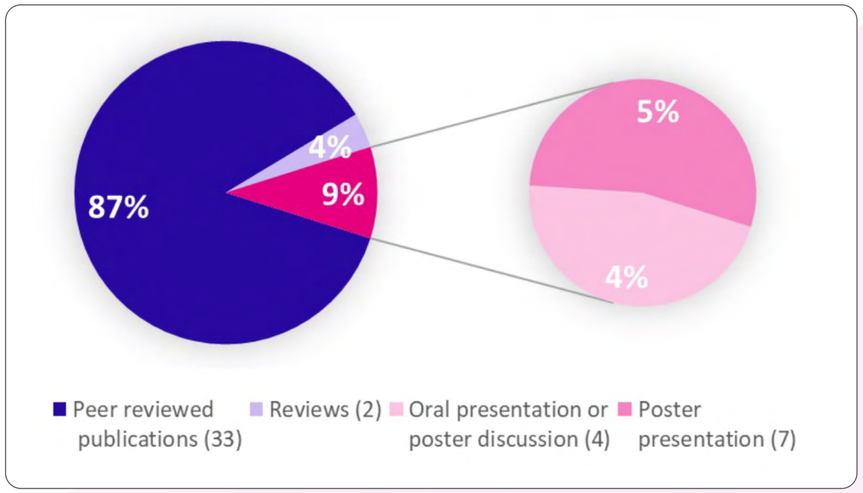


Figure 4: Overview of GBG's in-house grading for publications in 2023

# Congress Contributions

## ESMO-Breast Cancer,
May 11-13, 2023

In 2023 the ESMO Breast Cancer again gathered the internationally leading breast cancer clinicians and researchers in Berlin. We had the opportunity to present some of our current projects as poster presentations at this congress. For more information please visit our website:
Link website

Schmidt M, et al. Updated long-term overall survival of older adjuvant ibandronate-treated patients with intermediate- or high-risk early breast cancer compared with additional adjuvant capecitabine treatment – The ICE Randomized Clinical Trial; poster presentation.
Link presentation

Westhoff C, et al. Impact of TROP-2 and its cellular localization on prognosis of breast cancer in the GAIN cohort; poster presentation.
Link presentation

Marmé F, et al. Deep learning-based whole slide image analysis to predict sentinel node status in the INSEMA cohort; poster presentation.
Link presentation

Laakmann E et al., Clinical characteristics and prognostic factors in patients with breast cancer and leptomeningeal metastases: a subanalysis of the German Brain metastases in Breast Cancer registry (BMBC); poster presentation.
Link presentation

### Further congress contributions with GBG participation:

Oliveira M et al., Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR+/HER2- advanced breast cancer: subgroup analyses from the Phase 3 CAPItello-291 trial; oral presentation.

Click here for more info

## American Society of Clinical Oncology (ASCO),
June 2-6, 2023

This year's highlights in the field of early breast cancer were results from three adjuvant CDK4/6 inhibitor trials. Dennis J Slamon presented primary results from the NATALEE trial, with 3-year invasive disease free survival rates that met the trial's primary endpoint at the second interim efficacy analysis with a median follow up of 27.7 months. Subgroup analyses from the MonarchE trial consistent with the overall efficacy as well as quality of life data were reported by Erika P. Hamilton. Insights from a retrospective translational research project from our PENELOPE$^{B}$ / GBG 78 trial were presented by Nicholas Turner and assessed the association between ctDNA detection after completion of neoadjuvant chemotherapy and surgery and a very high risk for early relapse.

Inspiring translational research findings from our GeparNuevo / GBG 89 trial were shared by Hanna Hübner. The GeparNuevo trial recruited 174 triple negative breast cancer patients between June 2016 and October 2017, and evaluated the addition of the immune checkpoint inhibitor durvalumab to standard neoadjuvant chemotherapy (NACT). A moderate increase in pathological complete response (pCR) rate with an absolute difference of 9% translated into a significant improvement of the secondary endpoints iDFS, DDFS and OS Loibl Annals of Oncol 2020. At the ASCO conference Dr. Hübner presented translational research results of RNA expression level analyses of peripheral immune cells by multiplex RNA hybridization.

The aim of the subgroup analysis was to investigate changes of leukocyte RNA expression per signature levels during therapy and their association with treatment outcomes. This analysis included quantification of 290 immune-related genes (evaluated as multigene or single gene signatures) in blood leukocytes collected before therapy and at defined time points during therapy. Multigene signatures were further classified as immune cell type scores (specifying 16 immune cell types) and immune signaling scores (specifying 26 immune pathways or functions). Genes responsive to checkpoint inhibitor (n=31) or individual gene scores were considered. Key outcome parameters for which associations were tested included pCR rate (ypT0/ypN0) and distant disease-free survival (DDFS).

There was a significant shift in immune cell type scores during treatment. Scores representing macrophages and neutrophils increased, whereas scores for B cells, th1 cells and cytotoxic cell scores decreased regardless of treatment arm (durvalumab vs placebo). This suggests that alterations in peripheral immune cells during therapy were influenced by chemotherapy rather than immune checkpoint therapy. Notably, within the durvalumab arm, patients with elevated CCL3 expression before therapy demonstrated a lower pCR rate compared to those in the placebo arm, indicating a significant interaction. Moreover, patients in the durvalumab arm with high regulatory T cell scores prior to therapy experienced a reduced risk of DDFS-events in contrast to those with low scores. Additionally, the expression of DPP4, MYC, and ICOS was associated with DDFS, irrespective of the treatment arm.

The findings from the subgroup analysis highlight the crucial role of peripheral immune phenotype in treatment responses and survival outcomes, that need to be investigated for implications on clinical treatment decisions including checkpoint inhibitors.

GBG GERMAN BREAST GROUP — ASCO 2023 Annual Meeting, 2-6 June — Uniklinikum Erlangen

# RNA expression levels from peripheral immune cells, a minimal-invasive liquid biopsy source to predict response to therapy, survival and immune-related adverse events in patients with triple negative breast cancer enrolled in the GeparNuevo trial

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2023 ASCO ANNUAL MEETING — #ASCO23 — PRESENTED BY: Hanna Huebner, PhD

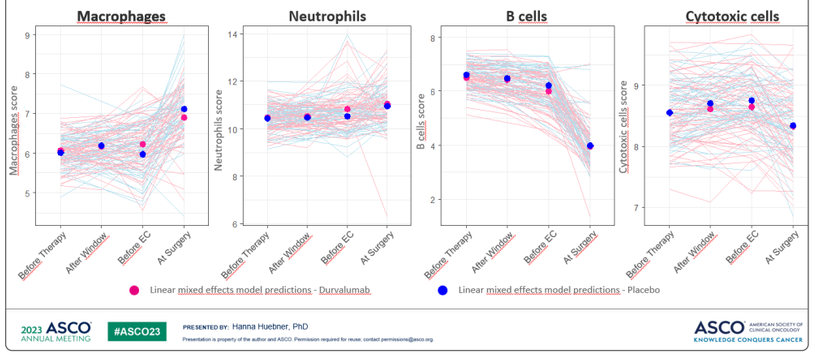


ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY — KNOWLEDGE CONQUERS CANCER

GBG GERMAN BREAST GROUP — ASCO 2023 Annual Meeting, 2-6 June — Uniklinikum Erlangen

## Results: Change of immune cells

Immune cell type scores representing macrophages and neutrophils significantly increased during treatment, while B cell and Cytotoxic cell scores decreased (p<0.0001, respectively) regardless of treatment arm.




2023 ASCO ANNUAL MEETING — #ASCO23 — PRESENTED BY: Hanna Huebner, PhD

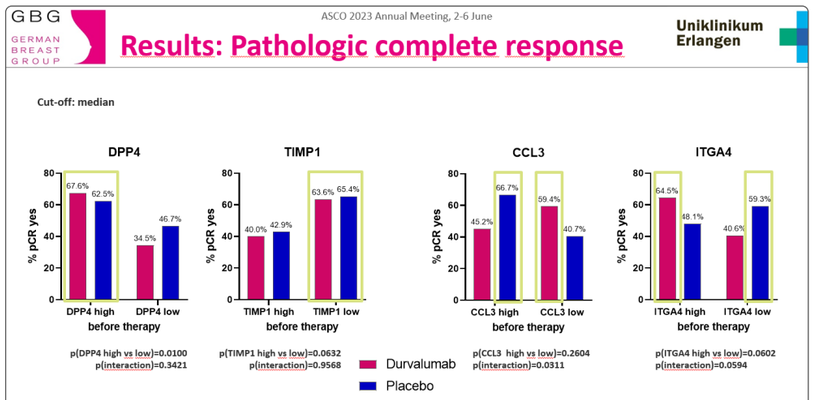


ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY — KNOWLEDGE CONQUERS CANCER

GBG GERMAN BREAST GROUP — ASCO 2023 Annual Meeting, 2-6 June — Uniklinikum Erlangen

## Results: Pathologic complete response

Cut-off: median




2023 ASCO ANNUAL MEETING — #ASCO23 — PRESENTED BY: Hanna Huebner, PhD



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## Conclusions

- **Changes of peripheral immune cells** under therapy seemed to be dependent on **chemotherapy** but not immune checkpoint therapy
- It appears that patients in the **durvalumab** arm who had **high levels of CCL3** expression before therapy had a **lower pCR rate** compared to patients in the placebo arm (significant interaction)
- Patients of the **durvalumab** arm who had **high levels of regulatory T cell** scores before therapy had **lower risk of distant disease-free events** compared to those with low levels
- **DPP4, MYC and ICOS** expression was associated with **distant disease-free survival** regardless of treatment arm
- While these findings offer promising insights, **further research** is necessary to **validate** and **expand** upon these initial results

**RNA expression levels from peripheral immune cells could enable differentiation between patients who might benefit from neoadjuvant immune checkpoint therapy compared to standard therapies**

2023 ASCO ANNUAL MEETING — #ASCO23 — PRESENTED BY: Hanna Huebner, PhD



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Link full presentation

## Further GBG congress contributions and contributions with GBG participation are listed below:

Turner N, et al. Detection of circulating tumor DNA following neoadjuvant chemo-therapy and surgery anticipates early relapse in ER positive and HER2 negative breast cancer, analysis from the PENELOPE[B] trial; oral presentation.

Link full presentation

Hurvitz S, et al. A phase 3 study of gedatolisib plus fulvestrant with and without palbociclib in patients with HR+/HER2- advanced breast cancer previously treated with a CDH4/6 inhibitor plus a non-steroidal aromatase inhibitor (VIKTORIA-1); poster presentation.

Link full presentation

## Annual Congress of the German Society for Senology (DGS),
July 6-8, 2023

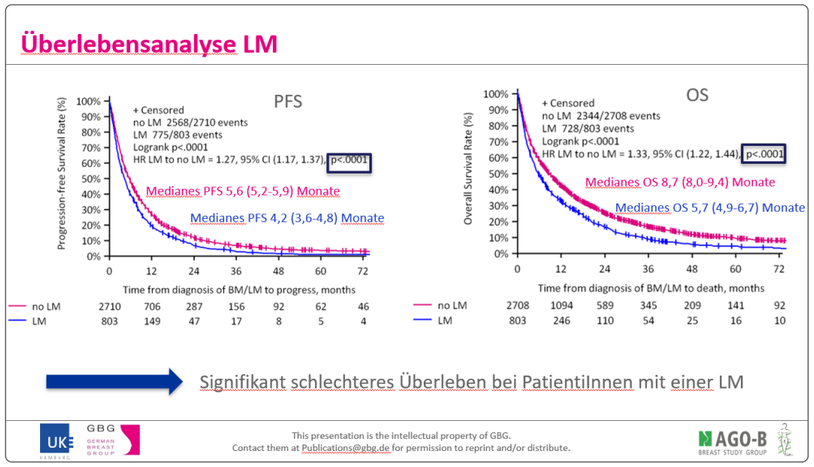
The 2023 meeting took place in Munich and Elena Laakmann presented a subanalysis of the German registry for Brain Metastases in Breast Cancer (BMBC) with focus on prognostic factors in breast cancer (BC) patients with leptomeningeal metastases (LM). We are very proud to share that Dr. Laakmann received the Klaus-Dieter Schulz Supply Research Prize for this presentation.

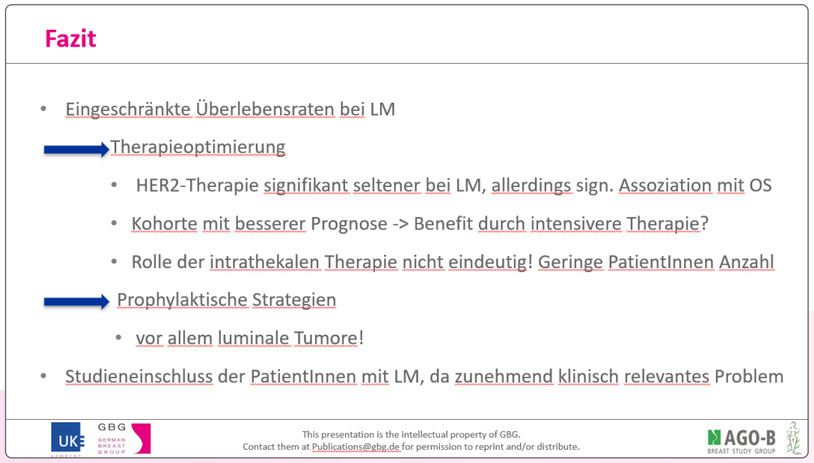
The biology of LM is poorly understood and there has recently been no progress in clinical management of BC with LM. Currently, there are only a few evidence-based treatment recommendations and the prognosis for patients with LM remains poor. The BMBC registry collects clinical data and biomaterial from patients with breast cancer and central nervous system (CNS) metastases. Currently already around 4000 patients are registered in BMBC, and we are glad to announce that international cooperating partners will join the project.

The primary objective of the current analysis was to characterize a large cohort of BC patients with LM from the BMBC registry and evaluate specific prognostic factors in this patient cohort. Patient data collected until January 2023 were included in the analysis. In total, data from 3857 patients with CNS metastasis in BC were available for analysis, with 859 of them having confirmed LM.

The analysis revealed that some patients developed LM despite having BC with favorable characteristics. For instance, more frequently patients with luminal-A/B-like tumors and less frequently patients with G3 differentiated tumors were among those who developed LM. There was no clear link between LM development and the extent of known extracranial metastases, challenging the hypothesis of a connection with aggressive tumor biology. Patients with LM had significantly shorter progression-free survival (PFS; 4.2 vs 5.2 months; HR 1.27 CI 1.17-1.37; p<0.0001) and overall survival (OS; 5.7 vs. 8.7 months; HR 1.33 CI 1.22-1.44; p<0.0001) compared to those without LM. Among the patients with LM, factors such as higher age, poor general condition, luminal-A/B-like or triple-negative tumor biology, and a higher number of cerebral metastases were associated with a higher risk of death. Longer survival was linked to cerebral radiotherapy, endocrine therapy for hormone receptor-positive BC, and HER2-targeted therapy for HER2-positive BC. An impact of intrathecal therapy in LM patients on survival could not be investigated, as only 7.2% of the patients with LM received this therapeutic option.


In summary, this analysis reveals that patients with LM have poor outcomes. It is essential to develop more effective therapeutic approaches to enhance the survival rates of patients with LM, and the data from BMBC can serve as a foundation for planning future research in this area.

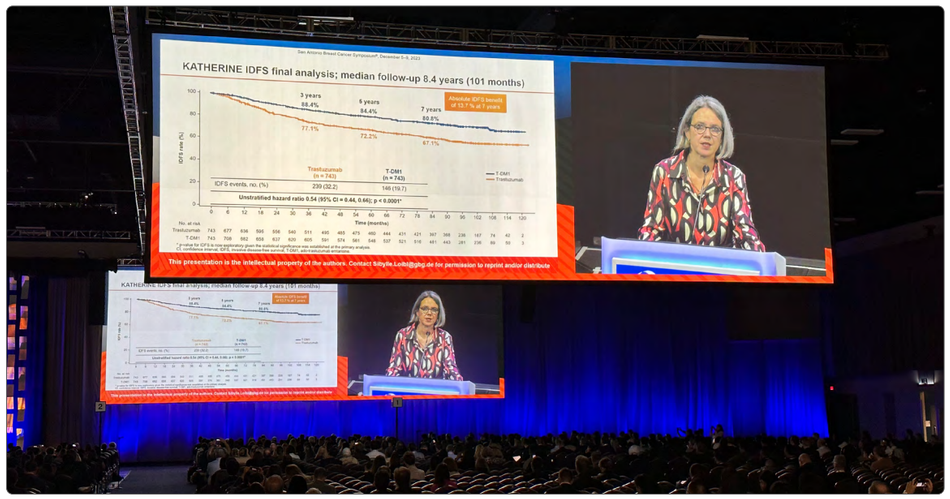

**All data of this presentation is available in the poster presentation of Elena Laakmann presented at the ESMO Breast Cancer Conference**

**Click here for more info**

## San Antonio Breast Cancer Symposium (SABCS), December 5-9, 2023

Our highlights of the 2023 San Antonio Breast Cancer Symposium (SABCS) were the positive results reported by the Inavo120 trial and the final invasive disease-free survival (IDFS) and updated overall survival (OS) analysis from the KATHERINE / NSABP B-50-I / GBG 77 trial. Komal Jhaveri presented the primary analysis of the Inavo120 trial on inavolisib vs placebo in combination with palbociclib and fulvestrant in patients with *PIK3CA*-mutant, HRpos/HER2neg metastatic breast cancer. A doubling of progression free survival (PFS) from 7.3 months to 15.0 months with the addition of inavolisib was received to be practice changing and provides rationale for our ongoing GeparPiPPa / GBG105 trial.

Apart from various GBG contributions to SABCS 2023, we are especially delighted that the final analysis of IDFS and updated OS analysis of the KATHERINE trial was completed in time to be presented as late breaking contribution by Sibylle Loibl on behalf of the GBG and NSABP.



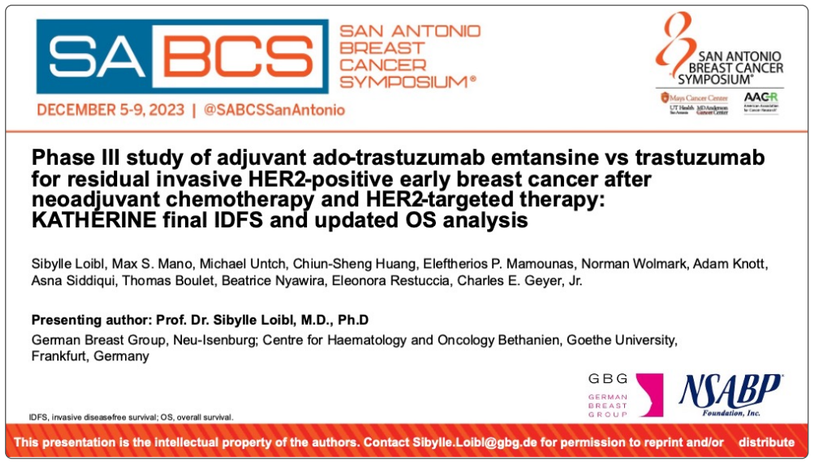

The results from the primary iDFS analysis of the KATHERINE trial were practice changing in the treatment of HER2-positive early breast cancer (von Minckwitz N Engl J Med 2019). This postneodajuvant phase 3 trial randomizing 1486 patients with residual invasive disease after neoadjuvant chemotherapy and HER2-targeted therapy 1:1 to either ado-trastuzumab emtansine (T-DM1) or trastuzumab demonstrated remarkable benefits for T-DM1 over trastuzumab in IDFS and OS, respectively. The 7-year IDFS rate favored T-DM1, standing at 80.8% compared to 67.1% with trastuzumab, with an absolute IDFS benefit of 13.7%, which is consistent with the 3-year analysis, reported Prof. Loibl.

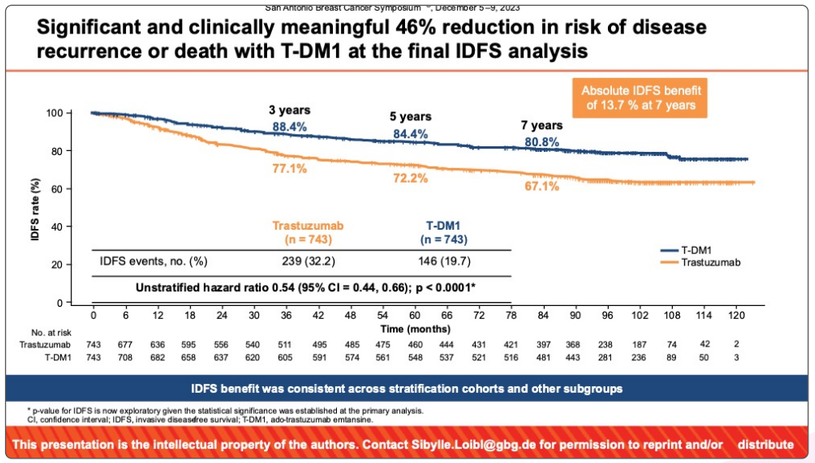
> **Subgroup analyses of IDFS underline the treatment effect of T-DM1 across all subgroups.**

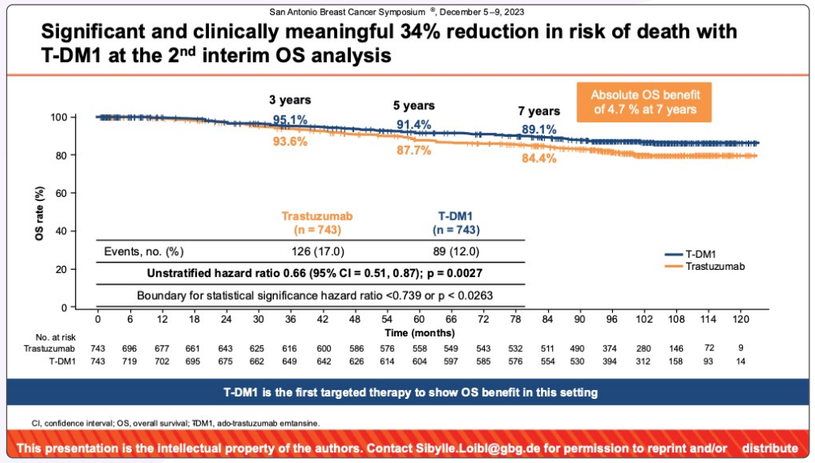
Furthermore, at a median follow-up of 8.4 years, T-DM1 showcased a 5-year OS rate of 91.4% compared to trastuzumab's 87.7%, translating to a 4.7% absolute OS benefit at 7 years. Prof. Loibl highlighted that T-DM1's consistent benefits in OS extended across subgroups. Notably, T-DM1's superiority in OS was not evident in the initial 3-year analysis conducted in 2018, making this long-term follow-up a landmark advancement.

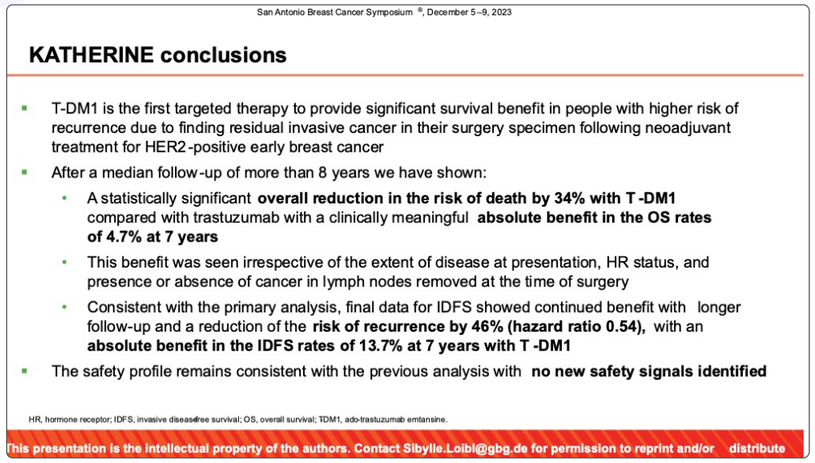
Addressing concerns about safety, the extended follow-up analyses found no new safety signals in adverse event (AE) data. Incidence of cardiac disorders, a rare AE, was consistent at 0.7% in both arms.

The findings from the KATHERINE trial underscore T-DM1 as a game-changer in the postneoadjuvant setting for HER2-positive early breast cancer, offering a substantial and clinically meaningful improvement in both IDFS and OS. Follow-up is ongoing for the final OS analysis.






Link full presentation

## Further GBG congress contributions are listed below and can be found on our website Link website

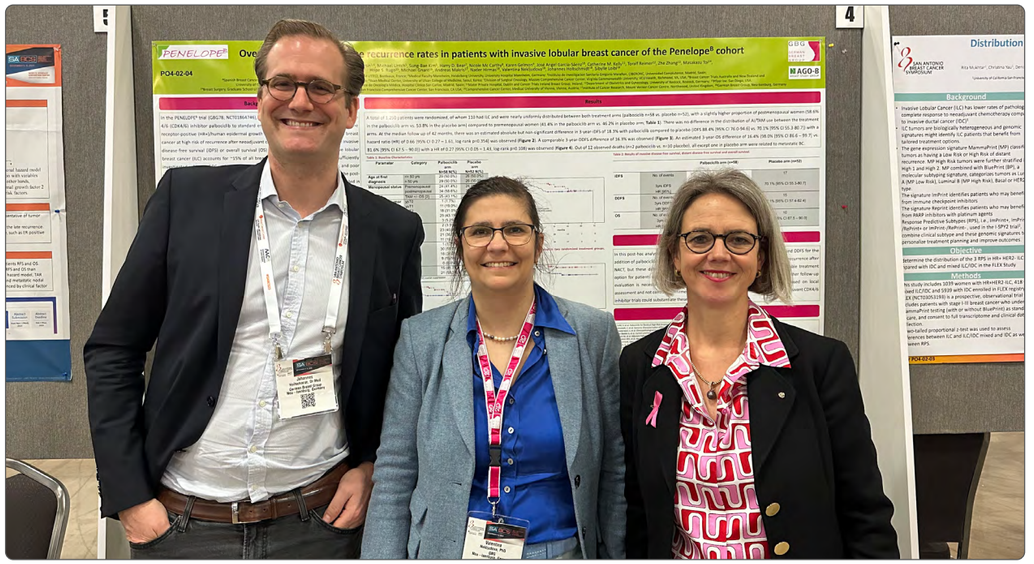
### Poster Spotlight Presentation:

Hübner H, et al. Exploring Circulating Leukocyte RNA Expression: Implications for Treatment Outcomes and Immune-Related Adverse Events in Patients with Triple Negative Breast Cancer Enrolled in the GeparNuevo Trial; poster spotlight presentation; PS14-07.
Link presentation

### Poster presentation:

Schmutzler R, et al. Germline mutation status of BRCA1/2 and other breast cancer predisposition genes as predictive and prognostic biomarker: Results of the GeparX study (GeparX-BRCA); poster presentation; PO1-02-13.
Link presentation

Bonnefoi H, et al. Overall survival and disease recurrence rates in patients with invasive lobular breast cancer of the Penelope[B] cohort; poster presentation; PO4-02-04.
Link presentation




Presentation of the Penelope[B] poster at SABCS: Dr. J. Holtschmidt, Dr. V. Nekljudova and Prof. Dr. S. Loibl (from left to right).

Knappskog S, et al. *CDH1* mutations predict resistance to neoadjuvant taxane therapy; poster presentation; PO5-25-12.
Link presentation

## Further congress contributions and contributions with GBG participation are listed below:

### Oral Presentation:

Protocol-defined biomarker analysis in the PALLAS (AFT-05) adjuvant trial: Genomic subtype derived from RNA sequencing of HR+/HER2- early breast cancer; oral presentation.

Are nodal ITCs after neoadjuvant chemotherapy an indication for axillary dissection? The OPBC05/EUBREAST-14R/ICARO study; oral presentation.

**Poster Spotlight Presentations:**

- Patient-reported outcomes from the Phase 3 CAPItello-291 trial investigating capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR-positive/HER2-negative advanced breast cancer; poster spotlight presentation.
- Impact of Baseline Oestradiol and Testosterone on the Preventive Effect of Anastrozole; poster spotlight presentation.
- Capivasertib and fulvestrant for patients with aromatase inhibitor-resistant HR positive/ HER2-negative advanced breast cancer: exploratory analysis of PFS by AKT pathway gene from the Phase 3 CAPItello-291 trial; poster spotlight presentation.
- Clinical and Genomic Features of ER-Positive/HER2-negative Metastatic Breast Cancer in AURORA Molecular Screening Initiative (BIG 14-01): Mechanisms of Endocrine Therapy Resistance and Implications for Adjuvant Approaches; poster spotlight presentation.

**Poster Presentations:**

- COGNITION / -GUIDE – Implementation of Precision Oncology in Early High-Risk Breast Cancer; poster presentation; PO1-19-05.
- Clinical characterization, prognostic and predictive values of HER2-low in early breast cancer in the PALLAS trial; poster presentation; PO1-01-13.
- ELEVATE: A phase 1b/2, open-label, umbrella study evaluating elacestrant in various combinations in patients (pts) with estrogen receptor-positive (ER+), HER2-negative (HER2-) locally advanced or metastatic breast cancer (mBC); poster presentation; PO2-05-04.
- A phase 3 randomized open-label study of extended adjuvant therapy with camizestrant vs standard endocrine therapy in patients with ER+/HER2– early breast cancer and an intermediate or high risk of recurrence (CAMBRIA 1); poster presentation; PO2-18-09.
- A Phase 3 study of gedatolisib plus fulvestrant with and without palbociclib in patients with HR+/ HER2- advanced breast cancer previously treated with a CDK4/6 inhibitor plus a non-steroidal aromatase inhibitor (VIKTORIA-1); poster presentation; PO2-20-02.
- AXSANA – EUBREAST-3: An international prospective multicenter cohort study to evaluate different surgical methods of axillary staging in clinically node-positive breast cancer patients treated with neoadjuvant chemotherapy; poster presentation; PO4-19-04.
- A Phase 3, randomized, open-label study of upfront camizestrant vs standard endocrine therapy as adjuvant treatment for ER-positive/HER2-negative early breast cancer with intermediate-high or high risk of recurrence (CAMBRIA-2); poster presentsation; PO4-27-07.
- Omission of SLNB in triple-negative and HER2-positive breast cancer patients with radiologic and pathologic complete response in the breast after NAST: a single-arm, prospective surgical trial (EUBREAST-01 trial, GBG 104); poster presentation; PO5-18-10.

**2023** was a special year for the **GBG,** as we celebrated our **20th Annual Scientific Meeting.**

GBG 114 ELEMENT
EU-CT-Number: 2023-504925-38

# Interview with Dr. Kristina Lübbe

***A phase II study evaluating the addition of elacestrant, an oral selective estrogen receptor degrader (SERD), to niraparib, a PARP-inhibitor, compared to niraparib alone in patients with hormone receptor (HR)-positive, HER2-negative locally advanced or metastatic breast cancer with g/tBRCA1/2 and/or g/tPALB2 mutations***

***Q1: ELEMENT will use niraparib in both study arms as a poly(ADP-ribose) polymerase inhibitor (PARPi). What is special for niraparib? What is the potential impact of PARPi therapy on quality of life in comparison to palliative chemotherapy?***

Niraparib is one of the PARP-Inhibitors employed for the treatment of ovarian cancer regardless of homologous recombination deficiency (HRD) or *BRCA* status. Studies involving niraparib as maintenance therapy have demonstrated a significant survival benefit for patients with ovarian cancer. The convenience of oral administration eliminates the need for clinic visits for infusion therapy. Given its well tolerated toxicity, we can infer that the impact on quality of life of patients undergoing palliative treatment is minimal.

***Q2: ELEMENT study will also use elacestrant as an oral selective estrogen receptor degrader (SERD) in one of the study arms in combination with niraparib. What is the difference between the SERD elacestrant and conventional endocrine therapy options? What are the results of previous trials comparing elacestrant to conventional endocrine therapy options?***

Elacestrant is an oral selective estrogen receptor alpha (ERα) antagonist with receptor degrading activity. It acts in a dose-dependent manner and inhibits estradiol-dependent ER-directed gene transcription and tumor growth. Its oral availability and convenient dosing schedule distinguish elacestrant from other endocrine therapies.
The phase III EMERALD study recruited patients with advanced or metastatic HR+, HER2- breast cancer who have progressed after 1 or 2 lines of endocrine therapy, one of which was given in combination with a CDK4/6 inhibitor. Patients were randomized to receive either an endocrine therapy of investigator's choice (fulvestrant or aromatase inhibitors) or 400 mg elacestrant orally daily.
The primary endpoint of the study was progression-free survival (PFS), which was significantly prolonged in the elacestrant arm in comparison to standard endocrine therapy (12-month PFS rates of 22.32% vs. 9.42%, respectively). Patients with an *ESR1* mutation achieved the greatest benefit (12-month PFS rates of 26.76% vs. 8.19%, respectively), even in comparison with fulvestrant, the approved SERD that requires intramuscular administration. These results led to the approval of elacestrant in this setting.

Oral elacestrant is more convenient for patients than intramuscular fulvestrant, thus eliminating the need for specific time intervals for follow up with one's doctor in everyday practice. In addition, considering its superior efficacy, especially for patients whose tumors harbor *ESR1* mutations, elacestrant holds promise for better outcomes, even for those developing this mutation during trial participation.

***Q3: What is the rationale for setting up ELEMENT?***

Despite the good data from the EMERALD trial, there was initially a significant gradual decrease in PFS in both treatment arms, suggesting a potential development of general endocrine resistance independent of an *ESR1* mutation. This indicates that relying solely on endocrine monotherapy may not be sufficient in such cases.
PARPi therapy is well established in advanced breast cancer treatment, but its use is limited to patients with germline *BRCA1/2* mutation. In particular, patients with a *BRCA1/2* or *PALB2* mutation (germline or somatic) may also benefit from PARPis. That is why the ELEMENT trial was designed to include these patients as well.
In the ELEMENT trial, patients will be randomized to either a single target therapy with niraparib or a combination target therapy with niraparib and elacestrant independent of *ESR1* mutation.

***Q4: Which patients will be enrolled in ELEMENT and how many? In clinical practice, how can we identify potentially suitable patients for this study?***

In the ELEMENT trial 176 patients with HR+/HER2- locally advanced or metastatic breast cancer who have progressed to advanced disease after at least one line of treatment, may be included. Eligibility criteria include the presence of tumors harboring a somatic or germline mutation in *BRCA1/2* or *PALB2* genes.
Genomic counselling of patients with familial history and testing for genetic alterations predisposing for breast or ovarian cancer is of paramount importance to preclude preventable further cancer diagnoses in those patients and their relatives. Somatic testing is also carried out for other tumor entities (e.g., tumor tissue in ovarian carcinoma) and is well established.
Since the approval of PARPis for the treatment of metastatic HER2- breast cancer, germline testing for *BRCA* mutations to evaluate a potential PARPi indication is reimbursed by insurance. However, the aforementioned opportunities are not implemented to full extent, which unfortunately deprives patients with unidentified *BRCA* mutations from less toxic therapies with PARPis.
In the usual course of treating HR+/HER2- metastatic breast cancer, the initial palliative approach often involves endocrine-based therapy, typically incorporating CDK4/6 Inhibitors. To enhance patient eligibility for the ELEMENT trial, I recommend initiating mutation testing promptly upon the first-time diagnosis of metastasis. This proactive testing approach opens the possibility for patients to be considered in the second line of treatment, increasing the chances of inclusion in the ELEMENT trial and providing access to potentially beneficial therapies.

**Contact Projectmanagement:**
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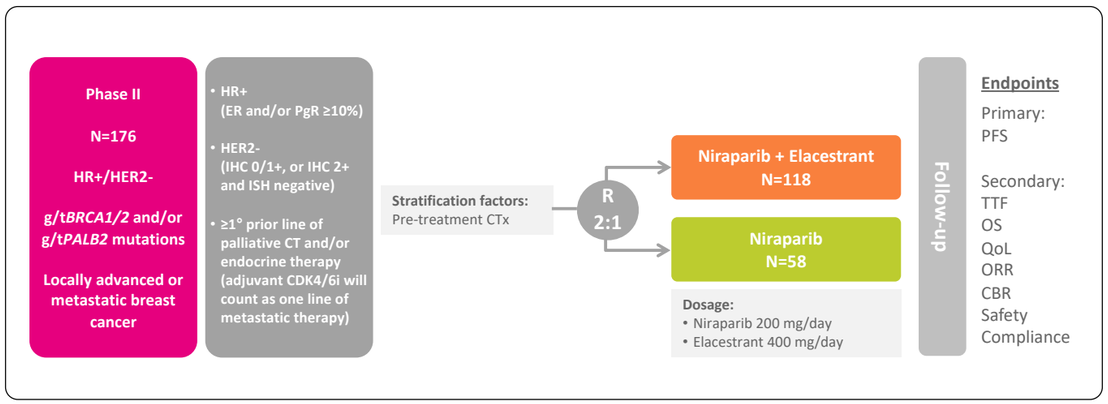
**Cooperationpartner/Sponsor:**
GBG Forschungs GmbH




Study Design of the Element trial

GBG 118 LOBSTER
EU-CT-Number: 2023-509292-17

# Interview with Prof. Dr. Jens-Uwe Blohmer

***A phase II study evaluating neoadjuvant administration of capivasertib and endocrine therapy with fulvestrant in patients with primary high-risk lobular breast cancer.***

***Q1: Could you describe the hypothesis that will be tested in this phase II trial? What is the biological background? Why do we focus on lobular cancer in this trial?***

Invasive lobular breast cancer (ILC) is the second most common breast cancer subtype. However, ILC is underrepresented in clinical trials as well as in diagnostic and therapeutic concepts. There is limited awareness of the disease and clear treatment strategies for patients are lacking. The treatment of ILC is challenging because of its inferior response to chemotherapy characterized by lower rates of pathologic complete response compared to breast cancer of no special type (NST) and invasive ductal breast cancer (Loibl S et al. Breast Cancer Res Treat 2014)). Additionally, ILC exhibits distinct patterns of metastases including intra- and retroperitoneal spread, leading to worse overall survival compared to NST.

In ILC, *CDH1* mutations are highly prevalent, occurring in up to 65% of cases. Additionally over 50% of ILC tumors exhibit mutations in the phosphatidylinositol 3-kinase pathway involving genes like *PIK3CA*, *PTEN*, and *AKT1* (Basudan A et al. Mol Cancer Res 2019; Denkert C et al. Ann Oncol 2021; Li Z et al. Cancer Res 2022). These mutations have shown response to AKT inhibitors such as capivasertib.

The combination of fulvestrant and of capivasertib in endocrine therapy has shown promising results for patients with advanced HR+/HER2- breast cancer. Notably, findings from the FAKTION study, indicate that this outperformed fulvestrant alone in terms of progression-free survival (PFS: 10.3 vs 4.8 months; HR=0.58; p=0.0044). This was observed in patients with aromatase inhibitor (AI)-resistant HR+/HER2- locally advanced or metastatic breast cancer. This observed effect of improved PFS in this study was independent of PI3K/AKT/mTOR pathway activation. These findings are consistent with the outcomes of CAPItello study, where the combination of capivasertib combined with fulvestrant resulted in an improved PFS compared to fulvestrant plus placebo (7.2 vs 3.6 months; HR=0.60; p<0.001). The positive impact extended to patients with HR+/HER2- advanced breast cancer, including those with AKT pathway-altered tumors as demonstrated in the latter study.

Furthermore, Ki-67 is strongly linked to cancer proliferation, making its reduction a valuable predictive marker for treatment benefit and improved long-term outcomes. Taking these data into account, the hypothesis of the LOBSTER study is that preoperative treatment with fulvestrant combined with capivasertib will achieve a better response (Ki-67 drop) compared with fulvestrant alone in patients with operable ILC.

***Q2: What is the primary objective of this trial?***

The primary objective of this trial is to demonstrate differences in the rate of complete cell cycle arrest (CCCA), assessed through Ki-67 (≤2.7%), following eight weeks of treatment with capivasertib in combination with fulvestrant, in comparison to fulvestrant alone.

***Q3: Which patients qualify for LOBSTER?***

The LOBSTER study is specifically designed for postmenopausal women who have confirmed HR+ status (ER/PR ≥ 10%) and HER2- (IHC 0-1 or FISH negative) untreated ILC and a high risk of recurrence. To qualify for this trial, these patients should exhibit a high risk of recurrence, meeting the criteria of either cT1c with clinical nodal involvement (cN+) or cT2 (irrespective of nodal involvement). Additionally, those with Ki-67 exceeding 10% and no clinical evidence of distant relapse are eligible. A histological confirmation of nodal involvement is not mandatory for inclusion in the LOBSTER trial.

***Q4: The planned study design looks very interesting. Can you tell us about the planned main study procedures? And how long will patients be treated?***

The planned study design encompasses several key steps. The first step is the histological confirmation of ILC through a central pathology laboratory. Concurrently a clinical evaluation of tumor size and axillary nodal involvement is made. Imaging tests for staging are performed as per country guidelines. Following successful screening and randomization, patients will undergo a pre-operative treatment with the study medication for a duration of ten weeks. During this period, biopsies of breast cancer tissue will be taken before, during and at the end of drug therapy (surgery or core biopsy) to assess study objectives such as the Ki-67 drop two and ten weeks after treatment as well as other relevant parameters. Subsequent treatment will adhere to to national and international guidelines. This design will ensures a thorough assessment of treatment efficacy and will hopefully guides clinical decisions based on the study outcomes.

**Contact Projectmanagement:**
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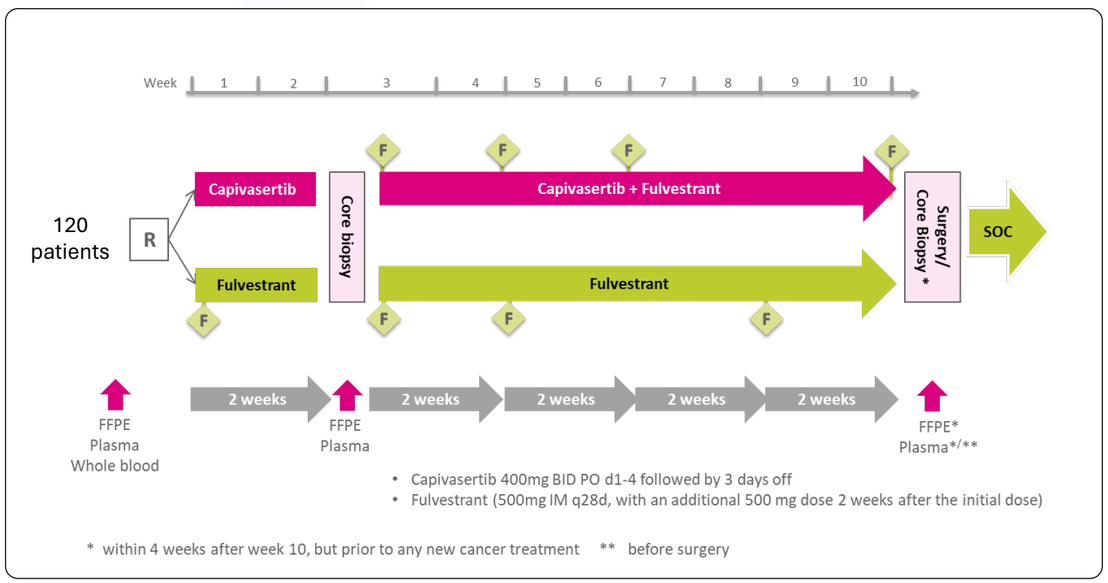
lobster@gbg.de

**Cooperationpartner/Sponsor:**
GBG Forschungs GmbH and NOGGO




Study Design of the LOBSTER trial

GBG 105 GeparPiPPa
EU-CT-Number: 2022-501152-28

# Interview with PD Dr. Mattea Reinisch

***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***

***Q1: Can you tell us about the study rationale as well as the different treatments used in this study?***

Nowadays, a challenging aspect in the treatment of breast cancer is to gain a better understanding of the tumor biology and tumor-specific treatment approaches. As a result, issues related to escalating and de-escalating therapies are often raised, promoting ongoing efforts to address these complexities. In case of HER2+ early breast cancer, the standard approach involves employing well-tolerated anti-HER2 directed drugs, usually in combination with chemotherapy. However, evidence from earlier studies suggests that chemotherapy may not always be necessary.

Neoadjuvant treatment approach for patients with HER2+ breast cancer seeks to attain a pathological complete response (pCR), as it correlates with lowest rates of disease recurrence. However, a noteworthy factor adversely influencing pCR in these patients is the occurrence of a *PIK3CA* mutation. This mutation detected in 20-30% of HER2+ breast cancers (Loibl et al. Ann Oncol 2016) is associated with estrogen receptor-independent growth, as highlighted in the studies Miller et al. (J Clin Invest 2010) and Crowder et al. (Cancer Res 2009).

The GeparPiPPa study investigates whether inavolisib, a PI3K inhibitor, added to anti-HER2 therapy leads to a higher pCR rate compared to anti-HER2 therapy alone. Analyses of *PIK3CA* mutational status as well as HR and HER2 status are analyzed by a central pathology laboratory, providing high-quality standard to the study. One distinct aspect of the GeparPiPPa study is the exploration of an exclusive option for omitting chemotherapy in the treatment of HER2+ breast cancer, which is part of the standard treatment recommendation.

***Q2: What are the main objectives of this study? How many patients and sites are expected to participate in this study?***

The primary objective of the GeparPiPPa study is to investigate the pCR rate associated with two distinct treatment options: The standard treatment employing pertuzumab and trastuzumab fixed-dose combination administered as a single subcutaneous injection (PH-FDC SC) into the thigh versus PH-FDC SC in combination with orally administered inavolisib, in patients with HR+/HER2- breast cancer who also present with a *PIK3CA* mutation. Additionally, all patients enrolled in the study receive endocrine therapy. A total of 35 German sites are participating in the trial.

***Q3: A protocol amendment has been in development. Can you tell us about the main changes in the study design and procedures, including the concept of a screening failure registry?***

As the GeparPiPPa study recruits patients with HR+ and HER2+ breast cancer, endocrine therapy is an important component of the treatment. As mentioned earlier, the screening involves assessment of centrally confirmed tumor-specific markers. Despite the screening timeframe not leading to meaningful tumor growth, the eagerness of patients to start treatment promptly after the diagnosis of breast cancer is evident. The current amendment allows the treating physicians to start endocrine therapy instantaneously with the diagnosis and prior to starting treatment within the GeparPiPPa trial. This amendment anticipates a positive impact on patient satisfaction and compliance levels during the waiting period for the screening results.

Notably, patients lacking a *PIK3CA* mutation are classified as screening failures and, consequently, are ineligible for inclusion in the GeparPiPPa trial. However, recognizing the significance of gathering insights into alternative treatments administered to these patients and understanding the pathological response (pCR rate), the current amendment introduces the concept of an “observational cohort.”

***Q4: What is a major challenge for recruitment so far in this study? How do you expect things to improve with the amendment?***

A major challenge in the recruitment for this study is identifying eligible patients with HR+/HER2+ and *PIK3CA*-mutated tumors. Given that only approximately 20% of all HR+/HER2+ tumors exhibit *PIK3CA* mutation, it translates a scenario where only 20% of the initially screened patients eventually qualify for inclusion in the GeparPiPPa study. There is shared reluctance among patients and treating physicians due to concerns about potential tumor growth during this waiting period, as the screening process takes place. This concern, as stated earlier, has been addressed by the recent protocol amendment allows for starting endocrine therapy immediately after diagnosis.

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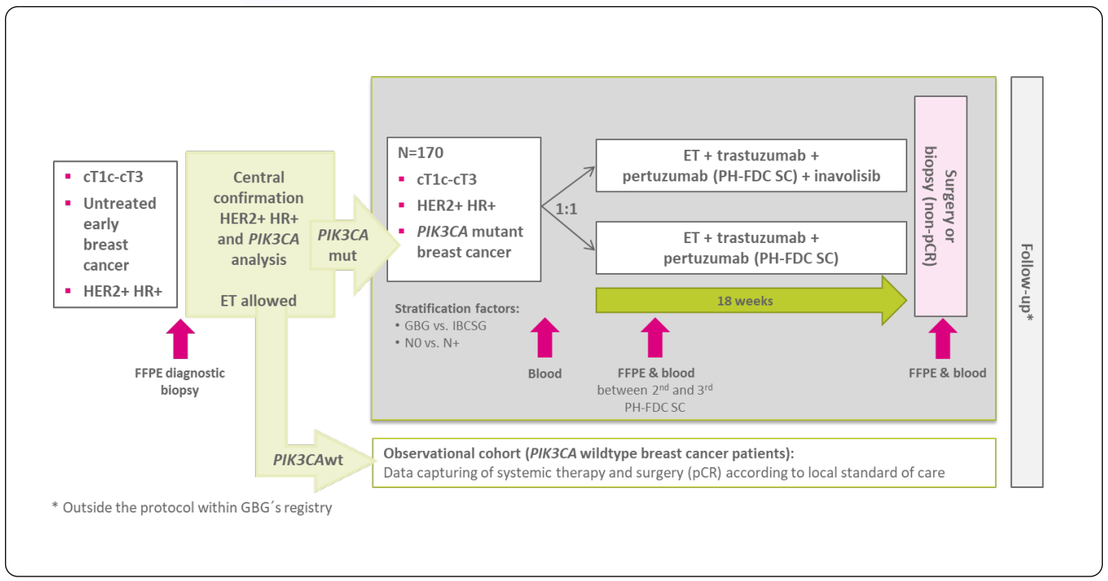
**Cooperationpartner/Sponsor:**
GBG Forschungs GmbH



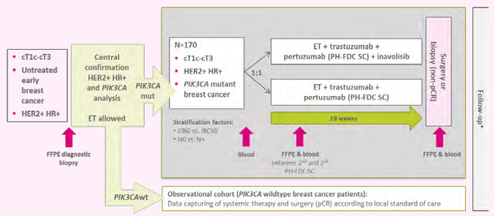

Study Design of the GeparPiPPa trial

# GeparPiPPa

## GBG 105 / EU-CT 2022-501152-28

### Trial Design

neoadjuvant, multicenter, randomized, open-label, phase II study




### Recruitment

planned: 170 pts
recruited: 8 pts

### Study Sites

planned : 50
active: 15 DEU

### Study Population

- Patients with early HER2+/HR+ and *PIK3CA*-mutant BC
- cT1c-cT3, any cN, M0

### Endpoints

Primary Endpoint:
- pCR (ypT0/is ypN0)

Secondary Endpoints (Selection):
- other pCR definitions
- iDFS and OS
- breast conserving rate
- safety, tolerability and compliance

### Cooperations

AGO-B BREAST STUDY GROUP

IBCSG International Breast Cancer Study Group

### Sponsor

GBG GERMAN BREAST GROUP

### Contact

Coordinator:
PD Dr. Mattea Reinisch

Clinical Project Manager:
Konstantin Reißmüller
geparpippa@gbg.de

## BACKGROUND

*PIK3CA* mutations can be found in about 20-30% of HER2-positive breast cancers with a higher rate in hormone receptor (HR)-positive than in HR-negative/HER2-positive tumors. It was shown that the pathological complete response (pCR) rate with standard treatment is lower in patients in *PIK3CA* mutant HER2-positive breast cancer, especially in HR-positive breast cancer.[1]

The rationale for the GeparPippa study is based on experimental and clinical evidence concerning the alteration of the PI3K pathway. The PI3K pathway is frequently altered in HR-positive breast cancer and seems to be involved in resistance to endocrine therapies. Approximately 40% of HR+ breast cancers harbor a *PIK3CA* mutation leading to estrogen receptor independent growth (Crowder et al. 2009, Miller et al. 2010). Therefore, combination therapies targeting both HR and PI3K pathways may be warranted.

## STUDY DESIGN AND OBJECTIVES

Patients with *PIK3CA* mutant breast cancer are randomized in a 1:1 ratio to receive neoadjuvant endocrine therapy in combination with dual anti-HER2 blockade consisting of ready-to-use fixed-dose combination of pertuzumab and trastuzumab as subcutaneous (PH-FDC SC) formulation q3w for 6 cycles (18 weeks) with inavolisib or without inavolisib. Endocrine therapy consists of either tamoxifen 20mg or an aromatase inhibitor +/- GnRH analogue for premenopausal women and men.

All patients will undergo surgery or biopsy after completing study therapy to assess pCR rate. In case of ycT0 and no tumor residuals in the biopsy, it is recommended to undergo surgery; in case of tumor residuals in the biopsy, further ((neo-)adjuvant) treatments may be given.

Primary objective of GeparPiPPa is to compare pathological complete response (pCR=ypT0/is ypN0) rates between both study arms.

GeparPiPPa will also address translational research questions to evaluate potential new biomarkers for HR-positive/HER2-positive breast cancer and its association with responses and resistance to therapies.

Central pathology testing for screening including PIK3CA analysis was optimized and report will be available about 5 days after receipt of biospy material.

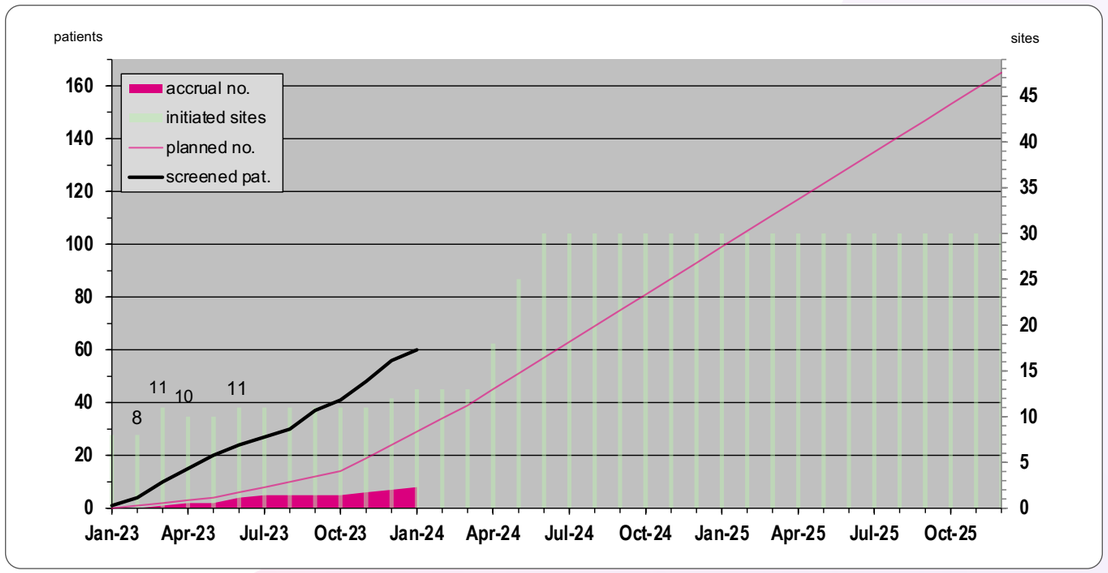
Furthermore with amendement 1 an endocrine therapy may be given during screening phase. Eligible patients who do not harbour a PIK3CA mutation in their tumor may be enrolled in an observational cohort assessing standard of care treatment.

## STUDY RECRUITMENT

The recruitment period is 36 months and interim safety analyses are planned after 20 and 40 patients have completed two treatment cycles. As the study does not include any specific post-neoadjuvant treatment examinations or surgeries, subsequent treatments after surgery are not within its scope. However, data on patients' health status will be collected via the patient self-reporting registry for German participants or via the GBG long-term registry for previous study participants (EternityB) for patients from other countries. The information will be systematically collected, ensuring a comprehensive understanding of the patients' well-being.

## PUBLICATIONS

1 Loibl S, Majewski I, Guarneri V et al. *PIK3CA* mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol 2016; 27 (8): 1519-1525.




### STUDY RECRUITMENT

As of December 31st, 2023, there are 8 German patients enrolled in the study. Further planned countries are Italy and Belgium. The end of recruitment is planned for QI/2026.

Click here for more info

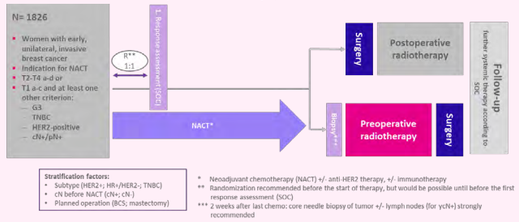
geparpippa@GBG.de

# NeoRad

## GBG 116 / NCT04261244

### Trial Design

randomized, multicenter, phase III study (non-AMG)




### Recruitment

planned: 1826 pts
recruited: 0/0 (DEU)

### Study Sites

planned : 40 DEU
active: 0 DEU

### Study Population

- women with invasive, unilateral breast cancer
- indication for NACT and radiotherapy
- T2-T4a-d OR T1a-c and G3, triple negative, HER2+, or cN+/pN+
- ECOG 0-2

### Endpoints

Primary Endpoint:

- DFS

Secondary Endpoints (Selection):

- local and locoregional recurrence rate, DDFS, BCSS, OS
- pCR
- safety and QoL
- rate lymphoedema/ plexopathy

### Cooperations

### Sponsor

### Contact

Coordinating Investigator:
PD Dr. Christiane Matuschek
Co-Investigators:
Prof. Dr. W. Budach and Prof. Dr. T. Fehm

Clinical Project Manager:
Angela Kell
neoRAD@GBG.de

## BACKGROUND

The standard of care for high-risk breast cancer consists of neoadjuvant chemotherapy (NACT) and surgery followed by postoperative whole breast/chest wall irradiation with or without an additional boost and/or irradiation of lymphatic drainage. Adjuvant radiotherapy significantly reduces ipsilateral breast recurrences, breast cancer specific mortality, and overall mortality. The optimal timing of radiotherapy in patients who are candidates for neoadjuvant chemotherapy is yet to be addressed in a randomized controlled trial.

The NeoRad trial explores the efficacy of preoperative radiotherapy in comparison to postoperative radiotherapy in patients that have received NACT for high-risk early breast cancer. Preoperative radiotherapy may shorten the overall treatment time by several weeks, potentially improving locoregional control. Past trials hinted at survival advantages, but careful interpretation is required as techniques have been relevantly changed in the meantime (Wallgren et al. 1978). Contemporary evidence from SEER database analysis and a matched pair analysis indicates enhanced disease-free survival (DFS) with preoperative radiotherapy (Poleszczuk et al. 2017, Wallgren et al. 1978). Concerns arising about jeopardizing the predictive value of pathological complete response (pCR) after preoperative radiotherapy, potentially impacting subsequent treatments in a smaller subgroup of patients can be overcome with minimally invasive biopsy of residual disease prior to initiation of radiotherapy. In summary, there is sufficient evidence to postulate that preoperative radiotherapy after NACT could improve DFS compared to postoperative radiotherapy, but data from a randomized trial using modern systemic treatment and contemporary radiation techniques is missing. Hence the NeoRad trial aims to determine if preoperative radiotherapy can significantly improve DFS, with a hierarchical test prioritizing non-inferiority followed by a test for superiority.

The trial further seeks to assess potential benefits of preoperative radiotherapy on cosmetic outcomes, particularly in flap-based reconstruction, where reduced fibrosis and shrinkage are anticipated. However, its advantage in breast-conserving surgery is less clear and surgical morbidity after preoperative radiotherapy will be monitored through early interim analyses to address potential adverse effects.

## STUDY DESIGN

All participants will undergo NACT, either with or without anti-HER2 therapy or other targeted therapies, in accordance with the current S3/AGO guidelines available during the treatment period.

In the standard arm, patients will proceed with surgery, sentinel lymph node biopsy, and potentially (targeted) axillary dissection. Subsequently, administration of adjuvant radiotherapy and systemic treatment including post-neoadjuvant therapies, will be performed in line with the corresponding S3/AGO guidelines.

In the experimental arm, patients will undergo whole breast irradiation (WBRT) with or without regional nodal irradiation (RNI) after completing NACT. Approximately 3 weeks (3 – 6 weeks) after radiotherapy, patients will undergo surgery, potentially including (targeted) axillary dissection. Post-surgery, patients will receive systemic treatment including post-neoadjuvant systemic therapy as recommended by corresponding S3/AGO guidelines.

## PRIMARY OBJECTIVES

The primary objectives of the study are to assess the superiority of preoperative radiotherapy (PRT) within the experimental treatment plan in relation in terms of disease free survival (DFS). The primary endpoint DFS is defined as the duration from randomization until the occurrence of specific events, including local recurrence, regional recurrence, contralateral breast cancer, distant recurrence, invasive second cancer, or death from any cause – whichever event occurs first.

### STUDY RECRUITMENT

NeoRad will start recruitment in QI/2024.

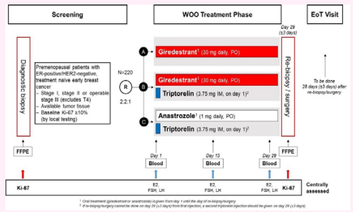
neoRAD@GBG.de

# PREcoopERA

## GBG 112 / EU-CT 2022-503013-32

### Trial Design

randomized, international multicenter, open-label, window-of-opportunity study




### Recruitment

planned: 220 pts
recruited: 0 (DEU)

### Study Sites

planned : 10 DEU
active: 0 DEU

### Study Population

- premenopausal pts with early ER+/HER2- BC
- stage I, II or operable III (T4 excluded)
- Ki 67 ≥10% in diagnostic biopsy (local testing), tumor size must be ≥1.0 cm
- ECOG 0-1

### Endpoints

Primary Endpoint:

- change in Ki-67 between pre-treatment and post-treatment biopsy

Secondary Endpoints (Selection):

- complete cell cycle arrest (CCCA)
- safety

### Cooperations

IBCSG International Breast Cancer Study Group

SOLTI

cancer trials ireland

### Sponsor

ETOP·IBCSG PARTNERS

### Contact

GBG Representative:
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Clinical Project Manager:
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## BACKGROUND

Current standard of care for premenopausal women with estrogen receptor (ER)-positive/HER2-negative early breast cancer and elevated risk of recurrence includes ovarian function suppression (OFS) in addition to tamoxifen or aromatase inhibitor (AI) therapy, as recommended by the SOFT and TEXT trials (Francis et al. 2018). However, younger patients may be less compliant and experience more discomforting side effects of OFS, potentially affecting their personal and sexual lives. While gonadotropin-releasing-hormone (GnRH) agonists for OFS are effective, the need for frequent injections may also be unacceptable to some patients. Giredestrant, a new oral selective ER degrader (SERD), shows promise as a potent anti-proliferative agent (Liang et al. 2021). Its administration in premenopausal patients is currently combined with OFS.

PREcoopERA is a biomarker-driven window-of-opportunity (WOO) study, lasting four weeks before surgery, that aims to assess giredestrant's efficacy with and without OFS in premenopausal patients. The study's rationale is based on the unmet need for endocrine treatments without OFS and preclinical data supporting giredestrant's potential to deliver that solution. The WOO time period is a suitable setting to clinically evaluate this potential and could justify larger clinical studys with giredestrant alone in ER-positive breast cancer.

## STUDY DESIGN

This is a multicenter, open-label, randomized WOO study designed to assess the activity and safety of three different treatment arms in premenopausal patients with ER-positive/HER2-negative operable stage I-III invasive breast cancer. The study follows a randomized allocation with a ratio of 2:2:1, assigning 220 participants to: giredestrant alone, giredestrant plus triptorelin, or anastrozole plus triptorelin.

## PRIMARY OBJECTIVES

The study aims to evaluate whether giredestrant plus triptorelin has superior activity compared to anastrozole plus triptorelin to decrease proliferation (reduction in Ki-67 between pre-treatment and post-treatment biopsy) in premenopausal patients with ER-positive/HER2-negative operable invasive breast cancer over a 4-week period. Additionally, the study seeks to determine if the anti-proliferative activity of giredestrant without triptorelin is non-inferior to that of giredestrant with triptorelin.

**STUDY RECRUITMENT**

PREcoopERA will start recruitment in QI/QII 2024.

Click here for more info

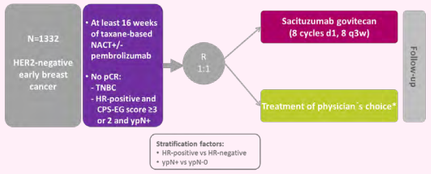
PREcoopERA@GBG.de

# SASCIA

## GBG 102 / Eudra-CT 2019-004100-35

### Trial Design

randomized, international multicenter, open-label, phase III study




*Capecitabine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation/endocrine therapy. Pembrolizumab in patients with TNBC who received pembrolizumab as neoadjuvant therapy is allowed as monotherapy in the TPC arm.
Background therapy: In patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

### Recruitment

planned: 1332 pts
recruited: 1363/748 (DEU)

### Study Sites

planned : 189
active: 177

### Study Population

- women and men with early HER2- BC
- ≥16 weeks of taxane-based NACT+/-pembrolizumab
- Non-pCR and:
  - TNBC
  - HR-positive and CPS-EG score ≥3 or 2 and ypN+

### Endpoints

Primary Endpoint:
- IDFS

Secondary Endpoints (Selection):
- OS, DDFS, LRRFI, IBCFS
- safety
- PROs
- QoL

### Cooperations

GEICAM spanish breast cancer group
UCBG
AGO-B BREAST STUDY GROUP
ABCSG
IBCSG

### Sponsor

GBG GERMAN BREAST GROUP

### Contact

GBG Representative:
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Clinical Project Manager:
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## BACKGROUND

Neoadjuvant chemotherapy (NACT) allows monitoring of tumor response to treatment, and a pathological complete response (pCR) is associated with improved survival, particularly in triple-negative breast cancer (TNBC). TNBC patients without pCR have a 5-year event-free survival rate of nearly 50%.[1] The CPS+EG system identifies patients with hormone receptor-positive and HER2-negative tumors at high risk of relapse after NACT.[2]

Post-neoadjuvant therapy has the potential to improve survival all the while avoiding overtreatment. Sacituzumab govitecan, an antibody-drug conjugate, shows promise in metastatic TNBC and HR-positive/ HER2-negative breast cancer (Bardia et al. 2018, Bardia et al. 2019); the ASCENT and TROPiCS-02 trials have demonstrated its clinical efficacy (Bardia et al 2021, Rugo et al. 2022). The SASCIA study will evaluate sacituzumab govitecan's activity in patients with HER2-negative tumors at high risk of relapse after NACT.

## STUDY DESIGN AND OBJECTIVES

Eligible participants (aged ≥18 years) must have received 16 weeks of taxane-based NACT, with at least 6 weeks of taxane treatment. High-risk criteria for recurrence post-NACT include centrally confirmed HER2-negative breast cancer (IHC score 0-1 or FISH negative per ASCO/CAP), assessed preferably on tissue from post-neoadjuvant residual breast disease. HR-negative patients (<1% positive cells) with residual disease >ypT1mi and/or ypN1>1mm, or HR-positive patients (≥1% positive cells) with CPS+EG score ≥3 or CPS+EG score 2 and ypN+ are eligible. Radiotherapy precedes study treatment. Patients are randomly assigned (1:1) to receive sacituzumab govitecan (days 1, 8 q3w for eight cycles; experimental arm) or treatment of physician's choice (TPC, capecitabine, platinum-based chemotherapy for eight cycles, or observation/endocrine therapy; control arm).

Protocol amendment 1 permits use of pembrolizumab in the TPC arm for TNBC patients who received it during NACT. Adjuvant pembrolizumab may be given until completion of radiotherapy before SASCIA trial randomization. Patients with known g*BRCA1/2* mutations are not eligible if adjuvant olaparib is indicated or planned.

Randomization factors include HR status (negative vs. positive) and ypN status (ypN+ vs. ypN0). HR-positive patients in the TPC arm will receive endocrine therapy, including CDK4/6 inhibitors, according to local guidelines and at the discretion of the investigator.

The primary objective of SASCIA is to compare invasive disease-free survival (iDFS) between sacituzumab govitecan and treatment of physician's choice. Secondary objectives include overall survival (OS), distant DFS, invasive breast cancer-free survival, locoregional recurrence-free interval, safety, compliance, patient-reported outcomes, and quality of life. Translational research explores ctDNA dynamics as early predictors and the predictive value of markers for sacituzumab govitecan. An interim analysis is planned after 264 events (2/3 of total events).

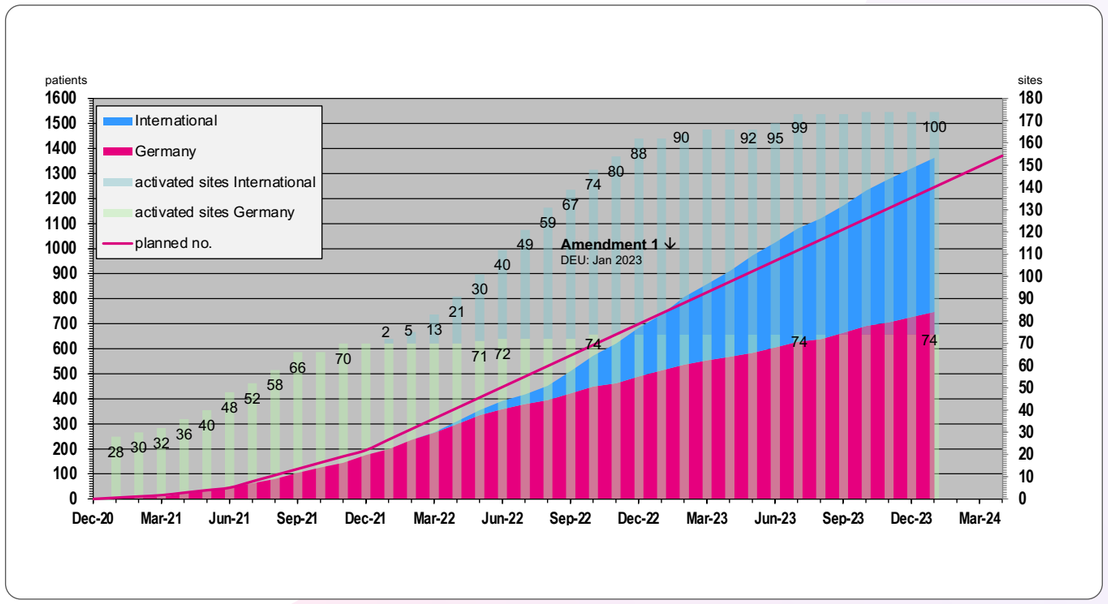
## PUBLICATIONS

1 Hahnen E, Lederer B, Hauke J et al. Germline Mutation Status, Pathological Complete Response, and Disease-Free Survival in Triple-Negative Breast Cancer: Secondary Analysis of the GeparSixto Randomized Clinical Trial. JAMA Oncol 2017; 3 (10): 1378-1385.

2 Marme F, Lederer B, Blohmer JU et al. Utility of the CPS+EG staging system in hormone receptor-positive, human epidermal growth factor receptor 2-negative breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer 2016; 53: 65-74.

### STUDY RECRUITMENT

As of December 31st, 2023, there are 1363 patients enrolled in the study. The other European recruiting countries are Spain, France, Austria, Ireland, Italy, Belgium, and Switzerland. The recruitement was completed in January 2024.



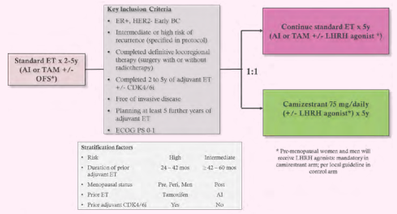

Click here for more info
SASCIA@GBG.de

# CAMBRIA-1

## GBG 110 / EU-CT 2022-501024-20-00

### Trial Design

randomized, international multicenter, open-label, phase III study




### Recruitment

planned: 4300 pts
recruited: 290/0 (DEU)

### Study Sites

planned : 30 DEU
active: 15 DEU

### Study Population

- women and men with early ER+/HER2- BC
- intermediate to high recurrence risk
- completion of 2 to 5 years adjuvant endocrine therapy +/- CDK4/6 inhibitor

### Endpoints

Primary Endpoint:
- IBCFS

Secondary Endpoints (Selection):
- IDFS, DRFS, OS
- safety
- changes in arthralgia, hot flushes, vaginal dryness
- QoL

### Cooperations

NSABP Foundation, Inc.; unicancer; ABCSG; GEICAM

### Sponsor

AstraZeneca

### Contact

International Study Chair:
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Clinical Project Manager:
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## BACKGROUND

Patients with early-stage estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2-) breast cancer face a lingering risk of recurrence beyond 5 years, prompting the exploration of extended treatment options. As shown in the metanalysis by Pan et al. late recurrence after 5 years of endocrine therapy (ET) is a relevant problem with cumulative distant recurrence rates for years 5 to 20 ranging from 13% for T1N0 to 41% for T2N4–9 disease (Pan et al. 2017). Multiple trials evaluated extended ET after 5 years of treatment aromatase inhibitors (AI) and/or tamoxifen. The ATLAS study showed that, compared with 5 years of tamoxifen, 10 years of tamoxifen provided significant further benefit to women with HR+ breast cancer in recurrence and breast cancer mortality with a “carry-over” benefit beyond 10 years (Davies et al. 2013). The MA.17R and NSABP B-42 trials reported significant improvements in disease free survival (DFS) with an additional 5 years of AI (Goss et al. 2016, Mamounas et al. 2023). Despite therapeutic advances, a risk of late recurrence persists in ER+/HER2- disease.

Camizestrant (AZD9833), a potent next-generation selective estrogen receptor degrader (SERD) and pure ER antagonist, emerges as a promising candidate. Its unique approach addresses two pivotal resistance mechanisms often encountered in current endocrine therapies. Primarily, camizestrant tackles the challenge of incomplete inhibition of ER signaling, aspiring to provide more comprehensive suppression of estrogen receptor signaling compared to traditional therapies. Additionally, it proves effective against mutations in the ER gene (ESR1 mutation), offering a targeted solution to combat resistance associated with aquired genetic alterations.

The SERENA 1 & 2 trial, investigating camizestrant endocrine resistant ER+/HER2- advanced breast cancer reported promising efficacy results with a statistically significant and clinically meaningful benefit in PFS for camizestrant (7.2 months at 75mg and 7.7 months at 150mg dose, respectively) compared to fulvestrant (3.7 months) with both dose levels of camizestrant being well tolerated (Baird et al 2021).

## STUDY DESIGN

Among other eligibility criteria, pre- or postmenopausal female or male patients with ER+/HER2- early breast cancer with intermediate or high risk of recurrence who have completed definitive locoregional therapy and at least 2 years and up to 5 years of standard adjuvant ET with or without a CDK4/6 inhibitor, with no signs of recurrent disease will be included. Patients will be randomized 1:1 to receive 75mg camizestrant once daily with or without luteinizing hormone-releasing hormone (LHRH) agonists or standard ET of physician’s choice with or without LHRH agonists each for a duration of up to 60 months.

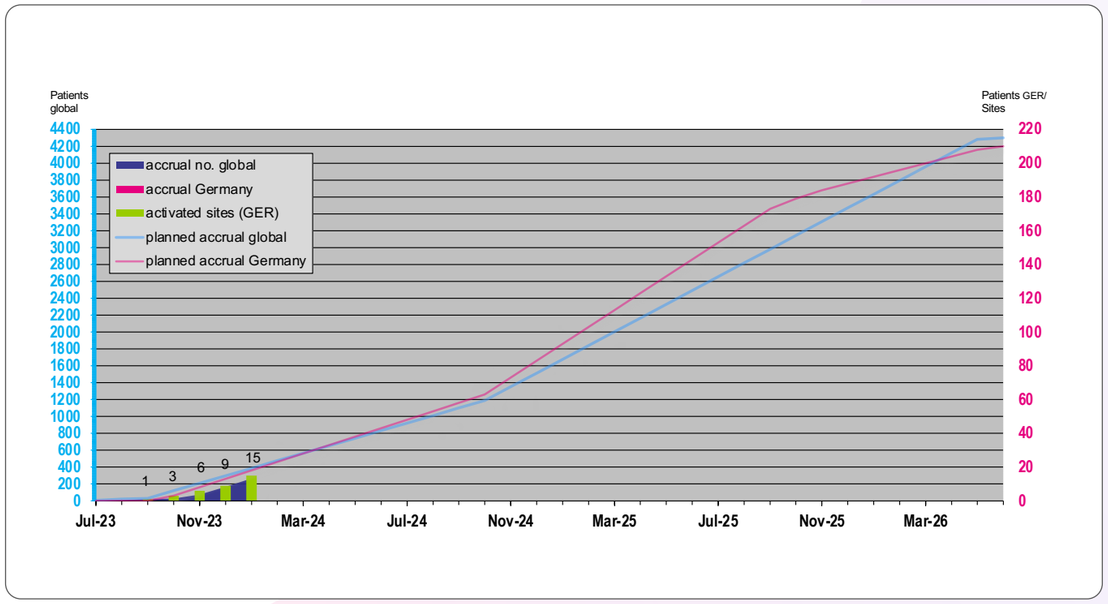
CAMBRIA-1 primarily involves a cohort already undergoing adjuvant ET. The main difference to the CAMBRIA-2 trial design is that patients can only be included after a minimum of 2 years of adjuvant ET and only after completion of adjuvant CDK4/6 inhibitor therapy if indicated.

## PRIMARY OBJECTIVES

The primary efficacy objective of the trial is to demonstrate superiority of extended therapy with camizestrant compared to standard ET by assessment of invasive breast cancer-free survival (IBCFS).

### STUDY RECRUITMENT

The study will be conducted in approximately 682 sites in 39 countries. It is planned to recruit 210 patients in Germany. So far, 290 out of a total of 4,300 patients have been recruited globally as of December 31, 2023.



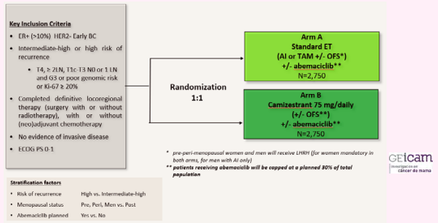

Click here for more info
cambria@GBG.de

# CAMBRIA-2

## GBG 115 / EU-CT 2023-504031-41

### Trial Design

randomized, international multicenter, open-label, phase III study




### Recruitment

planned: 5500 pts
recruited: 8/0 (DEU)

### Study Sites

planned : 30 DEU
active: 0 DEU

### Study Population

- women and men with early ER+/HER2-BC
- intermediate to high recurrence risk
- No prior adjuvant endocrine therapy

### Endpoints

Primary Endpoint:
- IBCFS

Secondary Endpoints (Selection):
- IDFS, DRFS, OS
- safety
- PROs (arthralgia, hot flushes, vaginal dryness)
- QoL

### Cooperations

SOLTI, Breast Cancer Trials, SAKK, GEICAM, unicancer, Alliance Foundation Trials, ABCSG

### Sponsor

AstraZeneca

### Contact

International Study Chair (in cooperation with ABCSG):
Prof. Dr. Sibylle Loibl

Clinical Project Manager:
Angela Kell
Azcambria-2@gbg.de

## BACKGROUND

Patients with early-stage, HR+HER2- breast cancer have a persistent risk of recurrence beyond 5 years. Late recurrence after 5 years of endocrine therapy (ET) is a relevant problem with cumulative distant recurrence rates for years 5 to 20 ranging from 13% for T1N0 to 41% for T2N>4 disease (Pan et al 2016). Extended endocrine therapy (ET) with additional aromatase inhibitor (AI) or tamoxifen after completion of 5 years initial ET is one effective approach to reduce the risk of late recurrence (Davies et al. 2023, Gray et al. 2013, Goss et al. 2016, Mamounas et al. 2023). A different approach is to offer adjuvant CDK4/6i treatment for 2-3 years of initial adjuvant ET (Slamon et al. 2023, Paluch-Shimon et al. 2023). Some countries have approved the addition of abemaciclib during the first 2 years of ET for high-risk patients according to the MonarchE trial. Even though the 4-year invasive disease free survival (iDFS) rate could be improved by an absolute 6% through the addition of abemaciclib, an absolute 14% did not remain free of invasive disease despite of adjuvant abemaciclib at this landmark.

Camizestrant (AZD9833) is a potent next-generation selective estrogen receptor degrader (SERD) and pure ER antagonist. Its unique approach addresses two pivotal resistance mechanisms often encountered in current endocrine therapies namely overcoming incomplete inhibition of ER signaling and sustain effectivity in acquired ER gene mutation (ESR1 mutation).

The SERENA 1 & 2 study, investigating camizestrant endocrine resistant ER+/HER2- advanced breast cancer reported promising efficacy results with a statistically significant and clinically meaningful benefit in PFS for camizestrant (7.2 months at 75mg and 7.7 months at 150mg dose, respectively) compared to fulvestrant (3.7 months) with both dose levels of camizestrant being well tolerated (Baird et al. 2021).

## STUDY DESIGN

Among other eligibility criteria, pre- or postmenopausal female or male patients with ER+/HER2- early breast cancer with intermediate or high risk of recurrence who have completed definitive locoregional therapy, with no evidence of disease and who may have received a maximum of 12 weeks of ET either in the neoadjuvant or adjuvant setting prior to randomization will be included. Patients will be randomized 1:1 to receive 75mg camizestrant once daily with or without abemaciclib (as approved by local/institutional guidelines) or standard ET of physician's choice with or without abemaciclib (as approved by local/institutional guidelines) each for a duration of up to 84 months. Pre- and peri-menopausal women and males will receive concurrent luteinizing hormone-releasing hormone (LHRH) agonist in with the exception of males receiving tamoxifen.

CAMBRIA-2 targets grossly a treatment-naive cohort. The main difference to the CAMBRIA-1 trial design is that patients may be included at the beginning of adjuvant ET and may receive concurrent abemaciclib as indicated by local guidelines or institutional standard.

## PRIMARY OBJECTIVES

The primary efficacy objective of the trial is to demonstrate superiority of camizestrant ± abemaciclib as compared to standard ET ± abemaciclib by assessment of invasive breast cancer-free survival (IBCFS).

### STUDY RECRUITMENT

The study will be conducted in approximately 710 sites in 43 countries aiming to enroll 5,500 patients in total. The recruitment in Germany is expected to start in QI/II 2024.

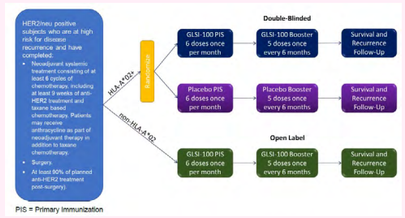
Azcambria-2@gbg.de

# Flamingo-01

## GBG 111 / EU-CT 2023-504323-25

### Trial Design

randomized, international multicenter, double-blinded, phase III study




### Recruitment

planned: 598 pts
recruited: 0 (DEU)

### Study Sites

planned : 40 DEU
active: 0 DEU

### Study Population

- early HER2+ BC HLA-A*02 + (exception: non-HLA-A*02 arm)
- stage I-III at initial diagnosis & non-PCR OR stage III with pCR after NACT
- neoadjuvant, surgical and adjuvant standard therapy completed

### Endpoints

Primary Endpoint:
- IDFS

Secondary Endpoints (Selection):
- OS, DDFS, IDFS
- safety
- QoL

### Cooperations

GEICAM investigación en cáncer de mama
unicancer

### Sponsor

Greenwich LifeSciences

### Contact

GBG Representative :
Prof. Dr. Marcus Schmidt

Clinical Project Manager:
Viktoria Tierbach
Flamingo01@gbg.de

## BACKGROUND

One promising approach in cancer treatment involves leveraging the body's immune mechanisms to target and eliminate tumor cells. The introduction of Trastuzumab, a monoclonal antibody targeting the HER2 receptor, as adjuvant therapy almost 20 years ago marked a turning point in the treatment of patients with HER2 positive early breast cancer (Piccart-Gebhart et al. 2005, Romond et al. 2005). Initially approved as adjuvant treatment it is nowadays also treatment of choice in high-risk HER2 positive early breast cancer given together with Pertuzumab and neoadjuvant chemotherapy. Post-neoadjuvant therapy with Trastuzumab-Emtansine (T-DM1) as introduced by the KATHERINE study can achieve further clinical meaningful improvement in invasive disease free survival (iDFS) and has recently shown also an overall survival benefit (von Minckwitz G et al. 2019, Loibl et al. 2023). An absolute improvement of 13.7% in 7-year iDFS from 67.1% with trastuzumab to 80.8% with T-DM1 is impressive. Nevertheless, almost 20% of these high risk patients will experience relapse despite of optimal anti-HER2 targeted therapy representing an unmet clinical need.

Immunizations targeting specific tumor antigens, such as HER2/neu, have gained attention for exploring long-term modulation of the immune system for a sustained response without continuous therapy. The immunogenic cytotoxic T lymphocyte (CTL) epitope GP2, derived from HER2/neu, is under investigation as a peptide immunization in HLA-A*02 subjects (Fisk et al. 1995, Peoples et al. 1995). The development of these immunizations holds promise for adjuvant therapies in high-risk breast cancer patients.

One such agent, GLSI-100, combines the GP2 peptide with granulocyte-macrophage colony-stimulating factor (GM-CSF; Patel et al. 2022). The Phase I study demonstrated GLSI-100's safety and efficacy, with the optimal dose identified as 500 mcg GP2 and 125 mcg GM-CSF. Subsequent Phase II studies, including a randomized study with 5-year follow-up, indicated a significant disease-free survival benefit in HER2-positive patients receiving GLSI-100 compared to the control group. Local and systemic toxicities were minimal, and GLSI-100 induced immune responses, including GP2-specific CTL expansion (Patel et al. 2022, Cliftin et al. 2016).

These findings support the potential of GLSI-100 as adjuvant therapy to prevent recurrence of HER2-positive breast cancer in HLA-A*02-positive patients. Further research aims to establish GLSI-100's role in combination therapies and its efficacy in different patient populations, contributing to the evolving landscape of cancer immunotherapy.

## STUDY DESIGN

FLAMINGO-01 is a prospective, randomized, double-blind, placebo-controlled, multi-center phase 3 study. Patients must be diagnosed with HER2-positive breast cancer at high risk of recurrence, defined as patients with stage III disease and pathological complete response (pCR) or stage I, II, or III and residual disease after surgery. Patients must have completed standard of care therapy, including neoadjuvant therapy, surgery, and adjuvant trastuzumab-based therapy. HLA-A02 subjects are randomized to GLSI-100 or placebo. Non-HLA-A02 subjects at select sites may receive open-label GLSI-100 therapy.

HLA type screening may be performed after surgery. This may result in HLA type screening up to one year prior to enrolment, as treatment begins after completion of adjuvant trastuzumab-based therapy. HLA-A*02 subjects receive GLSI-100 or placebo. The Primary Immunization Series (PIS) consists of six-monthly doses over six months. Subjects then enter the booster series, and receive five doses over 2.5 years.

## PRIMARY OBJECTIVES

The primary objective is to evaluate the efficacy of GLSI-100 compared to placebo in HLA-A*02-positive patients with HER2-positive early breast cancer at high risk of disease recurrence.

### STUDY RECRUITMENT

Recruitment is planned to start in QI/2024.

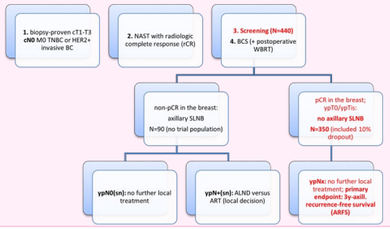
Click here for more info
Flamingo01@GBG.de

# EUBREAST-01

## GBG 104 / NCT04101851

### Trial Design

International multicenter, single-arm, surgical study (non-AMG)




### Recruitment

planned: 350 pts
recruited: 276/272 (DEU)

### Study Sites

active : 46 DEU
recruiting: 32 DEU

### Study Population

- 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

### Endpoints

Primary Endpoint:

- 3-year rate of axillary recurrence-free survival (ARFS) after BET

Secondary Endpoints (Selection):

- 5-year IDFS/DFS/OS/LRFS/ARFS
- diagnostic accuracy of imaging methods for breast pCR after NAST

### Cooperations

AGO-B BREAST STUDY GROUP

### Sponsor

Universitätsmedizin Rostock

### Contact

Coordinating Investigator:
Prof. Dr. Toralf Reimer

Clinical Project Manager:
Keyur Mehta
eubreast01@gbg.de

## BACKGROUND

Currently, axillary surgery for breast cancer is considered a staging procedure that does not seem to influence breast cancer mortality, as the risk of developing metastases depends mainly on the biological behavior of the primary tumor (seed-and-soil model). Thus, the postsurgical treatment strategy should be rather based on biologic tumor characteristics than nodal involvement.1

Improvements in systemic treatments for breast cancer have increased the rates of pathological complete response (pCR) in patients receiving neoadjuvant systemic therapy (NAST), offering the opportunity to reduce and perhaps eliminate axillary surgery in patients with pCR.

The trial proposes a unique approach, tailoring surgical strategies based on the NAST response rather than the traditional T and N status at presentation. In cases of radiologic complete remission and breast pCR, axillary surgery will be eliminated for patients with initial cN0 stage.

## STUDY DESIGN AND OBJECTIVES

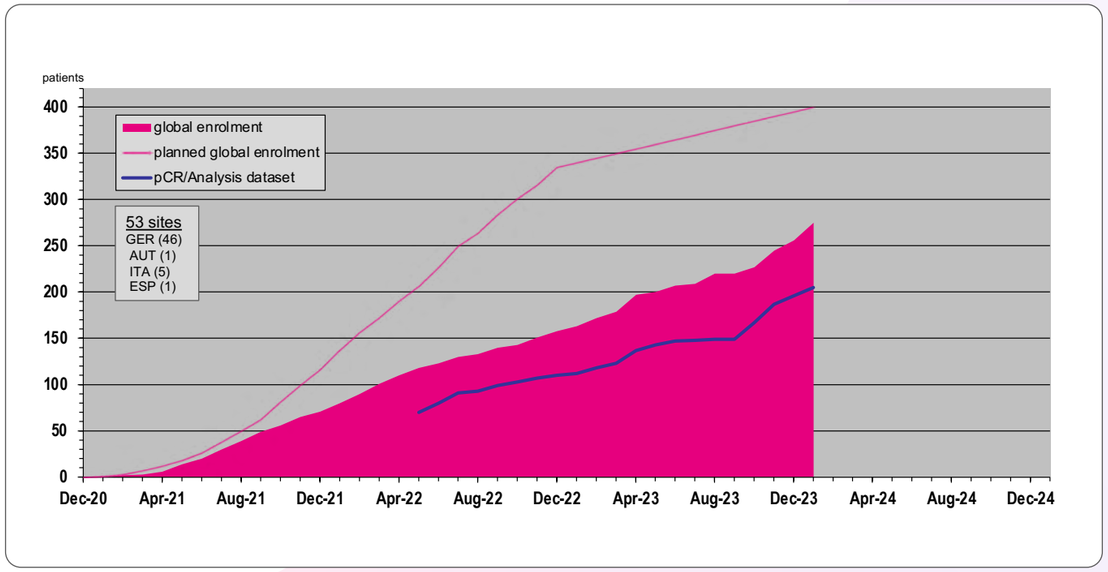
The multicenter study plans to recruit 350 patients with triple-negative or HER2-positive invasive breast cancer. Patients with a cT1c-cT3 tumor and initially cN0/iN0 status prior to NAST will be considered in this study. The primary objective is to assess the 3-year rate of axillary recurrence-free survival (ARFS) after breast-conserving surgery without axillary therapy. Secondary objectives cover various survival outcomes and the diagnostic accuracy of imaging methods for breast pCR after NAST.

## PUBLICATIONS

1 Reimer T, Glass A, Botteri E et al. Avoiding Axillary Sentinel Lymph Node Biopsy after Neoadjuvant Systemic Therapy in Breast Cancer: Rationale for the Prospective, Multicentric EUBREAST-01 Trial. Cancers (Basel) 2020; 12 (12).

### STUDY RECRUITMENT

EUBREAST-01 global recruitment started in January 2021 with first-patient-in in Germany on January 15th, 2021. As of December 31st, 2023, there were 275 patients enrolled in the study.




**Click here for more info**

**eubreast01@GBG.de**

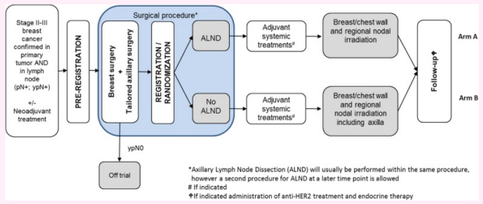
# TAXIS

## GBG 101/ NCT03513614

Universitätsspital Basel

### Trial Design

randomized, multicenter, phase III study (non-AMG)




### Recruitment

planned: 1500 pts
recruited: 909/60 (DEU)

### Study Sites

planned : 5 DEU
active: 5 DEU

### Study Population

- operable node positive BC, detected by palpation or imaging (most suspicious lymph node clipped)
- stage II-III
- eligible for primary axillary lymph node dissection or sentinel lymph node biopsy procedure

### Endpoints

Primary Endpoint:

- DFS

Secondary Endpoints (Selection):

- OS, BCSS, TTLR, TTRR, TTDR
- lymphedema, range of shoulder motion
- surgical site infections
- safety and QoL

### Cooperations

SAKK

International Breast Cancer Study Group
IBCSG

ABCSG

### Sponsor

Universitätsspital Basel

### Contact

Coordinating Investigator:
Prof. Dr. Walter Weber

Clinical Project Manager:
Jan Steffen
taxis@gbg.de

## BACKGROUND

Axillary lymph node dissection (ALND) was the standard treatment for all patients with breast cancer for almost a century until the introduction of sentinel lymph node procedure (SLNB), in which involves the selective removal of the first few lymph nodes in the lymphatic drainage system. Conventional ALND is still performed today for breast cancer that has spread to the lymph nodes. It causes significant morbidity in the form of lymphedema, impaired shoulder mobility, sensation disorders, and chronic pain in up to one third of all women who undergo the procedure.

The TAXIS trial evaluates the optimal treatment for breast cancer patients with confirmed nodal-positive disease at initial diagnosis in terms of surgery and radiotherapy. In particular, it investigates the value of tailored axillary surgery (TAS), a new technique that aims to selectively remove positive lymph nodes, with the potential to significantly reduce morbidity by avoiding surgical overtreatment. This trial has the potential to establish a new treatment standard with hopefully fewer side effects and a better quality of life, while maintaining the same efficacy as provided by conventional ALND.

## STUDY DESIGN AND OBJECTIVES

Women or men aged ≥18 years with node-positive breast cancer (histologically or cytologically proven in both primary tumor and lymph node) at AJCC/UICC stage II-III (all molecular subtypes) are eligible for the trial. Participants will be randomized 1:1 to TAS (SLNB + removal of clipped positive nodes and palpably suspicious nodes) followed by ALND and regional nodal irradiation excluding the dissected axilla (arm A) or TAS followed by regional nodal irradiation including the full axilla (arm B). All patients receive adjuvant whole-breast irradiation after breast conserving surgery and chest wall irradiation after mastectomy. Neoadjuvant treatment can be given prior to TAS, if indicated, and adjuvant systemic treatment can be given after TAS and prior to radiotherapy, if indicated.

The trial aims to enroll 1,500 patients (750 per arm). Radiation therapy (RT) should commence within 8 weeks post-surgery, not exceeding 12 weeks, and within 6 weeks after the last chemotherapy cycle but not later than 8 weeks. The dose to the breast/thoracic wall and regional nodal pathways is 50 Gy in 25 fractions of 2 Gy or 50.4 Gy in 28 fractions of 1.8 Gy; hypofractionated schedules are allowed. The follow-up period consists of 10 years after randomisation for each patient.

The TAXIS trial's primary objective is to demonstrate that TAS and axillary RT are non-inferior to ALND in terms of disease-free survival (DFS). Secondary endpoints include quality of life (QoL), overall survival (OS), breast cancer-specific survival (BCSS), time to local recurrence (TTLR), time to regional recurrence (TTRR), time to distant recurrence (TTDR), reported morbidity outcomes (lymphedema and decreased range of shoulder motion), adverse events, late radiotherapy-related adverse events, and surgical site infections (SSI).

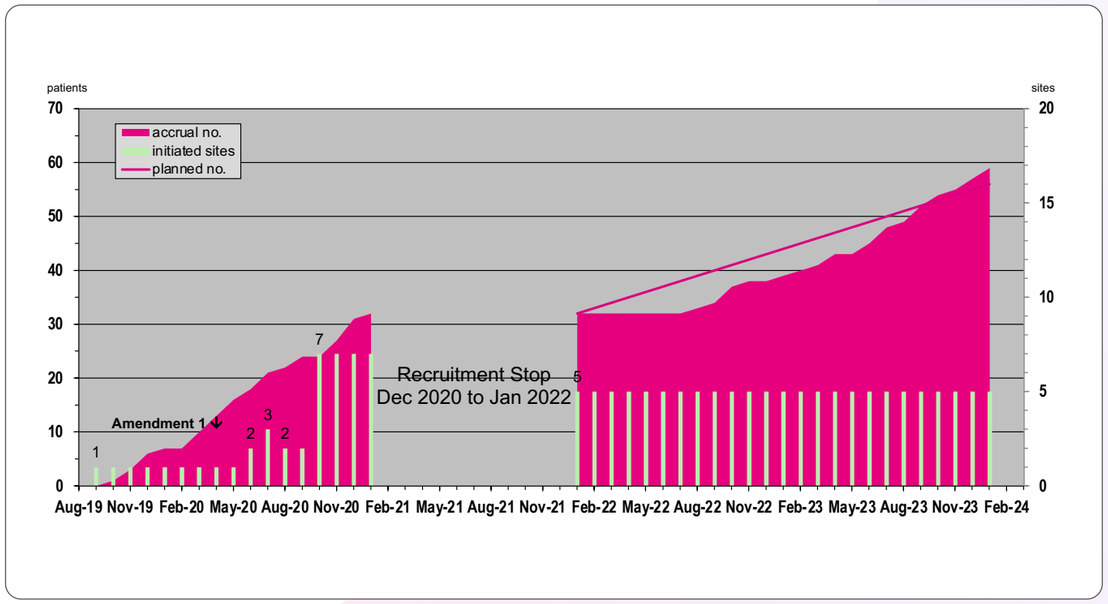
## PUBLICATIONS


1 Tausch C, Daster K, Hayoz S et al. Trends in use of neoadjuvant systemic therapy in patients with clinically node-positive breast cancer in Europe: prospective TAXIS study (OPBC-03, SAKK 23/16, IBCSG 57-18, ABCSG-53, GBG 101). Breast Cancer Res Treat 2023; 201 (2): 215-225.

2 Weber WP, Matrai Z, Hayoz S et al. Association of Axillary Dissection With Systemic Therapy in Patients With Clinically Node-Positive Breast Cancer. JAMA Surg 2023; 158 (10): 1013-1021.


## STUDY RECRUITMENT

TAXIS recruitment started in August 2019 in Germany. Recruitment was stopped due to different issues of the sponsor at the end of 2020, and the trial was re-opened again for recruitment in January 2022 in collaboration with a new sponsor (Universitätsspital Basel). As of December 31st, 2023, 60 patients were enrolled in the study in Germany (914/1500 patients global). The end of trial treatment is determined as QIII/2025. Follow-up is planned for up to 10 years. The end of the trial (i.e., last visit of the last patient randomized) is planned for QIV/2034.[1, 2]




Click here for more info

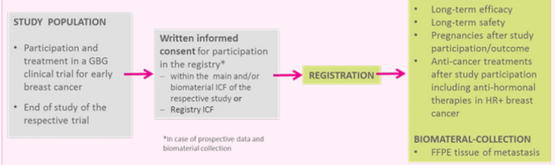
taxis@GBG.de

# ETERNITY[B]

## GBG 107 / NCT05739591

### Trial Design

international, multicenter, prospective/retrospective, non-interventional observational study (registry)




### Recruitment

planned: n.a.
recruited: 32 pts

### Study Sites

planned : n.a.
active: 16

### Study Population

- participation and treatment in a GBG clinical trial for early breast cancer
- prospective registration: written informed consent

### Objectives

Primary Objective:
- to evaluate long-term-survival

Secondary Objectives (Selection):
- to determine long-term toxicity
- to determine further anti-cancer therapies after study participation
- to determine pregnancies after study participation and their outcome

### Cooperations

AGO-B BREAST STUDY GROUP
GEICAM Investigación en cáncer de mama
IBCSG
Japan Breast Cancer Research Group
ABCSG
Cancer Trials Ireland
unicancer
KCSG 대한항암요법연구회

### Sponsor

GBG GERMAN BREAST GROUP

### Contact

Coordinator:
Prof. Dr. Sibylle Loibl

Clinical Project Manager:
Dr. Thomas Ballhausen
eternity@gbg.de

## BACKGROUND

Although the impact on long-term patient survival and safety is a critical factor for drawing conclusions about the risk-benefit- 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 established the international registry study ETERNITY[B] to collect a similar data set to that of GBG 71 with a focus on long-term outcomes.

## STUDY DESIGN AND OBJECTIVES

Patients eligible for ETERNITY[B] must have previously participated and been treated in a GBG clinical trial for early breast cancer. Inclusion in the ETERNITY[B] study is dependent on a signed informed consent form. Data collection and follow-up documentation starts after the regular conclusion of the corresponding GBG trial or at the start of the post-study follow-up period, as outlined in the respective study protocol.

Linking the follow-up registry with specific study databases is feasible through participant identification numbers, facilitating analysis of long-term therapy effects by group, and correlating effectiveness with potential delayed side effects. Post-study long-term outcome follow-up aligns with local/national guidelines and require at least annual documentation in the registry. Assessments, including relapse and safety evaluations and collection of survival status, are performed for all registered patients. These may be conducted at regular follow-up visits or by alternative means such as telephone or written communication, particularly in the event of a patient's death.

If disease recurrence is confirmed, a histological examination is recommended. While the provision of an FFPE tumor tissue block from the metastatic lesion to GBG is encouraged, biomaterial submission is not mandatory for participation in ETERNITY[B].

### STUDY RECRUITMENT

The ETERNITY[B] recruitment started in September 2022. As of December 31st, 2023, there are 32 patients enrolled in the study. The end of study is estimated for 2030.

Click here for more info
eternity@GBG.de

# Brain Metastases in Breast Cancer (BMBC)

## GBG 79

### Trial Design

international, multicenter, prospective/retrospective, non-interventional observational study (registry)


### Recruitment

planned: n.a.
recruited: 4109 pts

### Study Sites

planned : n.a.
active: 151

### Study Population

- brain metastases and history of breast cancer or metastatic breast cancer (diagnosed since the year 2000)
- patients with leptomeningeal disease without brain metastases are eligible

### Objectives

Objectives (Selection):

- To assess the incidence of brain metastases
- To assess number/size and location of brain metastases
- To assess histopathological characteristics
- To assess the influence of treatment strategies on prognosis
- Collection of tissue samples

### Cooperations

AGO-B BREAST STUDY GROUP
UKE HAMBURG

### Sponsor

GBG GERMAN BREAST GROUP

### Contact

Coordinator:
Prof. Dr. Volkmar Müller

Clinical Project Manager:
Udo Pfeil
brainmet@gbg.de

## BACKGROUND

The emergence of brain metastases significantly diminishes the quality of life and survival rates in patients with breast cancer. Recent years have witnessed a rise in the incidence of brain metastases (Fisk et al. 1995). Approximately 10-40% of patients with metastatic breast cancer develop brain metastases, influenced by the biological subtype of the primary tumor. Overall prognosis for patients with brain metastases is generally grim, with factors such as good performance status and a limited number of brain metastases being associated with prolonged survival (Ogawa et al. 2008). Treatment options include surgery, radiotherapy, systemic chemotherapy, or a combination of these.

Limited analysis of small and diverse patient groups has left gaps in understanding the risk factors for brain metastases development and the impact of early detection. Given the anticipation of an increased incidence of patients with brain metastases, especially with improved control of systemic disease outside the nervous system, there is a demand for enhanced treatment strategies. A comprehensive and multidisciplinary approach promptly integrating new treatment strategies is crucial for patients developing brain metastases, with the goal of extending survival, preserving neurological function, and enhancing quality of life.

The Brain Metastases in Breast Cancer (BMBC) registry was established to include breast cancer patients diagnosed with brain metastases from the year 2000 onwards. Prospective registration of patient data requires informed consent, while retrospective entries are permitted without individual consent if the patient cannot sign the informed consent, ensuring anonymous data capture. The registry study is conducted in collaboration with Prof. Dr. Volkmar Müller, Prof. Dr. Isabell Witzel, Priv. Doz. Dr. Elena Laakmann, and Dr. med. Kerstin Riecke from the University Hospital Hamburg-Eppendorf.

**Amendment 1 enables the inclusion of patients with meningeosis carcinomatosa. For patients in the prospective part of the study, tumor tissue from the primary tumor, the metastatic tumor or the brain tumor, as well as blood samples and cerebrospinal fluid, if available, are collected centrally in the GBG biobank after the patient has given consent.**

## STUDY OBJECTIVES

The BMBC registry aims to collect comprehensive data on brain metastases, encompassing their incidence, number, size, location, histopathological characteristics, diagnostic tool sensitivity, performance status, prognosis, and treatment impact on prognosis and neurological function. Additionally, the registry facilitates translational research by utilizing tumor specimens from primary and metastatic tumors. Planned analyses involve studying treatment patterns, patient outcomes, and validating prognostic scoring systems within a multicenter context and in the context of new targeted therapies. Translational research projects will explore glycosylation impact, resistance mechanisms against HER2-targeted therapies, the blood-brain barrier's role, and evaluating markers of radio-resistance and genomic alterations linked to breast cancer cells' brain tropism.

## PUBLICATIONS

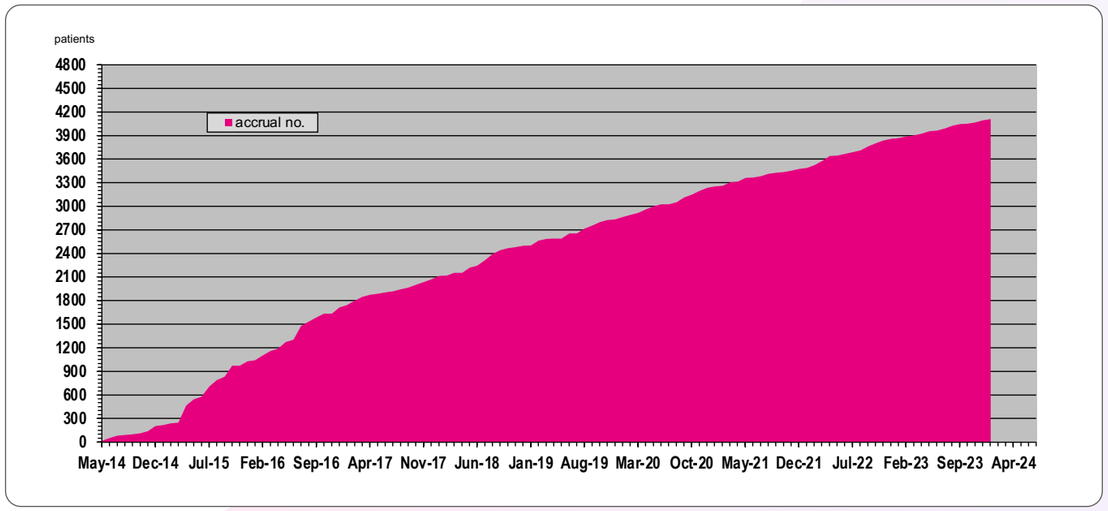
1. Laakmann E, Witzle I, Neunhoffer T et al. Charteristics of patients with brain metastases from human epidermal growth factor receptor 2-positive breast cancer: subanalysis of Brain Metastases in Breast Cancer Registry. ESMO Open 2022; 7 (3): 100495.
2. Riecke K, Muller V, Neunhoffer T et al. Long-term survival of breast cancer patients with brain metastases: subanalysis of the BMBC registry. ESMO Open 2023; 8 (3): 101213.
3. Riecke K, Muller 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).

*BMBC goes international: Additionally, the study has broadened its international reach, attracting a more extensive pool of participants. The registration of the first international patient from Belgium occurred on October 9th, 2023.*

*Consequently, both the clinical database and biobank have undergone expansion. Initial data from 857 patients of the Netherlands has already been recorded.*

*The study was opened for documentation in April 2014 with more than 50 participating centers. As of December 31st, 2023, 4,110 patients have been registered and 547 tissue samples have been received. Registration of patients is ongoing.*

In July 2023, the 4,000th patient was admitted, originating from the Apaglesion Diakonieklinikum Rotenburg Wümme Clinic for Gynecology and Gynecological Oncology, Elise-Averdieck-Strasse 17, 27356 Rotenburg. Gratitude is extended to Dr. Tobias Hesse, Ms. Svenja Behrens, and the entire study team for their contributions.




Click here for more info
brainmet@gbg.de

# Patient Self-Reported Outcome Registry (PSRO)

(GBG 071)

### Trial Design

- non-interventional observational study (registry)
- collection of long-term safety and efficacy parameters of former German GBG study participants from prospective clinical trials
- data reporting by the patient via questionnaire

### Recruitment

planned: n.a.
recruited: 13290 pts

### Study Sites

450 sites
20 trials

### Study Population

- participation and treatment in a GBG clinical trial for breast cancer in Germany

### Objectives

- to determine long-term outcome
- to determine long-term toxicity

### Cooperations

ZKS Köln – Zentrum für Klinische Studien

### Sponsor

GBG – German Breast Group

### Contact

Clinical Project Manager:
Jan Steffen
follow.up@gbg.de

## METHODS

Patients are invited to participate in the PSRO registry by the site investigator. Upon consent, their name, address, and unique study identifier are collected, and they would hereby agree to regular receipt of health status questionnaires. In compliance with German privacy laws and good clinical practice (GCP) regulations, the sponsor cannot store patient-identifying data. Therefore, we designed the registry with a strict separation of patient-identifying data and pseudonymized medical data through a data trustee. This trustee, financially and organizationally independent from the GBG, manages patient names and addresses in a database inaccessible to GBG.

Upon notification from GBG, the trustee sends out questionnaires querying the current health status, including details like recurrence dates, secondary malignancies, and date of death. In case of the patient's demise, the questionnaires may be completed by a third party. Forms sent to GBG only carry the unique study identifier as a pseudonym. Address changes or withdrawals of consent can be communicated to the trustee via another form. Consequently, GBG connects updated data with the original study database and informs the respective site about their patients if patient consented to such option.

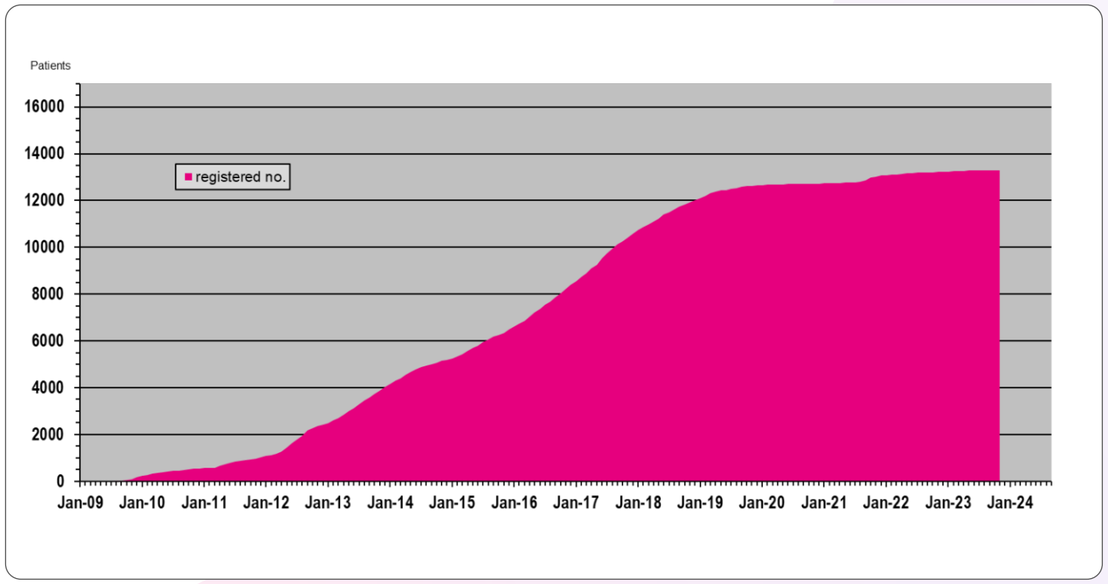
Participation is open to individuals from numerous GBG trials for breast cancer, with over 13,000 participants from 20 trials and 450 sites currently enrolled in this registry.

follow.up@GBG.de

## BACKGROUND

Long-term follow-up in early breast cancer trials is of paramount importance for a comprehensive understanding of treatment efficacy and the emergence of late or chronic toxicities. This extended observation period allows for reassessment of the overall patient benefit, which may evolve beyond the initial assessment when the primary endpoint was determined. However, logistical and financial challenges often prevent extended data collection by study sites and sponsors.

To overcome this challenge, we established a patient self-reported outcome (PSRO) registry in 2010, facilitating patient consent and written correspondence to collect important health status information.



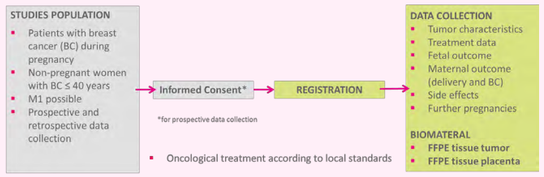
# Breast cancer in Pregnancy (BCP)

## GBG 029 / NCT00196833

BCP
Breast Cancer in Pregnancy

### Trial Design

international, multicenter, prospective/retrospective, non-interventional observational study (registry)




### Recruitment

planned: n.a.
recruited: 3669 pts

### Study Sites

planned : n.a.
active: 273

### Study Population

- patients with breast cancer during pregnancy
- non-pregnant women with breast cancer ≤ 40 years
- M1 possible

### Endpoints

Primary Endpoint:
- fetal outcome 4 weeks after delivery

Secondary Endpoints (Selection):
- maternal outcome of pregnancy
- breast cancer characteristics and
- treatment
- safety
- other outcome parameters

### Cooperations

INCIP ESGO International Network of Cancer, Infertility and Pregnancy

BIG Breast International Group

### Sponsor

GBG German Breast Group

### Contact

Coordinator:
Prof. Dr. Sibylle Loibl

Clinical Project Manager:
Dr. Ioannis Gkantiragas
bcp@gbg.de

## BACKGROUND

Breast cancer during pregnancy is often considered a rare occurrence. However, around 7% of women diagnosed with breast cancer are under 40, with a slight increase in incidence in recent years (DeSantis et al. 2011, Eisemann et al. 2013). The median age of first pregnancy in Germany is 30, and as breast cancer incidence under 40 rises, coinciding with pregnancy becomes more common due to delayed childbirth. Despite this trend, the specific incidence in Germany and Western Europe remains unclear.

In 2003, the German Breast Group initiated a registry, expanded globally through the Breast International Group, to systematically study breast cancer during pregnancy and generate evidence for treatment strategies. Amendment to the protocol allows the inclusion of a non-pregnant control group—women diagnosed with breast cancer at or below 40 years of age. These individuals can be matched to pregnant breast cancer patients as controls treated in routine clinical practice.

All women with histologically confirmed breast cancer who are pregnant and those aged 40 or younger, not pregnant but with confirmed breast cancer, can be included in the registry upon providing informed consent for data and biomaterial collection. Retrospective participants may be added anonymously without individual consent.

## STUDY OBJECTIVES

The primary goal of the BCP study is to evaluate the fetal outcome four weeks post-delivery. Secondary endpoints include maternal outcomes during pregnancy, tumor stage at presentation, biological characteristics, breast cancer therapy, type of surgery, mode of delivery (vaginal vs. caesarean), the newborn's outcome five years after diagnosis, and the breast cancer outcome five years after diagnosis. Moreover, the registry facilitates the exploration of translational research inquiries utilizing tumor specimens and placental tissue from individuals with breast cancer during pregnancy.

## STUDY REPORT

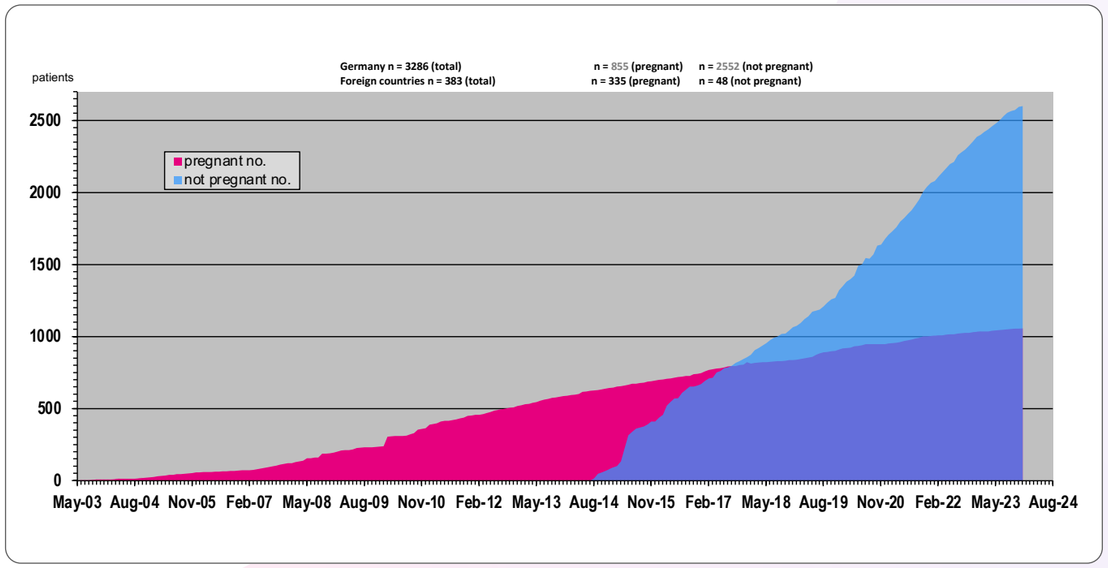
A recent evaluation of the outcome of breast cancer patients assumed that outcome of women with breast cancer treated with chemotherapy during pregnancy is comparable to young non-pregnant women. After a median follow-up of 66 months, the observed disease-free survival and overall survival were comparable for pregnant and non-pregnant patients. These results support initiation of chemotherapy for breast cancer during pregnancy when indicated according to clinical guidelines.[1,2] Further analyses (for example according to *BRCA*-status) are planned in 2024.

## PUBLICATIONS

1 Amant F, Lefrere H, Borges VF et al. The definition of pregnancy-associated breast cancer is outdated and should no longer be used. Lancet Oncol 2021; 22 (6): 753-754.
2 Amant F, Nekljudova V, Maggen C et al. Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. Eur J Cancer 2022; 170: 54-63.

### STUDY RECRUITMENT

As of 31st December 2023, a total of 3,669 patients have been registered, 3,286 in Germany (855 pregnant and 2,552 non pregnant women).



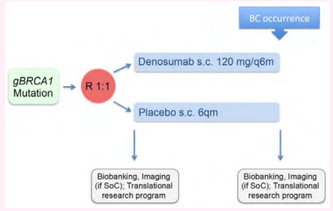

Click here for more info
bcp@GBG.de

# BRCA-P

## GBG 106 / NCT04711109

### Trial Design

randomized, double-blinded, international, phase III prevention study




### Recruitment

planned: 2918
recruited: 258/10 (DEU)

### Study Sites

planned : 6 DEU
active: 4 DEU

### Study Population

- women with g*BRCA*-1 mutation
- age ≥ 25 to ≤ 55 years
- no suspicion of breast/ovarian cancer at randomisation
- ECOG 0 or 1

### Endpoints

Primary Endpoint:
- time to the occurrence of any BC (invasive or DCIS)

Secondary Endpoints (Selection):
- time to invasive BC
- time to invasive TNBC
- time to ovarian, fallopian and peritoneal cancer
- safety

### Cooperations

UNIKLINIK KÖLN
BREAST CANCER TRIALS
ICO Institut Català d'Oncologia
MANCHESTER

### Sponsor

ABCSG

### Contact

GBG Representative:
Prof. Dr. K. Rhiem

Clinical Project Manager:
Dr. Christin Wünsche
BRCAP@gbg.de

## BACKGROUND

Individuals with a germline (g)*BRCA1* mutation - a genetic predisposition for several cancer diseases, have an increased risk to experience such a cancer diagnosis, including an approximately 70% likelihood of developing breast cancer and a roughly 40% likelihood of developing ovarian cancer over their lifetime (Casaubon et al. 2024). *BRCA1* mutation carriers can choose from several preventive actions. Enhanced early detection via more frequent and additional screening investigations is one option and preventive surgery to reduce breast cancer genesis is another. Lately, long-term follow up results from the IBIBS-II trial have lead to the approval of anastrozole as a preventive treatment for healthy individuals with an elevated risk for developing breast cancer (Sigl et al. 2024). These results are encouraging. Even though the IBIS-II study did not select for genetic alterations, it provides rationale to investigate pharmaceutical options to reduce breast cancer incidence in high risk populations. Two reports have independently shown that RANKL blockade might be a promising strategy in the prevention of breast cancer particularly in *BRCA1* mutant patients (Sigl et al. 2016, Nolan et al. 2016).

The BRCA-P study aims to explore the safety and efficacy of RANK ligand inhibitor denosumab to prevent breast cancer in healthy women with a g*BRCA1* mutation.

The Austrian Breast & Colorectal Cancer Study Group (ABCSG) is the sponsor for the BRCA-P trial in Germany and Austria. This unique breast cancer prevention study is open to women aged 25 to 55 with a g*BRCA1* mutation and intact breast tissue that has not been surgically removed (ABCSG50).

## STUDY DESIGN

BRCA-P is a prospective, randomized, double-blind, placebo-controlled, multi-center, international Phase 3 prevention trial.

Participants will be randomized 1:1 to receive denosumab 120 mg or placebo subcutaneously every 6 months for a duration of 5 years. Daily supplements, including calcium and vitamin D, are strongly advised throughout the entire course of the study treatment.

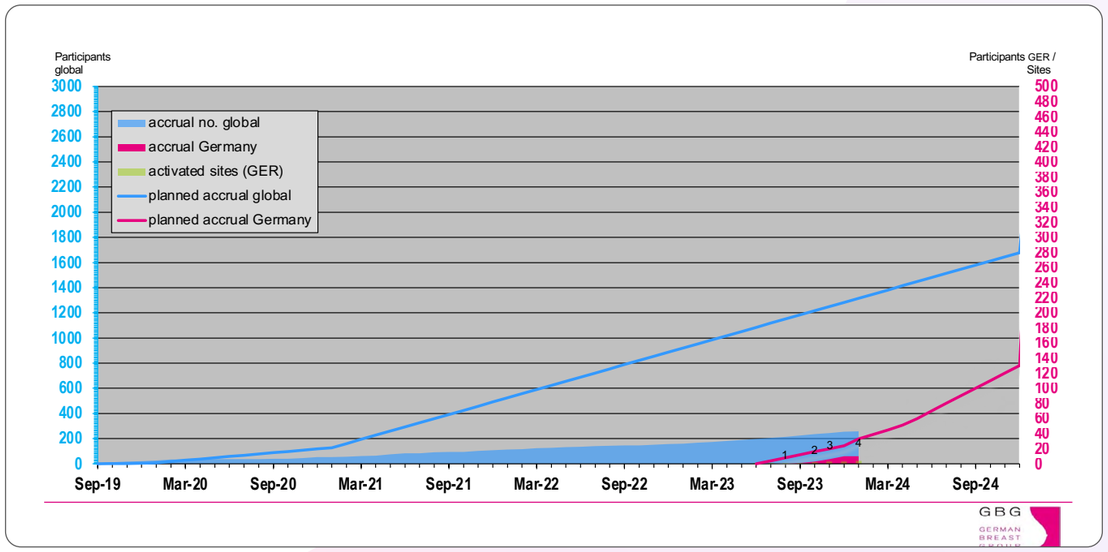
The primary objective is to evaluate the reduction in the risk of any breast cancer (invasive or ductal carcinoma in situ) in women with g*BRCA1* mutation who are treated with denosumab compared to placebo.

The primary endpoint analysis is event-driven and anticipating a 50% dropout rate at five years due to individual lifestyle changes, family planning, and the adoption of alternative prevention strategies, a total of 2918 subjects will be randomized.

Patients will undergo follow-up every 12 months after the last administration of investigational product for 5 years, utilizing clinic visits, telephone contacts, emails, or other communication means to assess oncological events, overall survival, clinical fractures, and specific adverse events.

### STUDY RECRUITMENT

It is planned to recruit 500 patients in Germany. So far, 10 of these 500 patients in Germany and 255 out of a total of 2,918 patients have been recruited globally as of December 31, 2023.




Click here for more info

BRCAP@GBG.de

# The following studies are currently in the follow-up phase. We encourage all participating sites to provide follow-up data for their patients.

## Our newest Follow-up studies: Appalaches and PADMA

### Adjuvant studies

### Appalaches
(GBG 100, NCT03609047)

is a randomized, international, phase II study. Patients aged ≥70 with stage II or III early invasive breast cancer were registered centrally at EORTC upon informed consent. Randomization, stratified by country, TNM stage, and G8 geriatric score, assigns a 2:1 ratio to receive either adjuvant endocrine therapy + palbociclib for up to 2 years (experimental) or adjuvant chemotherapy followed by endocrine therapy for ≥5 years (control).

In the experimental arm, palbociclib (125mg daily for 21 days, with 7 days off in a 28-day cycle) is given as a 2-year study medication. Standard endocrine therapy, lasting ≥5 years, can be extended based on patient and investigator agreement. Radiation therapy precedes palbociclib if indicated. Patients in the control arm undergo initial adjuvant chemotherapy (selecting from four regimens) before endocrine therapy, starting ≤13 weeks post-surgery. Radiation therapy, if needed, follows chemotherapy completion.

APPALACHES' primary goal is to compare the efficacy of endocrine therapy + palbociclib to adjuvant chemotherapy followed by endocrine therapy in older patients with ER+/HER2- stage II-III early breast cancer. Secondary objectives cover time-to-event endpoints, toxicity, treatment discontinuation, dose reduction rates, completion of oral therapy, health-related quality of life (HRQoL), and geriatric assessment effects.

Translational research involves evaluating aging biomarkers during treatment with blood samples collected at baseline, 6 months, and 3 years, centrally stored at IBBL, Luxembourg.

APPALACHES recruitment in Germany started in March 2020. A total of 373 patients are enrolled. Of these, 30 patients are from Germany. Last patient out is expected in November 2027. Planned end of study is in QI 2033.

### Metastatic studies

### PADMA
(GBG 93, NCT03355157)

is a randomized, multicenter, open-label, phase IV study. PADMA investigates whether palbociclib + endocrine therapy (ET) can substitute chemotherapy (CT) with or without ET maintenance therapy. A 1:1 randomization assigns patients to either ET with palbociclib or CT with or without endocrine maintenance therapy. Stratification factors include hormone resistance versus hormone sensitive, and symptomatic versus asymptomatic status. Treatment continues until disease progression, unacceptable toxicity, patient withdrawal, or change in initial treatment plan.

The primary objective of PADMA is to compare time-to-treatment failure (TTF) between predefined chemotherapy strategies and palbociclib + ET. TTF is defined as the time from randomization until treatment discontinuation due to disease progression, toxicity, patient preference, or death. Secondary objectives include various survival endpoints, patient wellbeing, healthcare utilization, quality of life, safety, and treatment compliance. Translational research is investigating biomarkers that predict response to CDK inhibition and circulating tumor DNA to monitor tumor progression.

Amendment 1 reduced planned patients and removed an interim analysis and an activity tracker. Amendment 2 further reduced planned patients, extended the study duration, and introduced molecular screening to identify changes of therapeutic relevance in precision medicine.

The PADMA study recruitment started in March 2018 in Germany. End of recruitment (last patient in) took place at the end of 2023. Overall, 130 patients were enrolled in the study.

## Neoadjuvant studies

### GeparDouze
(GBG 96, NSABP B-59, NCT03281954)

is an international, multicenter, prospective, randomized, double-blind, phase III trial in collaboration with the NSABP Foundation, Inc. evaluating neoadjuvant administration of atezolizumab/placebo with paclitaxel weekly in combination with carboplatin every 3 weeks followed by atezolizumab/placebo in combination with AC/EC, and then adjuvant continuation of atezolizumab/placebo in patients with triple-negative breast cancer. Recruitment was completed in May 2021 with 1,550 patients worldwide, 805 of whom were recruited in Germany. In Q2 2023, we conducted the first interim analysis of event-free survival.

### GeparOLA
(GBG 90, NCT02789332)

is a multicenter, prospective, randomized open-label phase II study that has recruited 107 patients with HER2-negative early breast cancer and homologous recombination deficiency to compare the efficacy of neoadjuvant paclitaxel and olaparib vs. paclitaxel and carboplatin followed by epirubicin/cyclophosphamide (EC). While long-term data revealed an overall inferior outcome in patients without *BRCA1/2* tumor or germline mutation treated with olaparib instead of carboplatin, no difference was found in survival outcomes between olaparib and carboplatin in patients with these mutations.

Manuscript in preparation on long-term survival of the GeparOLA study.

Oral presentation at SABCS 2022 by Prof. Dr. Peter Fasching

### GeparNuevo
(GBG 89, NCT02685059)

is a multicenter, prospective, randomized, double-blinded, placebo-controlled phase II study that has recruited 174 patients and compared pCR rates of nab-paclitaxel + durvalumab followed by epirubicin/cyclophosphamide + durvalumab vs. nab-paclitaxel + placebo followed by epirubicin/cyclophosphamide + placebo.

Manuscripts in preparation on further translational analyses of the GeparNuevo study.

Oral presentation at ASCO 2023 by PD Dr. Hanna Hübner entitled
“RNA expression levels from peripheral immune cells, a minimal-invasive liquid biopsy source to predict response to therapy, survival and immune-related adverse events in patients with triple negative breast cancer enrolled in the GeparNuevo trial.”
Link presentation

Spotlight poster presentation at SABCS 2023 by PD Dr. Hanna Hübner entitled
“Exploring circulating leukocyte RNA expression: Implications for treatment outcomes and immune-related adverse events in patients with triple negative breast cancer enrolled in the GeparNuevo trial”

### GeparX
(GBG 88, NCT02682693)

is a multicenter, prospective, 2x2 randomized, open-label, phase IIb study that has recruited 780 patients to evaluate the efficacy and safety of adding denosumab to anthracycline/taxane-containing neoadjuvant chemotherapy and the choice of weekly or 2- out of-3 weeks nab-paclitaxel schedules for primary breast cancer.

Manuscript published in Clinical Cancer Research entitled
“Rank Expression as an Independent Predictor for Response to Neoadjuvant Chemotherapy in Luminal-Like Breast Cancer: A Translational Insight from the Geparx Trial.”
IF 13.8
Link manuscript

Manuscript published in Breast Cancer Research entitled
“The Effect of Denosumab on Disseminated Tumor Cells (Dtcs) of Breast Cancer Patients with Neoadjuvant Treatment: A Geparx Translational Substudy.”
IF 8.41
Link manuscript

Poster presentation at SABCS 2023 by Prof. Dr. Rita Schmutzler entitled
“Germline mutation status of *BRCA1/2* and other breast cancer predisposition genes as predictive and prognostic biomarker: Results of the GeparX study (GeparX-BRCA).”
Link presentation

## Post-neoadjuvant studies

### KATHERINE
(GBG 77, NCT01772472)

is a multicenter, randomized, open-label phase III trial in collaboration with NSABP Foundation Inc., investigating 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. 1,487 patients have been recruited.

Manuscript published in Clinical Cancer Research entitled
“Biomarker Data from the Phase Iii Katherine Study of Adjuvant T-Dm1 Versus Trastuzumab for Residual Invasive Disease after Neoadjuvant Therapy for Her2-Positive Breast Cancer.”
IF 13.8
Link manuscript

Oral presentation at SABCS 2023 by Prof. Dr. Sibylle Loibl entitled
“Phase III study of adjuvant ado-trastuzumab emtansine vs trastuzumab for residual invasive HER2-positive early breast cancer after neoadjuvant chemotherapy and HER2-targeted therapy: KATHERINE final IDFS and updated OS analysis.”
Link presentation

### Penelope$^{B}$
(GBG 78, NCT01864746)

is a prospective, international, multicenter, randomized, double-blind, placebo-controlled, post-neoadjuvant phase III study that evaluated the addition of the CDK4/6 inhibitor palbociclib as post-neoadjuvant treatment for HER2-/HR+ patients with high relapse risk after neoadjuvant chemotherapy (NACT). The study has recruited 1,250 patients, 434 of whom in Germany.

Manuscripts in preparation on premenopausal patients and on *BRCA1/2* mutated patients in the PENELOPE$^{B}$ study.

Manuscript being prepared on the topic of HTG in Penelope$^{B}$.

Poster presentation at SABCS 2023 by Prof. Dr. Hervé Bonnefoi entitled
“Overall survival and disease recurrence rates in patients with invasive lobular breast cancer of the Penelope$^{B}$ cohort.”
Link presentation

Poster presentation at ASCO 2023 by Prof. Dr. Nicholas Turner entitled
„Detection of circulating tumor DNA following neoadjuvant chemotherapy and surgery anticipates early relapse in ER positive and HER2 negative breast cancer, analysis from the PENELOPE$^{B}$ trial”
Link presentation

### Destiny-Breast05 / TruDy
(GBG 103, NCT04622319)

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 HER2+ primary breast cancer who have residual invasive disease in breast or regional lymph nodes following neoadjuvant chemotherapy. In collaboration with the sponsor Daiichi-Sankyo and AGO-B and the Spanish Breast Cancer Research Group (SOLTI), a total of 1,635 patients were recruited worldwide, of whom 69 in Germany.

## Adjuvant studies

### PALLAS
(GBG 87, NCT02513394)

is a multicenter, prospective, international, randomized, open-label, adjuvant phase III study evaluating the addition of 2 years of palbociclib to standard adjuvant endocrine therapy for patients with HR+/HER2- early breast cancer. In collaboration with ABCSG, NSABP Foundation Inc., PrECOG, LLG., and the Breast International Group, 5,796 patients were recruited worldwide.

Oral presentation presented at SABCS 2023 entitled
“Protocol-defined biomarker analysis in the PALLAS (AFT-05) adjuvant trial: Genomic subtype derived from RNA sequencing of HR+/HER2- early breast cancer.”

Poster presentation presented at SABCS2023 entitled
“Clinical characterization, prognostic and predictive values of HER2-low in early breast cancer in the PALLAS trial.”

### OLYMPIA
(GBG 82, NCT02032823)

is a multicenter, double-blind, parallel group, placebo-controlled, randomized phase III trial investigating the efficacy of olaparib compared with placebo in an adjuvant/post-neoadjuvant setting in patients with germline BRCA1/2 mutations and high-risk HER2- early breast cancer trial. 1,836 patients were recruited.

## APHINITY
(GBG 67, NCT01358877)

is an adjuvant, prospective, two-arm, randomized, multicenter, international, double-blind, placebo-controlled phase III adjuvant trial comparing the safety and efficacy of a combination therapy with two anti-HER2 agents (trastuzumab and pertuzumab) added to chemotherapy, compared to chemotherapy with trastuzumab alone. In collaboration with Genentech, Inc., and the Breast International Group, 4,805 patients were recruited.

Manuscript in preparation on further analyses in the Aphinity Trial.

Oral presentation at ESMO Virtual Plenary 2022 by Prof. Dr. Sibylle Loibl entitled
“Updated results of APHINITY at 8.4 years median follow up.”
**Link presentation**

## Alexandra/Impassion030
(GBG 98, NCT03498716)

is an international, multicenter, randomized, open-label, controlled phase III trial comparing atezolizumab (anti PD-L1 antibody) in combination with adjuvant Anthracycline/Taxane-based chemotherapy versus chemotherapy alone in patients with early operable triple-negative breast cancer. In collaboration with Breast International Group, Alliance Foundation Trials (AFT), Institut Jules Bordet/Clinical Trials Support Unit (IJB/CTSU), and Frontier Science & Technology Research Foundation, Inc., 2,203 patients were recruited worldwide.

### Metastatic studies

## PATINA
(GBG 94, AFT-38, NCT02947685)

is an international, multicenter, randomized, open-label, phase III trial evaluating the efficacy and safety of palbociclib + anti-HER2 therapy + endocrine therapy versus anti-HER2 therapy + endocrine therapy after induction treatment for HR+/HER2+ metastatic breast cancer. In collaboration with Alliance Foundation Trials (AFT), LLC, 496 patients were recruited worldwide and 34 in Germany.

## AURORA
(GBG 85, NCT02102165)

is an exploratory, multinational, collaborative molecular screening programme designed to better understand the genetic aberrations in metastatic breast cancer, and to discover the mechanisms of response or resistance to therapy, and ultimately to identify the right therapy for each individual patient. 1,160 patients were recruited.

Poster Spotlight Presentation presented at SABCS 2023 entitled
“Clinical and Genomic Features of ER-Positive/HER2-negative Metastatic Breast Cancer in AURORA Molecular Screening Initiative (BIG 14-01): Mechanisms of Endocrine Therapy Resistance and Implications for Adjuvant Approaches.”

## INSEMA
(GBG 75, NCT 02466737)

is a prospective, multicenter, randomized, surgical trial comparing 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). A total of 5,545 patients from 152 trial centers were recruited into the study. Of these, 5387 patients came from Germany and 158 patients from Austria. A total of 3236 patients were integrated into the patient self-reporting outcome (PSRO), so that further analyses for evaluation will be carried out together with these follow-up data.

Manuscript published in European Journal of Cancer entitled
“Deep Learning to Predict Breast Cancer Sentinel Lymph Node Status on Insema Histological Images.”
**Link manuscript**

IF 10

Poster presented at ESMO BC 2023 entitled:
“Deep learning-based whole slide image analysis to predict sentinel node status in the INSEMA cohort”
**Link presentation**

# AMiCA

## GBG 97 / NCT 03555877

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

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

## BACKGROUND

At the time of trial conception, clinical practice guidelines recommended the use of endocrine therapy (ET) as 1st line therapy for patients with hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (BC). However, about 30% of patients received chemotherapy. Although 1st line chemotherapy is effective in this subset of patients, progression-free survival (PFS) is usually around 6-8 months.

Maintenance treatment strategies are standard of care in breast cancer, and also in other tumor entities, like lung cancer (Gentzler et al. Ther Adv Med Oncol 2014), colorectal cancer (Esin et al. Cancer Treat Rev 2016), and lymphoma (Hagemeister et al. Curr Oncol Rep 2010). Maintenance treatment with ET is an accepted treatment strategy in everyday clinical practice in the management of patients with HR+/HER2- advanced BC, and at the time of trial conception, but prospective data were lacking.

Cyclin-dependent kinase (CDK) 4/6 inhibitors combined with ET are the standard-of-care for ER+/HER2- metastatic BC, with improved PFS and overall survival (OS), and a good toxicity profile seen in several trials (Finn et al., N Engl J Med 2016; Hortobagyi et al., N Engl J Med 2016; Im et al., N Engl J Med 2019; Slamon et al., N Engl J Med 2020). Also, ET plus CDK4/6 inhibition yields similar or better efficacy compared to chemotherapy (Martin et al., Ann Oncol 2021; Park et al., Lancet Oncol 2019) and is associated with less toxicity, making it the preferred treatment, unless a patient has imminent organ failure. Ribociclib is a CDK 4/6 inhibitor that has been evaluated in several combination phase I-III clinical trials with ET and has shown efficacy and safety in patients with HR+/HER2- metastatic BC.

The AMICA trial evaluated the impact of the addition of the CDK4/6 inhibitor ribociclib to ET maintenance treatment of physicians' choice in pre- and post-menopausal women with HR+/HER2- metastatic BC with at least stable disease after first line chemotherapy and with up to one line of ET prior to chemotherapy.

## STUDY DESIGN AND OBJECTIVES

Patients were initially randomized to receive or not receive open-label treatment with ribociclib in addition to their maintenance ET. Later, the trial was amended after inclusion of 37 patients and changed into a single-arm study, and all subsequent patients received ET + ribociclib. Due to slow accrual of the trial, and in accordance with the Independent Data Monitoring Committee recommendations, the trial was prematurely stopped on December 31st, 2021.

AMICA primarily aimed to estimate the median PFS of an ET maintenance therapy with ribociclib after first line chemotherapy. Secondary objectives included the median OS, safety, treatment compliance, clinical benefit rate, as well as patient-reported outcomes. Potential biomarkers as well as the role of several mutations predicting response to treatment will be determined later.

## STUDY REPORT

Between March 2018 and July 2022, 53 patients were enrolled and started therapy in the AMICA trial (43 received ribociclib and ET, 10 received ET only). Among patients who received ribociclib + ET, the median PFS was 4.75 months [95%CI: 1.0, 10.3]. Among patients who received ET monotherapy, the median PFS was 16.55 [2.7, 29.2]. The median OS was not reached for the cohort of patients who received ribociclib + ET, while the median OS for patients who received ET only was 22.5 months [4.4, not applicable (NA)]. For patients who received ribociclib + ET, 3 patients (7.0%) had a complete response, 10 patients (23.3%) had partial response, 15 patients (34.9%) had stable disease, 10 patients (23.3%) had progressive disease, and 5 patients (11.6%) were not evaluable.

The toxicity profile observed in the study was in line with the known safety profile of ribociclib with no new safety concerns. A total of 17 serious adverse events (SAEs) were reported in 12 patients, mainly being gastrointestinal disorders (4 SAEs), infections and infestations (3 SAEs), and nervous system disorders (3 SAEs). Adverse events were tolerated and were managed with dose reductions or interruptions. Most treatment discontinuations occurred due to tumor progression and were not treatment related. Quality of life was comparable between study baseline and at the end of the trial.

During treatment and in the 30 days following last treatment, 15 patients died – 14 (93.3%) due to tumour-related causes and onedue to pneumonia. Of all SAEs, one was fatal but was not tumor- or treatment-related. Furthermore, 12 patients treated with ribociclib + ET reached the end-of-study period, 10 of whom (83.3%) continued ribociclib after the study ended.

The results of the AMICA trial demonstrate a promising efficacy of of ribociclib added to ET as a maintenance treatment after at least stable disease following first line chemotherapy in patients with HR+/HER2- metastatic BC. Treatment with ribociclib has an acceptable safety profile and may delay tumor progression after chemotherapy in this patient population.

## PUBLICATIONS:


1. Decker T, Lüdtke-Heckenkamp K, Melnichuk L, et al. Anti-hormonal maintenance treatment with the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in hormone receptor positive/HER2 negative metastatic breast cancer: A phase II trial (AMICA). Breast. 2023; 72, 103575.
2. Decker T, Denkert C, Lübbe K, et al. Anti-hormonal maintenance treatment with or without the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in hormone receptor positive/HER2 negative metastatic breast cancer: a phase II trial (AMICA) GBG 98. Ann Oncol. 2018; 29 (suppl_8): viii90-viii121.
3. Decker T, Lüdtke-Heckenkamp K, Melnichuk, L, et al. Anti-hormonal maintenance treatment with the CDK4/6 inhibitor ribociclib after 1st line chemotherapy in hormone receptor positive/HER2 negative metastatic breast cancer: a phase II trial (AMICA). San Antonio Breast Cancer Symposium, December 6-10, 2022.


Official results of the AMICA trial were published in 2023 in the journal The Breast **Click here for more info**

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

**Study Group:**
GBG GERMAN BREAST GROUP

**Sponsor:**
German Breast Group

**Study Chairs:**
Prof. Dr. Sibylle Loibl,
German Breast Group, Neu-Isenburg
Prof. Dr. med. Thomas Decker,
Gemeinschaftspraxis Onkologie Ravensburg,
Ravensburg

**Contact:**
Amica@gbg.de

# Translational Research & Biobanking

## Spatial analyses with CellDIVE (Leica Microsystems) at the Institute of Pathology, University Hospital Marburg

In order to capture and visualize intratumoral heterogeneity and expand the Institute's research equipment for spatial analyses, the Institute of Pathology at the University Hospital Marburg has set up CellDIVE (Leica Microsystems) for multiplex immunofluorescence imaging in 2023. By using fluorophore-conjugated antibodies, it is possible to detect up to 48 different targets on one single FFPE slide processing a maximum of four antibodies simultaneously. By integrating these datasets to the deep learning neuronal networks of HALO, a modular designed analyzing software by Indica Labs, it is possible to generate phenotypes and perform AI-based analyses to create a precise geographic reflection of the tumor microenvironment, its interactions and functional states up to a single cell level. The Institute of Pathology at the University Hospital Marburg has focused on investigating the immuno-stromal reactions within the most common tumor types and has therefore developed and validated a panel specifically for larger clinical trials using tissue microarrays (TMAs).

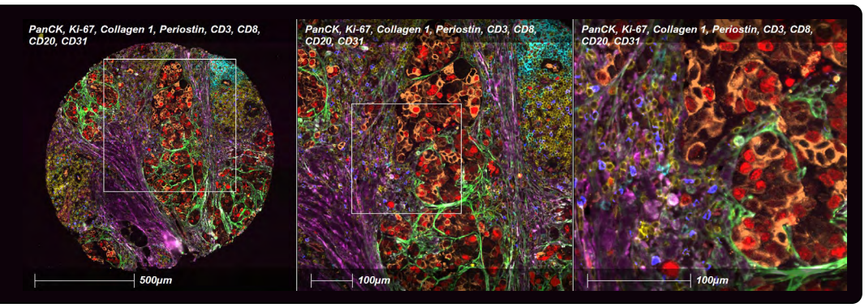



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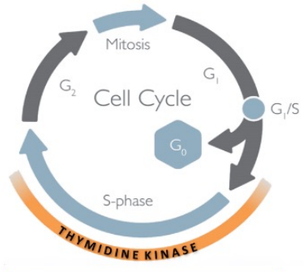
**Figure 1 Multiplex immunofluorescence imaging on TNBC with CellDIVE.**
The TMA-Core shows a subset of antibodies from the Immuno-Stroma-Panel validated at the Institute of Pathology of the University Hospital Marburg. (PanCK=orange, Ki-67=red, Collagen 1=magenta, Periostin=green, CD3=yellow, CD8=dark-blue, CD20=light-blue, CD31=bordeaux-red)

## New Research Activities

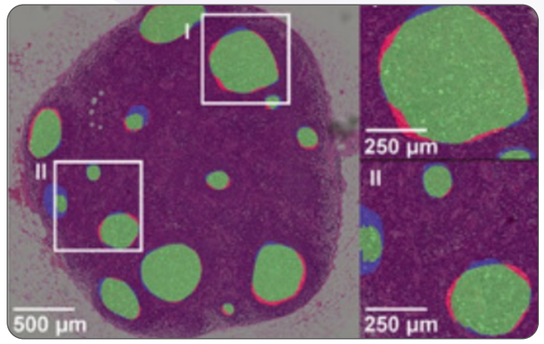
**TK (thymidine kinase) monitoring in Penelope$^{B}$ serum samples**

Thymidine kinase isoform a (TKa) is an enzyme that has a key function in the synthesis of DNA. The expression and activity of TKa is tightly linked to the cell cycle and can therefore be used as a biomarker for cell proliferation. TKa diffuses from proliferating tumor cells to the bloodstream, and its activity can be measured in serum samples from blood. Several clinical studies have investigated the possible use of this proliferation marker in clinical routine for precise prognosis and early evaluation of therapy efficacy in breast cancer.
In this project, GBG cooperates with Prof. Harry Bear from VCU (Virginia Commonwealth University, USA) and BIOVICA, a Swedish biotech company developing blood-based biomarker assays. Using BIOVICA's DiviTum®TKa assay, the serum samples collected at several timepoints (before, during and after the treatment phase) of the Penelope$^{B}$ study will be screened for TKa activity. The results will then be correlated to the available outcome data to evaluate the prognostic and predictive role of TKa.




**Immune phenotyping of lymph node tissue from TNBC patients by artificial intelligence (AI)**

Lymph nodes (LNs) are highly organized secondary lymphoid organs, reflective of the dynamic and systemic immune response to the presence of cancer. Dynamic structures within lymph nodes that act as immunological hubs for B cells are so-called germinal centers. It was previously shown that a lack of germinal center formation in axillary lymph nodes of BC patients leads to a higher risk of developing distant metastasis (Grigoriadis et al., JP Clinical Research 2018; Lui et al., npj breast cancer 2021). However, the identification of germinal centers in FFPE tissue sections by conventional histological evaluation of a pathologist is very time consuming. Therefore, the lab of Prof. Anita Grigoriadis (King's College London) has recently implemented deep learning methodologies to capture germinal centers and sinuses in LNs on digitized whole slide images (WSIs). In a cooperation with Prof. Grigoriadis, WSIs from the GAIN-2 trial cohort will be analyzed by AI algorithms to evaluate the presence of germinal centers, and subsequently correlated to outcome data.




Germinal centres

## Update on ongoing projects

**SATURN$^{3}$ - an interdisciplinary research network to address tumor heterogeneity**

The aim of the SATURN3 consortium is to investigate the biological background of intratumoral heterogeneity (ITH), which can be the cause of resistance to therapy and the development of metastatic clones. For this purpose, it is necessary that tumor biopsies are not only taken from patients when they are first diagnosed, but that tissue samples are taken from the tumors several times during the course of the disease. In this way, the researchers also obtain tumor cells that have already developed resistance.
We will contribute to this research consortium by providing samples from our large tumor tissue bank for validation of biomarkers. Additionally, GBG is currently setting up the "MOMENTUM" patient registry, which focuses on patients with therapy-resistant tumors and tissue collection over a long period of time. This sample collection will contribute significantly to research into tumor heterogeneity and thereby help to develop new therapeutic strategies in the clinical setting.

**Gut microbiome analyses within the "ONCOBIOME" project**

"ONCOBIOME" is an international collaboration project, which is coordinated by Prof. Laurence Zitvogel (Institute Gustave Roussy) and funded by the EU research program Horizon 2020. The aim of the 5-year running project is to determine the relationship between intestinal microbial signatures and the prognosis and treatment resistance in four common cancer entities including breast cancer.
GBG participates in the project with sample collections (tumor tissue and stool samples) as well as expertise in clinical translational research. In the GeparDouze study, stool samples were collected before start of the study therapy that will be analyzed for their microbiome composition. Additionally, HTG EdgeSeq expression data have been generated at the Institute of Pathology at Marburg (Prof. Denkert), using the corresponding pre-therapeutic FFPE tumor samples.
The role of gut microbiome signatures in the development of cancer have been addressed in a recent review article (Gut OncoMicrobiome Signatures (GOMS) as next-generation biomarkers for cancer immunotherapy. Thomas et al. 2023, Nature Reviews Clinical Oncology).

**New proposals may also be submitted by groups that are currently not represented in any GBG subboard.**

**gbg.de/de/forschung/trafo.php**

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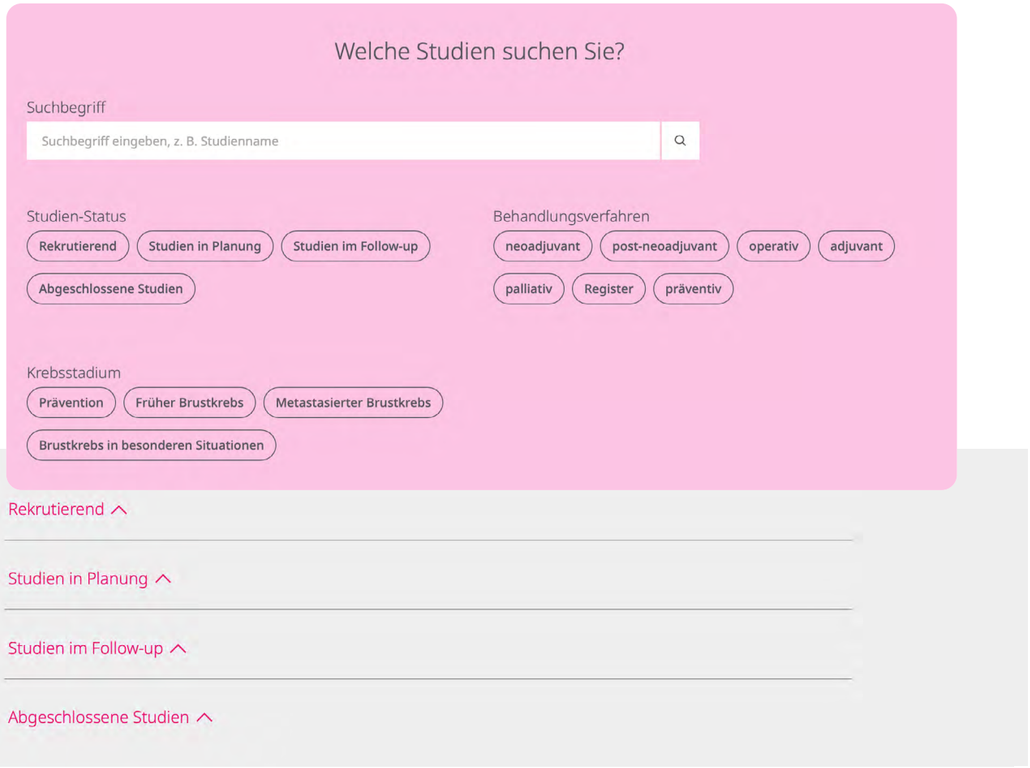
# How to use our new Study Finder on GBG website




The well-known Study Finder at the end of the Annual Scientific Report has been replaced by a digital and optimized version on our website. You can find it under the following link: https://www.gbg.de/studien

The user interface offers a range of search parameters: among other things, you can search for relevant studies directly using a search term such as the study name or a drug name. You can also refine your search by selecting the study status (recruitment, planned, follow-up, completed), the cancer stage (screening, early breast cancer, metastatic breast cancer, breast cancer in special situations), and the treatment modality (neoadjuvant, post-neoadjuvant, surgical, adjuvant, palliative, preventive, registry).

If your search is successful, you will see tiles below the Study Finder with study suggestions that match the search criteria. This tile view contains all the necessary information to give you a brief overview of the studies. If you are interested in the details of the study, you can click through to study page with just one click.

**Click here for more info**





# Thank you ...

... **to all patients** who have participated or are still participating in our trials. Without you, our clinical studies would be worthless.

... **to all our Study Chairs**, our investigators and all their team members at participating centers for their commitment and efforts so far.

... **to all our partner organizations**, collaborating study groups, Independent Data Monitoring Committees (IDMC), Ethics Committees and competent authorities for their great support.

... **to all members of our Subboard and Scientific Board members** for their ideas, knowledge, and tireless ambition to advance clinical research.

... **to all our pharmaceutical partners** for providing drugs and study budget to realize our clinical research projects.

## SOME IMPORTANT LINKS

GBG

GERMAN
BREAST
GROUP

Leading in Breast Cancer Research

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