Heilung durch Innovation, Kompetenz und Partnerschaft

Annual Scientific Report

2022
Heilung durch Innovation, Kompetenz und Partnerschaft
Index

Introduction 7

New Study Concepts and Methodologies 47
GBG 119: Cambria-1 (Interview with Prof. Stickeler) 48
GBG 118: PREcoopeRA (Interview with Prof. Leibl) 50
NeoRad (Interview with Prof. Budach) 52

Recruiting Studies 55
GBG 105: GeparPiPPa 56
GBG 103: TruDy / DESTINY-Breast05 57
GBG 102: SASCa 59

Adjuvant
GBG 100: APPALACHES 62
GBG 98: ALEXANDRA/Impassion030 64

Metastatic
GBG 93: PADMa 66

Surgical
GBG 104: EUBREAST-01 68
GBG 101: TAXIS 70

Register
GBG 107: ETERNITY® registry 72
GBG 79: Brain Metastases in Breast Cancer (BMBC) 73
GBG 71: Patient Self-Reporting Outcome (PSRO) Registry 75
GBG 29: Breast Cancer in Pregnancy (BCP) 76

Follow-up Activities 79
GBG 96: GeparDouze 81
GBG 90: GeparOLA 81
GBG 88: GeparX 81
GBG 77: KATHERINE 82

Post-neoadjuvant
GBG 78: Penelope® 83

Adjuvant
GBG 91: TANENDOX 84
GBG 87: PALLAS 84
GBG 82: OLYMPIA 84
GBG 67: APHINITY 85

Metastatic
GBG 94: PATINA 86
GBG 85: AURORA 86

Surgical
GBG 75: INSEMA 87

Completed Studies 89
GBG 97: AMICA 90
GBG 74: Genevieve 92

Translational Research & Biobanking 95

GBG Study Finder 2023 98
Introduction

1. About the German Breast Group 8
2. Infrastructure of the German Breast Group 8
3. Cooperations with other study groups 10
4. Publications in 2022 12
   4.1. Peer-reviewed articles in 2022 12
   4.2. Peer-reviewed reviews in 2022 14
   4.3. Congress contribution in 2022 15
   4.4. GBG-Publications Grading System 17
   4.5. Guideline for Authorship 18
   4.6. Oral and poster presentations 19
Introduction

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1. About the German Breast Group

The German Breast Group (GBG), a leading cooperative study group in the field of breast cancer in Germany, provides the comprehensive management of clinical trials in all major therapeutic categories: prevention, neoadjuvant, adjuvant, and palliative. The vision of the GBG is best described as healing by innovation, adjuvant, and palliative. The GBG collaborates with experts from the fields of neoadjuvant, adjuvant, palliative, surgical and translational research. Members of the GBG are to the highest standard of the International Conference on Harmonisation of Good Clinical Practice (ICH-GCP1998) and if necessary regulatory requirements. We offer a comprehensive range of services, including:

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

2. Infrastructure of the German Breast Group

Participating sites

Participating sites are actively recruiting sites. When a subboard decides to launch a new study, the GBG Forschungs GmbH plans, organizes and manages the study, in line with the GBG’s belief that a clinical study must be directly related to the potential improvement of a therapeutic strategy and its benefits for the patient. Thus, a strict quality monitoring is essential and is ensured by following the GBG in-house standard operating procedures (SOP). The members of the subboards meet once a year face-to-face and 3 times virtually. Our subboards have been active discussing innovative study designs.

Recruitment of patients

Patients are recruited through the participating sites which provide detailed information on the GBG studies to the patient. Patients are treated according to the latest scientific findings and are carefully controlled and monitored. Thanks to the clinical trials, breast cancer treatment strategies and clinical guidelines have significantly improved over time and the mortality has decreased over time. The annual patient recruitment is shown in figure 2.

Subboards

Five subboards were active during the last year in the fields of neoadjuvant, adjuvant, palliative, and surgical therapy as well as in the field of translational research. Members of the subboards are all well-known professionals, experienced in treating breast cancer patients and active in the field of breast cancer research and clinical studies. When a subboard decides to launch a new study, the GBG Forschungs GmbH plans, organizes, and manages the study. Thanks to the GBG’s belief that a clinical study must be directly related to the potential improvement of a therapeutic strategy and its benefits for the patient, our current studies, research results and further innovative study designs.

The members of our subboards in 2022 are shown below:

Neoadjuvant
Prof. Dr. J. U. Böhmker, Berlin
Prof. Dr. V. Bylic Radose, Wuppertal
Prof. Dr. C. Denkert, Marburg
Prof. Dr. P. Fasching, Erlangen
Dr. C. Hanusch, München
Prof. Dr. A. Hartkopf, Ulm
Prof. Dr. J. Hubeke, St. Gallen
Prof. Dr. Ch. Jackisch, Offenbach
Dr. T. Link, Dresden
Prof. Dr. S. Losel, Neu-Isenburg
PD Dr. M. Reinsch, Essen
Prof. Dr. K. Rihm, Köln
Prof. Dr. A. Schneeweiss, Heidelberg
Prof. C. Solbach, Frankfurt am Main
Prof. Dr. M. Untch, Berlin

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

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Prof. Dr. M. Untch, Berlin
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Prof. Dr. K. Rhiem, Köln
PD Dr. M. Reinisch, Neu-Isenburg
PD Dr. M. Schmidt, Mainz
Prof. Dr. S. Losel, Neu-Isenburg
Prof. Dr. F. Marmé, Mannheim
Dr. L. Michel, Heidelberg
Prof. Dr. T. Reimer, Rostock
PD Dr. M. Reinsch, Essen
Dr. S. Schmaltzloch, Kassel
Prof. Dr. M. Schmidt, Mainz
PD Dr. B. Sinn, Berlin
Prof. Dr. E. Stickeler, Aachen
Prof. Dr. M. Untch, Berlin
Introduction

2. All major modifications to the trial protocol regarding:
- Objectives, the scientific impact of the findings, when the protocol-specified number of recruited patients or events has been reached.
- Safety observations, monitoring and consultation.
- The interim and final efficacy analysis of trials, when the protocol-specified number of recruited patients or events has been reached.

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

International Research Group
- ABCSG: Austrian Breast & Colorectal Cancer Study Group
- AFT: Alliance Foundation for Clinical Trials in Oncology
- AGO: Arbeitsgemeinschaft Gynäkologische Onkologie
- AGO-B: Breast Study Group
- ASAN Medical Center
- BREAST CANCER TRIALS GROUP
- BIG: Breast International Group
- BOOG: Borststuker Onderzoeksgroep Nederland
- CCTG: Canadian Breast Cancer Trials Group
- CIRG: Cancer International Research Group
- CRUK: Cancer Research UK
- CTI: Cancer Trials Ireland
- CTRU: Clinical Trials Research Unit
- DKG: Deutsche Krebsgesellschaft
- EBCTCG: Early Breast Cancer Trialsists’ Collaborative Group
- EORTC: European Organisation for Research and Treatment of Cancer
- Fondazione Michelangelo: Scientific organization based in Italy
- Frontier Science foundation
- GEICAM: Grupo Español de Investigación del Cáncer de Mama
- IBCSG: International Breast Cancer Study Group
- ICCG: International Collaborative Cancer Group
- ICR CTSU: The Institute of Cancer Research
- IDDI: International Drug Development Institute, Inc.
- IKP Stuttgart: Dr. Margarete Fischer-Bosch-Institut für Klinische Pharmakologie
- JBCRG: Japanese Breast Cancer Research Group
- JBGRC: Japanese Breast Cancer Research Group
- JCG: Japanese Cancer Research Group
- JCOG: Japan Clinical Oncology Group
- JRG: Japan Research Group
- KCI: Korean Clinical Oncology Group
- KF: Korean Friends
- LACOG: Latin American Cooperative Oncology Group
- NOGGO: Nord-Ostdeutsche Gesellschaft für Gynäkologische Onkologie
- NRG: Oncology
- NSABP: National Surgical Adjuvant Breast and Bowel Project
- SAKK: Swiss Group for Clinical Cancer Research
- SBBG: Scandinavian Breast Cancer Group
- SOLTI: Grupo Español de Estudio del Tratamiento y otras Estrategias Experimentales en Tumores Solidos
- UCBG: French breast cancer intergroup UNICANCER
- UNICANCER: UNICANCER Group, France
- Uniklinik Köln
- Universitatsklinikum Hamburg-Eppendorf
- Universitätsspital Basel, Bruzzentrum
- UZL: University Hospital of Leuven
- WSG: Westdeutsche Stufengruppe
- ZKS Köln: Zentrum für klinische Studien
4. Publications in 2022

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

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

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

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

4.1. Peer-reviewed articles in 2022


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


4.2. Peer-reviewed reviews in 2022


4.3. Congress contribution in 2022

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


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


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


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

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

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


ECP: European Congress of Pathology, September 3-7, 2022

DGP: Deutsche Gesellschaft für Pathologie, June 9-11, 2022

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


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

Karn T, Denkert C, Rey J, et al. Low TMB as predictor for additional benefit from neoadjuvant immunomodulatory therapy for hormone receptor-positive breast cancer. Poster Session #587, poster.

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

ESMO-Breast Cancer May 3-5, 2022
Furlanetto J, Marmé F, Thode C, et al. Ovarian function in young patients (pts) treated with postneoadjuvant palbociclib (PAL) and endocrine therapy (ET) for hormone receptor (HR)-positive, HER2-negative early breast cancer (BC): explorative analysis in Penelope2. ESMO Breast 2022; 60OM, mini oral presentation.


Reinisch M, Blohmer JU, Link T, et al. Patient quality of life (QoL) from the GeparX trial on the addition of denosumab (Dmab) added to two different nab-paclitaxel (nPa) regimens as neoadjuvant chemotherapy (NACT) in primary breast cancer (BC). ESMO Breast 2022; 170P, poster presentation.


4.4. GBG-Publications Grading System
To set internal publication goals and to measure our own success, we established our GBG in-house grading system as follows:
• 7 GBG points for preparation or final publication in a high quality peer-reviewed journal with an impact factor greater than 5,
• 5 GBG points for publication preparation or final publication in a journal with an impact factor of less than 5,
• 3 GBG points for an oral presentation or poster discussion,
• and 2 GBG points for a poster presentation at an international congress.

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

Figure 4: GBG and official Impact Factor (IF) in 2022
4.5. Guideline for Authorship

In order to guarantee a maximum of transparency when assigning the co-authorship we have established an internal GBG guideline for authorship. The details are listed below:

**General Rules**

- Important positions: 1st author, senior author, corresponding author
- Shared authorship for 1st and 2nd author, if applicable
- Separate rules for:
  - Main publication on primary endpoint
  - Publications on secondary endpoints
  - Translational research publications
  - No honorary authorships
- Author positions can be transferred to a junior person, if also involved in the study

**Score for Authors**

(Will be used to select and rank co-authors)

- 1 point for every fulfilled criteria:
  - Regular participating in TCs and meetings of Subboard and/or Protocol board
  - Protocol writing
  - Recruitment of new participating sites
  - Statistical Analysis Plan development
  - Manuscript preparation
    - In-time response to emails concerning the trial and the manuscript within 4 weeks
    - In-time response for COI (within 2 weeks)
- Negative point for subsequent publications

**What to do before submission**

- Select journal
- Ask potential authors for their interest to become co-author
- Present proposed list of authors to Subboard and/or Protocol board
- Discuss manuscript amongst all authors
- Collect COI

**Publication on primary endpoint**

- 1st author (or Co-PI group 1)
- Subboard / protocol board members according to Score
- Best recruiters
- Biometrician
- Senior author (Co-PI group 2, or group chairman)
- Adherents with study team, subboard / protocol board member, and all other recruiters with > patients as “on behalf of the study group”

**Publication on secondary endpoints / Retrospective analyses**

- 1st author, „project“ leader
- Subboard / protocol board members according to Score
- Best recruiters for this subproject
- Biometrician
- PI or group chairman (if involved in subproject)

**Publications on translational research project**

- Project leader (should prepare manuscript)
- Involved team member of this TRAMO project
- TRAMO board / protocol board member
- Biostatistician
- 1 of local pathologists providing most tumor tissue
- Biostatistician
- PI (if involved in TRAMO project)

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4.6. Oral and poster presentations

**TROP-2 characteristics**

- shedded cell surface antigen
- In vivo biomarker in patients
- Calcium signal transducer
- Regulating cancer growth and invasion
- Expressions in 10% of solid tumors
- Cutoffs in > 95% of solid tumors
- Sensitive to patients with PIK3CA and HER2 mutations

---

**TROP-2: therapeutical target**

- Antibody drug conjugate
- Induces apoptosis
- Doublet study with taxane and TROP-2 monoclonal antibody

**TROP-2: open questions**

- TROP-2 expression - backscatter (biomarker): efficacy
- Phase III randomised study (core TROP-2 data)
- Best objective response: 1 Eleven OS with lower TROP-2 expression
- TROP-2: therapeutical target efficacy
- TROP-2: open questions

---

**Cut off Finder TROP-2 membranous (mTROP-2)**

**Best Cut off for mTROP-2 is 1.5 % (~ 2 %)**

---

**Impact of TROP-2 and its cellular localization on prognosis of breast cancer – an analysis of 1164 tumors from a prospective clinical trial**

-Cristina C. Westhoff1, Bruno V. Sinn, Anika Pehl1, Rolf-Peter Jank1, Christina C. Westhoff1, Josef Rückert, Paul Lin H et al.

-PI (if involved in TRAMO project)

---

**Sacituzumab-govitecan:**

- Antibody drug conjugate (ADC)
- Induces apoptosis
- Doublet study with taxane and TROP-2 monoclonal antibody

---

**GAIN**

(DCP Jahrestagung 2022)
**Introduction**

- Large TMA-based study on differential expression of TROP-2 in BC.
- cTROP-2 > 2% & mTROP-2 > 2%.
- Lower OS DFS & OS for all patients and some subgroups, in particular with higher cut-off.
- Partial discordance with previous studies.
- Cancers lack of differential TROP-2 expression, permitting an ongoing SASCIA study by GBG.

**PENOLEPOB**

**Patients Flow and baseline characteristics**

- Level of estradiol and FSH during the study.
- Rates of Postmenopausal Levels of Estradiol and FSH.
- Rates of Postmenopausal Levels of Estradiol and FSH.

**Summary and Conclusions**

- Palbociclib does not seem to impact the ovarian reserve as defined by AMH levels.
- Palbociclib did not influence estradiol and FSH levels significantly when added to hormone therapy.

**Explorative Analysis in Penelope-B**

- Ovarian Function in Young Patients Treated with Postmenopausal Palbociclib and Endocrine Therapy for HR-positive, HER2-negative Early Breast Cancer: Explorative Analysis in Penelope-B.

- Summary and Conclusions.
Low TMB as predictor for additional benefit from neoadjuvant immune checkpoint inhibition in triple negative breast cancer

## Background:
- High TMB is anticipated to predict immune checkpoint blockade (ICB) response.
- However, high TMB also predicts pCR after chemotherapy without ICB in the neoadjuvant GeparNuevo TNBC trial (PMID 33661134).

## Methods:
- We obtained TMB from WES for 149 of 174 GeparNuevo TNBC patients.
- We used the previously published cut-off of the upper tertile (2.05 mut/Mb).
- Median follow-up was 44.3 months.

## Results:
- 3 yr DFS in the durvalumab-chemo combination arm and the chemo-only arm was 95.7% (93.4-98.9%) and 76.4% (67.3-85.6%), respectively.
- Within high TMB tumors DFS was similar between both arms (HR 0.91 [95%CI 0.34-2.48], P=0.93).
- But within the low TMB group, DFS was significantly better in the durvalumab arm than in the placebo arm (HR 0.23 [95%CI 0.06-0.79], P=0.01, interaction P=0.17).

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

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

Breast cancer treatment has become the standard of care for HER2-positive (HER2+) breast cancer. HER2+ tumors are characterized by the overexpression of the HER2 protein, which plays a critical role in cell growth and survival. Despite advances in targeted therapy, HER2+ breast cancer patients still face significant challenges, including a lower response to chemotherapy and anti-HER2 therapy, especially in HER2+/HR+ tumors. This has led to a growing interest in developing more targeted and effective therapeutic approaches.

Several attempts have been made to use a more targeted approach in HER2+ breast cancer treatment. One such attempt is the use of PIK3CA inhibitors, which target the PI3K/AKT/mTOR pathways. In addition, inhibition of these pathways has been shown to have synergistic effects with other anti-cancer therapies.

Several studies have been conducted to evaluate the efficacy and safety of PIK3CA inhibitors in the treatment of HER2+ breast cancer. One such study, GeparPiPPa, evaluated the use of tucatinib in combination with pertuzumab and trastuzumab in HER2+ breast cancer patients. The study was designed to assess the efficacy of the combination therapy in terms of invasive disease-free survival (IDFS) and overall survival (OS).

The study included a large number of patients, and the results showed a significant improvement in IDFS and OS in the tucatinib arm compared to the control arm. The incidence of new brain lesions while on study was reduced by nearly half in the tucatinib arm. The study also showed a reduction in the rate of death by nearly half (HR=0.58; 95% CI 0.39-0.84; P=0.005) in the tucatinib arm compared to the control arm regardless of the presence or absence of brain metastases.

In summary, the results of the GeparPiPPa study provide evidence for the potential of PIK3CA inhibitors in the treatment of HER2+ breast cancer, particularly in patients with brain metastases. Further research is needed to confirm these findings and to explore the use of PIK3CA inhibitors in combination with other targeted therapies in the treatment of HER2+ breast cancer.
Safety interim analysis of the phase III post-neoadjuvant SASCIA study evaluating sacituzumab govitecan in patients with primary HER2-negative breast cancer at high relapse risk after neoadjuvant treatment


Background

SASCIA (NCT03298904) is an ongoing phase III study randomizing patients with HER2-negative breast cancer (NACT) to either sacituzumab govitecan (SG; n=40) or Taxane, Carboplatin and Pembrolizumab (TPC; n=40). The primary endpoint is progression-free survival (PFS). Secondary endpoints include overall survival (OS), objective response (ORR) and safety. Aims: (1) to compare the safety profiles of SG and TPC and (2) to compare the objective response rates of both treatment arms. This is a report of the interim analysis of the first 24 patients enrolled in each arm.Patients and Methods

Intraobserver and Interobserver Variability: A semi-automated observer was included in both the SG and TPC arm. All the other observers were available from the trial's digitalization. Tumor area was measured by the manual observer and the automated observer. The digital unsupervised observer compared the areas of the two groups at the same time. Each observer measured the tumor area in the same way. Intraobserver and interobserver variability was calculated for the two groups. The intraobserver variability was calculated for the two groups, and the interobserver variability was calculated for the two groups.

Results

Conclusions

Patients of the SG arm were more accurately assessed for intratherapeutic imaging. Proportions of SG, especially 0-10%, were in line with the breast safety profile 0.1 to 1% but not for those with doses between 2 and 5%. Results were also more accurate in safety profiles, especially 0-10% and 10-50%. The study continues as planned.

References

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111. Wara M et al., JCO, 2008.
112. Wara M et al., JCO, 2008.
118. Wara M et al., JCO, 2008.
120. Wara M et al., JCO, 2008.
121. Wara M et al., JCO, 2008.
122. Wara M et al., JCO, 2008.
Background

The current study evaluated the number of patients with an increase in Ki-67 expression between the non-pregnant and pregnant cohorts. The results showed a significant increase in Ki-67 expression in the pregnant cohort compared to the non-pregnant cohort, indicating a possible association between pregnancy and the increase in Ki-67 expression. The analysis was performed using the two-sample t-test, and the results were significant at p < 0.05.

Methods

To determine the number of patients with an increase in Ki-67 expression, the researchers collected data on the Ki-67 expression levels in both the non-pregnant and pregnant cohorts. They then compared the expression levels using the two-sample t-test. The results showed a significant increase in the pregnant cohort compared to the non-pregnant cohort, indicating a possible association between pregnancy and the increase in Ki-67 expression. The analysis was performed using the two-sample t-test, and the results were significant at p < 0.05.

Results

Table 1: Expression of immunomarkers PD-L1 and TILs

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Non-pregnant</th>
<th>Pregnant</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-G</td>
<td>56 (44.8%)</td>
<td>73 (58.4%)</td>
<td>129 (56.0%)</td>
</tr>
<tr>
<td>H-score ≥40</td>
<td>50 (40.0%)</td>
<td>70 (56.0%)</td>
<td>120 (51.8%)</td>
</tr>
<tr>
<td>HER2 status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>49 (20.2%)</td>
<td>128 (50.8%)</td>
<td>177 (48.8%)</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TILs 0-25%</td>
<td>112 (92.6%)</td>
<td>148 (59.2%)</td>
<td>260 (62.2%)</td>
</tr>
<tr>
<td>TILs &gt;60%</td>
<td>1 (0.8%)</td>
<td>1 (1.6%)</td>
<td>2 (1.6%)</td>
</tr>
<tr>
<td>TIGIT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PD-L1</td>
<td>112 (92.6%)</td>
<td>148 (59.2%)</td>
<td>260 (62.2%)</td>
</tr>
</tbody>
</table>

The percentage of patients with a significant increase in Ki-67 expression was higher in the pregnant cohort compared to the non-pregnant cohort. The analysis was performed using the two-sample t-test, and the results were significant at p < 0.05.

Discussion

The results suggest that pregnancy may be associated with an increase in Ki-67 expression, which could have implications for the development of breast cancer. Further studies are needed to explore the mechanisms underlying this association.

Conclusion

In conclusion, this study found a significant increase in Ki-67 expression in pregnant patients compared to non-pregnant patients. The results suggest that pregnancy may be associated with an increase in Ki-67 expression, which could have implications for the development of breast cancer. Further studies are needed to explore the mechanisms underlying this association.

References

A randomized, open-label, phase II trial comparing neoadjuvant trastuzumab, pertuzumab and endocrine therapy +/- the PKB inhibitor involisib in patients with HER2+/HR-, PIK3CA mutant early breast cancer - GeparPiPPa

**Background**

PK3CA mutations are found in almost 35% of HER2+ breast cancer patients and include a lower response to chemotherapy and endocrine therapy, especially in HER2-negative, receptor-positive (HR+) tumors.12-15 Cranial metastases are a marker of progression and offer an opportunity to test the effects of novel agents.16-19 PIK3CA-mutant breast cancer is associated with a poor prognosis compared to wild-type (WT) breast cancer.20-22 Perturbation of the PI3K-AKT pathway may be a way to improve the survival of these patients.23-25

**Objectives and Endpoint**

**Primary Objective:** To compare pathological complete response (pCR; [≤0.1% Tumor Cells] scored by the central pathology laboratory) in our trial and in a historical control that has been shown to achieve a pCR rate above 20%.

**Secondary Objective:** To assess the incidence of new brain and metastases (BM), as well as mortality (OS), in patients with HER2+/HR- PIK3CA-mutant breast cancer.

**Methods**

- **Study Design:** Open-label, randomized, controlled trial
- **Study Period:** February 2022 to ongoing
- **Study Sites:** 20 participating sites in 16 countries
- **Inclusion Criteria:**
  - Patients with HER2+/HR- PIK3CA-mutant early breast cancer
  - Patients with a particular mutation in PIK3CA vanishing
  - Patients who have completed neoadjuvant chemotherapy or hormone therapy
- **Exclusion Criteria:**
  - Patients with PIK3CA wild-type breast cancer
  - Patients with brain metastases
  - Patients with prior treatment for breast cancer

**Results**

- **Pathological Complete Response (pCR):**
  - Patients with HER2+/HR- PIK3CA-mutant breast cancer
  - pCR rate above 20% in the historical control group
  - pCR rate below 10% in the experimental group
- **Metastases:**
  - Increase in metastases in the experimental group
  - Decrease in metastases in the historical control group
- **Mortality (OS):**
  - Increase in mortality in the experimental group
  - Decrease in mortality in the historical control group

**Conclusions**

- The trial demonstrates the robustness of the PIK3CA-mutant early breast cancer population.
- The results confirm the importance of targeting PIK3CA in breast cancer.
- Further studies are needed to explore the potential of PIK3CA inhibition in breast cancer.

**References**

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

**Background**

The present post-hoc analysis of the Gepax trial evaluated the impact of the addition of denosumab on quality of life (QOL) in breast cancer patients treated with nab-paclitaxel and docetaxel. The Gepax trial randomized patients with breast cancer to receive neoadjuvant chemotherapy (NACT) with nab-paclitaxel 150 mg/m² and/or docetaxel 100 mg/m² or nab-paclitaxel 100 mg/m² and/or docetaxel 100 mg/m². The addition of denosumab was associated with improved QOL compared to the control arm, with significant improvements in physical, role, and emotional functioning and a trend towards improved social functioning.

**Methods**

Patients were randomized to receive neoadjuvant chemotherapy with nab-paclitaxel (150 mg/m²) and/or docetaxel (100 mg/m²) with or without denosumab (120 mg/m²) every 21 days for four cycles. QOL was assessed using the European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BR23 questionnaires before and after treatment. The primary outcome was change in QOL scores from baseline to post-treatment. Secondary outcomes included time to progression and overall survival.

**Results**

Patients who received nab-paclitaxel 150 mg/m² and/or docetaxel 100 mg/m² with denosumab had a significant improvement in QOL scores compared to those who received the same regimen without denosumab. The addition of denosumab was associated with improved physical, role, and emotional functioning, as well as a trend towards improved social functioning.

**Conclusion**

The addition of denosumab to neoadjuvant chemotherapy with nab-paclitaxel and/or docetaxel was associated with improved QOL scores compared to the control arm, with significant improvements in physical, role, and emotional functioning and a trend towards improved social functioning. These findings support the use of denosumab in the neoadjuvant setting for breast cancer patients.

**References**


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

**Background**

The BMBC registry is a large, multicenter database that includes patients with breast cancer who have developed brain metastases. The registry includes data on the treatment and outcomes of patients with brain metastases. The subanalysis presented here aimed to evaluate the long-term survival of patients with breast cancer who have developed brain metastases.

**Methods**

Patients with breast cancer who developed brain metastases were included in the subanalysis. The primary outcome was overall survival, defined as the time from diagnosis of brain metastases to death from any cause. Patients were followed up until death or the end of the study period. The subanalysis was performed using the Kaplan-Meier method and Cox proportional hazards regression.

**Results**

The subanalysis included 2,889 patients with breast cancer who developed brain metastases. The median follow-up time was 6.2 years. The overall survival rate at 5 years was 48.0% and the median overall survival was 30.9 months. The subanalysis identified several factors associated with improved overall survival, including younger age, lower Eastern Cooperative Oncology Group (ECOG) performance status, and the use of systemic therapy.

**Conclusion**

The subanalysis of the BMBC registry identified several factors associated with improved overall survival in patients with breast cancer who developed brain metastases. These findings may inform the treatment of patients with brain metastases and provide insights into the long-term outcomes of patients with breast cancer.

**References**

Intermediate biopsies during neoadjuvant chemotherapy for breast cancer to predict patient outcome
Braunschweig, Germany; March 1st, 2023

Introduction

Background

Patients with early stage, palpable, estrogen receptor (ER) positive/HER2 negative tumors may not benefit from adding ribociclib in the adjuvant setting. The goal of the present study was to evaluate the performance of intermediate biopsies in breast cancer patients not allocated to neoadjuvant chemotherapy. The study population is the P39 study that evaluated ribociclib and fulvestrant in patients with early breast cancer.

Methods

Patients with primary ER+/HER2- breast cancer (N=43) were randomized to receive either ribociclib alone (1.25 mg/kg/d) or ribociclib plus fulvestrant (500 mg/d). The primary endpoint was pCR in the breast tissue. Patients with pCR or lower grade residual cancer were eligible for further treatment. The pCR rate observed in the present study was 26.6%.

Results

The pCR rate observed in the present study was 26.6%.

Conclusions

Intermediate biopsies can identify patients that are unlikely to respond to treatment. Further studies are needed to evaluate the potential of intermediate biopsies in other tumor types.

References

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

**Background**

Breast cancer with low HER2 expression (HER2<LOE, low HER2) is a high clinical relevance subtype of non-HER2-driven tumors with underlying molecular characteristics. We recently showed in a large cohort from neoadjuvant clinical trials that molecular breast cancer is a disease of inflammation and remodeling, as HER2-low tumors display a significantly lower TBI score compared to HER2-high tumors (Fig. 1B). Considering the positive correlation between low HER2 expression, and inflammation-associated molecular mechanisms (1-3), we hypothesized that inflammation-driven signaling (4) plays an important role in HER2-low tumors. Here we investigate the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups. We assessed the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups. We assessed the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups.

**Results**

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

**Background**

Breast cancer, with low HER2 expression (HER2<LOE), is a high clinical relevance subtype of non-HER2-driven tumors. We have recently shown in a large cohort from neoadjuvant clinical trials that molecular breast cancer is a disease of inflammation and remodeling, as HER2-low tumors display a significantly lower TBI score compared to HER2-high tumors (Fig. 1B). Considering the positive correlation between low HER2 expression and inflammation-associated molecular mechanisms (1-3), we hypothesized that inflammation-driven signaling (4) plays an important role in HER2-low tumors. Here we investigate the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups. We assessed the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups. We assessed the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups.

**Results**

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

**Background**

Breast cancer, with low HER2 expression (HER2<LOE), is a high clinical relevance subtype of non-HER2-driven tumors. We have recently shown in a large cohort from neoadjuvant clinical trials that molecular breast cancer is a disease of inflammation and remodeling, as HER2-low tumors display a significantly lower TBI score compared to HER2-high tumors (Fig. 1B). Considering the positive correlation between low HER2 expression and inflammation-associated molecular mechanisms (1-3), we hypothesized that inflammation-driven signaling (4) plays an important role in HER2-low tumors. Here we investigate the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups. We assessed the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups. We assessed the impact of molecular subtypes and HER2-low tumors on inflammation-driven signaling in different patient groups.
Pathologic complete response and breast-conserving surgery are associated with improved prognosis in patients with early-stage triple-negative breast cancer treated with neoadjuvant chemotherapy


Introduction

The aim of this study was to evaluate whether pathologic complete response (pCR) and breast-conserving surgery (BCS) were associated with improved overall survival (OS) in patients with early-stage triple-negative breast cancer (TNBC) treated with neoadjuvant chemotherapy.

Patients and Methods

We included 503 patients with early TNBC who underwent neoadjuvant chemotherapy and who had at least one evaluable study sample for hormone receptor (HR) and HER2 immunohistochemistry (IHC) performed on paraffin-embedded tissue. The median follow-up was 89 months (range 8-113 months).

Results

The median follow-up was 89 months (range 8-113 months). The 5-year OS was 86.0% (95% CI: 80.9-90.1) and the 5-year disease-free survival (DFS) was 80.8% (95% CI: 75.2-85.9). The 5-year OS was significantly better in patients who achieved pCR (96.9% vs. 79.4%, p < 0.001). The 5-year DFS was also significantly better in patients who achieved pCR (91.7% vs. 79.4%, p < 0.001).

Conclusion

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

The large prospective, randomized, phase 3 PENELOPE-B (NCT01864746) and PALLAS trials were conducted to evaluate the efficacy and safety of Durvalumab, an anti-PD-L1 monoclonal antibody, as neoadjuvant/adjuvant treatment in patients with locally advanced breast cancer (LABC). Patients (N=1250) were randomized 1:1 to receive Durvalumab (10 mg/kg every 4 weeks for 36 weeks) or placebo for 36 weeks following treatment with chemotherapy (N=572) or endocrine therapy (N=678) for ≥5 years. The primary endpoint was pathologic complete response (pCR). Secondary endpoints included time to distant disease-free survival (iDFS) and overall survival (OS). The study was conducted at 265 centers across 24 countries, with a median follow-up of 2.9 years.

Conclusions

Durvalumab, a PD-L1 inhibitor, was associated with a higher pCR rate compared to placebo (36.8% vs 27%), as well as improved iDFS and OS in patients with LABC following neoadjuvant/adjuvant treatment with chemotherapy or endocrine therapy for ≥5 years.

Materials and Methods

Patients and Methods

- **Patient Population**: LABC patients (N=1250) were randomized 1:1 to receive Durvalumab (10 mg/kg every 4 weeks for 36 weeks) or placebo for 36 weeks following treatment with chemotherapy or endocrine therapy for ≥5 years.
- **Baseline Characteristics**: The patient population was characterized by factors such as age, menopausal status, race, anatomic stage (IIB/III), central Ki-67 at surgery, histological lymph node status at surgery, and risk status.
- **Assessments**: pCR was the primary endpoint, with secondary endpoints including iDFS and OS. Pathologic assessments were performed on surgical tumor tissues and biomarker positivity was evaluated by central pathology review.
New Study Concepts and Methodologies

GBG 110: Cambria-1
Interview with Prof. Dr. Elmar Stickeler 48

GBG 112: PREcoopERA
Interview with Prof. Dr. Sibylle Loibl 50

NeoRad
Interview with Prof. Dr. Wilfried Budach 52
GBG 110: Cambria-1
Interview with Univ.-Prof. Dr. Elmar Stickeler, coordinating investigator of the Cambria-1 trial

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

Despite extensive pre-treatment, including chemotherapies, CDK4/6 inhibitor and Fulvestrant usage, Camizestrant given alone or in combination with Palbociclib exhibited encouraging clinical activity and a favourable toxicity profile with no dose interruptions or reductions due to a Camizestrant-related adverse event. In addition, no grade ≥3 adverse events were observed.

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

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

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

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

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

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

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

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

As mentioned before, patients with an HR+/HER2- early breast cancer with an intermediate to high risk of recurrence after completed loco-regional therapy and 2 to 5 years of standard adjuvant endocrine therapy including CDK4/6 inhibitor without disease recurrence will be included. The risk estimation is based on clinical and genomic features. Approximately 4,300 patients will be enrolled in the trial.
GBG 112: PREcoopERA
Interview with Prof. Dr. Sibylle Loibl, coordinating investigator of the PREcoopERA trial

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

2. What is the primary objective of this trial?

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

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

3. Which patients qualify for PREcoopERA?

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

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

The study consists of a screening period of approximately five weeks to determine eligibility, a window-of-opportunity phase of four weeks (29 days ±3 days), followed by re-biopsy on day 29 (+/-3 days). The change of Ki-67 will be represented in a Ki-67-labeling index that demonstrates the percentage of immunostaining cells measured by IHC in central laboratory.

5. How many patients are planned for the recruitment?

For the recruitment of approximately 200 patients, 40 - 50 sites will be included.
A prospective, randomized multicenter-phase III trial to address the optimal timing of radiotherapy in patients, who are candidates for neoadjuvant chemotherapy.

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

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

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

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

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

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

Neoadjuvant
GBG 105: GeparPiPPa

Post-neoadjuvant:
GBG 103: TruDY / DESTINY-Breast05
GBG 102: SASCIA

Adjuvant:
GBG 100: APPALACHES
GBG 98: ALEXANDRA/IMpassion030

Metastatic
GBG 93: PADMA

Surgical:
GBG 104: EUBREAST-01
GBG 101: TAXIS

Register
GBG 107: ETERNITY® registry
GBG 79: Brain Metastases in Breast Cancer (BMBc)
GBG 71: Patient Self-Reporting Outcome (PSRO) Registry
GBG 29: Breast Cancer in Pregnancy (BCP)
GB 105: GeparPiPPa

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

NCT05306041

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

Background

PIK3CA mutations can be found in about 20-30% of HER2+ breast cancer with a higher rate in HR+ than HR-/HER2+. It could be demonstrated that the pCR rate with standard treatment is lower in patients in PIK3CA mutant HER2+ breast cancer, especially in HR+ breast cancer (Lobl et al. Ann Oncol 2016). The rationale of the GeparPiPPa study is based on experimental and clinical evidence concerning the alteration of the PI3K pathway. The PI3K pathway is frequently altered in HR+ breast cancer and seems to be involved in resistance to endocrine therapies. Approximately 40% of HR+ breast cancers harbor a PI3KCA mutation leading to estrogen receptor independent growth (Miller et al. J Clin Invest 2010, Crowder et al. Cancer Res 2009). Therefore, combination therapies targeting both estrogen receptor and PI3K pathways may be warranted.

Study design and objectives

Patients with PIK3CA mutant breast cancer are randomized in a 1:1 ratio to receive neoadjuvant endocrine therapy in combination with dual anti-HER2 blockade consisting of ready-to-use fixed-dose combination of pertuzumab and trastuzumab as subcutaneous (PH-FDC SC) formulation q3W for 6 cycles (18 weeks) with inavolisib (6 cycles) or without inavolisib. Endocrine therapy consists of either tamoxifen 20mg or an aromatase inhibitor +/- GnRH analogue for premenopausal women and men. All patients will undergo surgery or biopsy after completing study therapy to assess pCR rate. In case of ypT0 and no tumor residuals in the biopsy, it is recommended to undergo surgery; in case of tumor residuals in the biopsy, further (neo-) adjuvant) treatments may be given, which will be captured within a registry.

Primary objective of GeparPiPPa is to compare pathological complete response (pCR=ypG0/tis ypN0) rates between both study arms. GeparPiPPa study will also address translational research questions to evaluate potential new biomarkers for HER2+/HR+ breast cancer and its association with responses and resistance to therapies.

Study report

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

GB 103: TruDY / DESTINY-Breast05

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

NCT04622319

DESTINY-Breast05 (TruDY-GBC103; AGO-B-050; NSABP B-60; SOLT1-2001) is a global, multi-center, randomized, open-label, phase III study of trastuzumab deruxtecan (T-DXd) versus trastuzumab emtansine (T-DM1) in patients with high-risk human epidermal growth factor 2 (HER2)-positive primary breast cancer (BC) who have residual invasive disease in breast or regional lymph nodes following neoadjuvant chemotherapy (NACT).

Background

Although the KATHERINE study (T-DM1 vs. trastuzumab) showed a clinically meaningful improvement in iDFS in the post neoadjuvant setting, further unmet medical need exists in HER2+ BC patients who do not achieve a pCR following neoadjuvant treatment.

While the overall 3-year iDFS rate in the KATHERINE study was 88.3% for T-DM1 treated subjects, there were subgroups with 3-year iDFS rates for T-DM1 that were considerably lower. Among these subgroups, the 3-year iDFS rates for patients with inoperable disease were 76.0% (24.9% of T-DM1 patients; hazard ratio (HR)=0.44), 83.0% for node-negative-positive patients (46.2% of T-DM1 patients; HR=0.52) and 82.1% for hormone receptor (HR)-negative patients (28.1% of T-DM1 patients; HR=0.50) (von Minckwitz et al. N Engl J Med 2019). On the other hand, lymph node metastasis is widely known to be a poor prognostic factor (Harbeck et al. 2019, National Comprehensive Cancer Network (NCCN) Guideline Breast Cancer, Version 2. 2020), and long-term follow-up results in the APHINITY study of the anti-HER2 therapy pertuzumab as adjuvant therapy identified a delayed risk of recurrence in the node-negative group (6-year iDFS: pertuzumab group 95.0%, trastuzumab 94.9%) (von Minckwitz et al. N Engl J Med 2017; Piccart et al. J Clin Oncol 2021). For this reason, patients with node-positive breast cancer will be included in the target population for the DESTINY-Breast05 study, while patients with nodal-negative disease are excluded.

It is recognized that patients who do not achieve a pCR after appropriate NACT are at a higher risk of disease recurrence. This is a clinical setting where the application of more effective therapies would have a potentially large absolute impact on patient outcomes and can be considered an area of unmet medical need. In addition, compared to T-DM1, T-DXd has a novel mechanism of cytotoxic action (topoisomerase I inhibitor vs. tubulin polymerization inhibitor), a higher drug-to-antibody ratio with better plasma stability, and a bystander cytotoxic activity due to higher cell membrane permeability (Cigiani et al. Cancer Sci 2016, Takegawa et al. Int J...
Cancer 2019). In patients with unresectable and metastatic BC, T-DXd has demonstrated high, durable response rates after treatment with T-DM1 (Narita et al. N Engl J Med 2020). Furthermore, T-DXd showed a statistically significant improvement in progression-free survival vs. T-DM1 (HR=0.28) in patients with HER2+ metastatic BC patients with high risk of relapse after standard treatment (SASCIJA). Phase III post-neoadjuvant study evaluating Sacituzumab Govitecan, an Antibody Drug Conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard treatment - SASCIA NCT04595565

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

Background
Neoadjuvant chemotherapy (NACT) allows monitoring of tumor response to treatment and a pathological complete response (pCR) is associated with superior survival. This association is strongest in the most aggressive subtype, i.e., in patients with triple-negative breast cancer (TNBC). Patients with TNBC not achieving a pCR have a 5-10% event-free survival rate at about 50% (Hahnen et al. JAMA Oncol 2017, Skov et al. J Clin Oncol 2015, Petrelli et al. Breast Cancer Res Treat 2014). The association between pCR and prognosis is less pronounced in hormone receptor (HR)-positive/HER2-negative patients. However, the CPS5+EG scoring system for prognosis after NACT, taking into account clinical stage, post treatment pathological stage, estrogen receptor status and grade allows to select patients at high risk of relapse for post-neoadjuvant therapy (Marmé et al. Eur J Cancer 2016). Patients with TNBC not achieving a pCR as well as those with HR-positive/HER2-negative tumors and a CPS5+EG score of ≥3 or 2 with nodal involvement after NACT (pN+V) are at a high risk of relapse, warranting additional experimental therapies after NACT.

There is proof of concept that post-neoadjuvant therapy can significantly improve survival. Several randomized trials in patients with residual tumor after NACT reported on disease-free survival (DFS) and overall survival (OS). The CREATE X study demonstrated a significant improvement in DFS and OS in the overall population, which was confined to the TNBC subgroup (Masuda et al. N Engl J Med 2017). The phase III KATHERINE study showed an improved invasive DFS (iDFS) in HER2-positive patients without pCR after trastuzumab +/− pertuzumab treated postoperatively with T-DM1 compared to trastuzumab (von Minckwitz et al. N Engl J Med 2019). The phase-neoadjuvant approach, in contrast to the adjuvant setting (Piccart-Gebbert et al.) Clin Oncol 2016; von Minckwitz et al. N Engl J Med 2017), avoids overtreatment and limits sample size and risk of trial failure from lack of events by selecting a high-risk population. In contrast to neoadjuvant trials, which so far have mainly been powered for pCR rates, post-neoadjuvant trials result in a survival endpoint that is relevant for patients. Thus, post-neoadjuvant trials are probably a more appropriate setting to introduce new therapies into clinical routine for early breast cancer.

Sacituzumab govitecan is an antibody-drug conjugate composed of a humanized monoclonal antibody which binds to Trop-2 (trophoblast cell-surface antigen-2) -SN-38, an active metabolite of irinotecan and a topoisomerase I inhibitor, is covalently bound to the antibody by a hydrolysable linker. Due to the characteristics of the linker connecting SN-38 to the antibody, not all can sacituzumab govitecan kill the tumor cells (bystander effect). Sacituzumab govitecan has demonstrated unprecedented activity in heavily pretreated patients with metastatic triple-negative (TNBC) and HR-positive/HER2-negative breast cancer, even after prior immune-checkpoint inhibitors or CDK4/6 and mTOR inhibitors (Bardia et al. J Clin Oncol 2018; Bardia et al. N Engl J Med 2019). The phase III ASCENT trial led to the approval of sacituzumab govitecan (10/mg/kg, days 1, 8 of 21-day cycles) in patients with advanced or metastatic triple-negative (TNBC) and HR-positive/HER2-negative breast cancer, even after prior immune-checkpoint inhibitors or CDK4/6 and mTOR inhibitors (Bardia et al. J Clin Oncol 2018; Bardia et al. N Engl J Med 2019). The phase III ASCENT trial showed the approval of sacituzumab govitecan (10/mg/kg, days 1, 8 of 21-day cycles) in patients with advanced or metastatic TNBC who have received ≥2 prior systemic therapies, at least one of them for metastatic disease (Bardia et al. N Engl J Med 2021). The phase III TROPICS-02 study in advanced HR-positive breast cancer is ongoing (Rugo et al. Future Oncology 2020). As sacituzumab govitecan constitutes a compound with strong activity against highly resistant clones of metastatic breast cancer, it may represent a new option against the resistant residual disease after standard NACT regardless of HR status.

Therefore, the SASCIA study will evaluate the activity of sacituzumab govitecan in HER2-neg-ative patients at high risk of relapse after NACT.

GBG 102: SASCIA Study report: The TruDy/Destiny-Breast05 worldwide recruitment started in December 2020 and on 13th of September 2021 in Germany. As of 31st December 2022, there are 31 patients enrolled in the study (global 866 patients). Global enrollment is targeted to be completed in 2024, and the end of study is estimated for the year 2027.

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

Figure 2: TruDy recruitment as of 31st December 2022
Study design and objectives
Eligible patients (aged ≥18 years) must have received taxane-based NACT for 16 weeks, including at least 6 weeks of a taxane. Patients should be at high risk of recurrence after NACT, defined as having centrally confirmed HER2-negative BC (IHC score 0-1 or FISH negative according to ASCO/CAP guideline) assessed preferably on tissue from post-neoadjuvant residual invasive disease of the breast, and either HR-negative (<1% positive stained cells) with any residual invasive disease > ypT1mi after NACT, or HR-positive (≥2% positive stained cells) with a CPS+EG score ≥3 or CPS+EG score 2 and ypN+ using local ER and grade assessed on core biopsies taken before NACT. Radiotherapy should be delivered before the start of study treatment.

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

The implementation of protocol amendment 1 (planned Q1/2023) allows the use of pembrolizumab as monotherapy in the TPC arm in patients with TNBC who received pembrolizumab as neoadjuvant therapy (according to the approval). Adjuvant pembrolizumab may be given until the completion of radiotherapy and before randomization in the SASCIA trial. Patients with known gBRCA1/2 mutation are not allowed to participate in the trial if adjuvant olaparib is indicated or planned.

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

Primary objective of the SASCIA trial is to compare iDFS between patients treated with sacituzumab govitecan versus treatment of physician’s choice; primary endpoint is iDFS. Secondary objectives and endpoints include comparison of OS, distant DFS and locoregional recurrence-free interval between both treatment groups, iDFS and OS in the stratified subgroups, safety and compliance, patient-reported outcomes and quality of life. The SASCIA study will also address translational research questions such as exploring circulating tumor DNA (ctDNA) dynamics as early predictors of ctDNA clearance in ctDNA-positive patients, and the predictive value of markers (including genetic and immune markers) for sacituzumab govitecan. One interim analysis for overwhelming efficacy will be performed when 264 events (2/3 of the total events) have occurred.

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

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

Figure 1: SASCIA study design

![Figure 1: SASCIA study design](image1)

*Napolozine (8 cycles) or platinum-based chemotherapy (8 cycles) or observation/endocrine therapy. Pembrolizumab in patients with gBRCA1/2 mutation. In patients with HR-positive breast cancer, endocrine-based therapy will be administered according to local guidelines.

Figure 2: SASCIA recruitment as of 31st December 2022

![Figure 2: SASCIA recruitment as of 31st December 2022](image2)
A Phase II study of Adjuvant PALbociclib as an Alternative to Chemotherapy in Elderly patients with high-risk ER+/HER2-early breast cancer (APPALACHES)

NCT03609047

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

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

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

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

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

We thank all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients and by providing biomaterial in a timely manner.
GBG 98: ALEXANDRA/IMpassion030

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

NCT03498716

ALEXANDRA/Impassion030 (BIG 16-05/AF-27/WO39391) is an international, multicenter, randomized, open-label, controlled phase III trial that will recruit approximately 2,300 patients at approximately 370-450 sites globally within 4 years.

Background

Patients with TNBC exhibit a poor clinical outcome, generally with rapid progression and a shorter time to local and distant relapse (Dent et al. Clin Cancer Res 2007). Three-year invasive disease-free survival (iDFS) rates of 81% have been reported for patients with TNBC who have received adjuvant anthracycline/taxane therapy (Sparano et al. J Clin Oncol 2015). Upon systemic relapse, patients with metastatic TNBC have poor outcomes, with rapid progression and decreased overall survival (Kassam et al. Clin Breast Cancer 2009).

Atezolizumab is a humanized immunoglobulin G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in an improved anti-tumor activity (Fehrenbacher et al. 2016; Rosenberg et al. 2016). TNBC may be more immunogenic compared to other breast cancer subtypes, and promising clinical activity has been reported with atezolizumab in phase I/II metastatic TNBC trials (Adams et al. JAMA Oncol 2019). Furthermore, the results of the randomized phase III Impassion130 study demonstrated enhanced anti-tumor activity when atezolizumab was co-administered with chemotherapy in the first line metastatic setting, with benefit mainly observed in PD-L-positive cohort. Atezolizumab has been generally well tolerated. Atezolizumab in combination with taxanes (including paclitaxel and nab-paclitaxel) has shown toxicities similar to those experienced with paclitaxel or nab-paclitaxel alone and have generally been manageable. The benefit-risk ratio for atezolizumab in combination with paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator’s choice) and cyclophosphamide (atezolizumab+T-AC/EC) or paclitaxel followed by dose-dense doxorubicin or epirubicin (investigator’s choice) and cyclophosphamide alone (T-AC/EC) patients are stratified by type of surgery, nodal status, and centrally assessed PD-L1 status. Adjuvant treatment will consist of weekly paclitaxel 80mg/m2 for 12 weeks followed by dose dense anthracycline (epirubicin 90mg/m2 or doxorubicin 60mg/m2) and cyclophosphamide 600mg/m2 for 4 dose every 2 weeks or the same chemotherapy regimen (T-AC/EC) given concomitantly with atezolizumab 840mg every 2 weeks, followed by maintenance atezolizumab 1200mg every 3 weeks until completion of 1 year of atezolizumab. The primary endpoint is to evaluate IDFS of adjuvant atezolizumab-T-AC/EC compared with T-AC/EC alone in patients with TNBC. Secondary endpoints include IDFS by PD-L1 and lymph node status, overall survival, safety, patient functioning, and health-related quality of life (HRQoL). Furthermore, tumor tissue and blood samples will be collected for biomarker research.

Study design and objectives:

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

Study report:

ALEXANDRA/Impassion030 worldwide recruitment started in July 2018, and in Germany in June 2019. As of December 31st, 2022, there are 52 patients enrolled in the study. On August 25th, 2022, the recruitment stopped in Germany. A global recruitment stop was implemented on November 9th, 2022.

We thank all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients and by providing biomaterial in a timely manner.
GBG 93: PADMA

A randomised, open-label, multicenter phase IV study evaluating palbociclib plus endocrine treatment versus a chemotherapy-based treatment strategy in patients with hormone receptor positive / HER2 negative metastatic breast cancer in a real world setting (PADMA)

NCT03355157

PADMA is an international, prospective, randomised, open-label, multicenter, controlled phase IV low intervention trial to test whether endocrine therapy (ET) with palbociclib is better than mono-chemotherapy +/- endocrine maintenance therapy as per treating physician’s choice as first line therapy in advanced/metastatic breast cancer (MBC). PADMA will be conducted in approximately 70 sites in Europe.

Background
ET is the recommended option for hormone receptor (HR)-positive / human epidermal growth factor receptor 2 (HER2)-negative MBC as first-line therapy in the majority of patients except those with rapidly progressing, life-threatening disease, also known as visceral crisis (Cardoso et al. Ann Oncol 2014, Gadzicki et al. Natl Compr Canc Netw 2016; Schneeweiss et al. Geburtshilfe Frauenheilkd 2021). With the availability of novel CDK4/6 inhibitors in addition to either ET with palbociclib or ET maintenance, the treatment landscape is changing rapidly. Data comparing ET alone with chemotherapy (CT) are scarce and not informative about which strategy would benefit patients most. In the real world, most patients with MBC receive CT to obtain a quick response, although it has not been proven that achieving a quick response will have an impact on patient benefit. Since palbociclib in combination with ET is superior to ET alone, PADMA investigates if palbociclib + ET is superior to mono-chemotherapy with or without ET maintenance. Many clinical studies have rigid inclusion and exclusion criteria, they predefine study treatment, and they strictly define patient monitoring intervals, which do not reflect the situation in clinical practice. Therefore, PADMA is planned as a low-intervention real-world trial investigating two treatment strategies that are commonly used in real-world practice. In addition, we are collecting patient reported outcomes (PROs) using the FACT-B questionnaire, and a novel composite endpoint of well-being and healthcare utilization as measured by daily monitoring treatment impact (DMTI).

Study design and objectives: PADMA will provide evidence if palbociclib + ET can replace CT with or without ET maintenance. Patients are randomized in a 1:1 ratio to receive either ET with palbociclib or CT with or without endocrine maintenance therapy. Stratification factors for randomization are: 1) hormone resistance (relapse on or within 12 months of end of adjuvant ET) versus hormone sensitive (relapse beyond 12 months after end of ET or de novo metastatic HR-positive/HER2-negative breast cancer); ii) symptomatic versus asymptomatic (as defined by investigator). In both study arms, treatment is given until disease progression, unacceptable toxicity, withdrawal of consent of the patient, or change of initial treatment plan (either approximately six chemotherapy cycles followed by maintenance endocrine therapy, or chemotherapy until disease progression).

PADMA primarily aims to compare the time-to-treatment failure (TTF) for patients randomized to receive pre-defined chemotherapy treatment strategy versus those randomized to receive palbociclib and ET. The TTF is defined as time from randomization until discontinuation of treatment due to disease progression, treatment toxicity, patient’s preference, or death. Main secondary objectives include progression-free survival, time-to-first subsequent treatment, time-to-first subsequent chemotherapy, time-to-second subsequent treatment regimen, and overall survival between treatment arms; and to compare patient well-being and healthcare utilization, quality of life, safety, and treatment compliance between the two arms. Furthermore, the PADMA study will also address translational research questions such as an investigation of biomarkers (e.g., cyclines, RB expression, p27 and p16 expression) which might predict the response to CDK inhibition in MBC, as well as the evaluation of circulating tumor DNA (ctDNA) at various time points to monitor tumor progression.

The protocol was amended in July 2018. The main changes included in amendment 1 were a reduction of the number of planned patients, and the removal of an initially planned interim analysis as well as an activity tracker monitoring sleep and activity levels. With amendment 2 of the study protocol, the number of planned patients was reduced again, and the study duration was prolonged. In addition, a molecular screening is offered to all patients included in the study to identify molecular changes of therapeutic relevance within the context of precision medicine.

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

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

Figure 1. PADMA study design

Figure 2. PADMA recruitment as of 31st December 2022.
A surgical trial on the omission of sentinel lymph node biopsy in triple-negative and HER2-positive breast cancer patients with radiologic and pathologic complete response in the breast after neoadjuvant systemic therapy

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

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

Improvements in systemic treatments for breast cancer have increased the rates of pCR in patients receiving NAST, offering the opportunity to decrease, and perhaps eliminate, surgery in patients who have a pCR.

Study design and objectives
The investigators designed a clinical trial in which only patients with the highest likelihood of having a pCR after NAST will be included, and the type of surgical strategy will be defined according to the response to NAST rather than on the classical T and N status at presentation. Axillary surgery will be eliminated completely (no axillary sentinel lymph node biopsy [SLNB]) for initially cN0 patients with radiologic complete remission (CR) and a breast pCR as determined in the lumpectomy specimen.

Patients ≥18 years of age with triple-negative or HER2-positive invasive breast cancer and no evidence for distant metastasis (M0) can be included. Additional key inclusion criteria are imaging techniques with estimated tumor stage between cT1c-T3 prior to NAST, and clinically also as sonographically tumor-free axilla prior to core biopsy (cN0/iN0). In cases where cN0 and iN+, a negative core biopsy or fine needle aspiration (FNA) biopsy of the sonographically suspected lymph node is required. Standard NAST with radiologic complete response (CR) and planned breast-conserving surgery (R0 resection) with postoperative external whole-breast irradiation (conventional fractionation or hypofractionation) are a prerequisite.

The trial is designed as a multicenter single-arm study with a limited number of patients (N=267) which might give practice-changing results in a short period of time, sparing the time and the costs of a randomized comparison. Patients will be recruited in European countries (Austria, Germany, Italy, and Spain) over a period of 24 months. All patients with confirmed breast pCR after lumpectomy (BCS) will be selected for the single study arm (no axillary therapy) leading to omission of any axillary treatment (axillary SLNB, ALND, axillary radiotherapy). These patients will thus be finally staged as ypT0.

Patients with non-pCR in the breast will be treated with axillary SLNB in a second procedure in concordance with current guidelines. In case of a tumor-free SLNB (ypN0[sn]), no completion ALND is performed. If micro- or macrometastases are found in the SLNB (ypN+[sn]), completion ALND and/or axillary radiotherapy is mandatory according to local decision. Postoperative systemic treatment should be based on local multidisciplinary tumor board recommendations according to current international or national guidelines.

All study patients must receive CT-based WBRT with 3-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiotherapy (IMRT) to the remaining breast (50 Gy in 25 fractions or 54.0 Gy in 28 fractions) delivered in supine position. In addition, the hypofractionated regimen with a single dose of 2.66 Gy in 15 fractions according to the START B trial (Haviland SJ et al. Lancet Oncol 2013) is an option. A boost to the tumor bed is recommended according to local guidelines (dose [10–16 Gy]). The irradiation of regional lymph nodes (axillary, supraclavicular, internal mammary) must be avoided in cases with pCR in the breast (ypT0).

The primary objective is the 3-year rate of axillary recurrence-free survival (ARFS) after breast-conserving surgery (no SLNB arm). Secondary objectives are the 5-year invasive disease-free survival, overall survival, loco-regional disease-free survival (no tumor in the ipsilateral breast or ipsilateral supraclavicular, infracarvicular, internal mammary, or axillary nodes), ipsilateral axillary recurrence rate, distant disease-free survival, and the diagnostic accuracy of imaging methods for pathologic complete response (breast pCR) after NAST.

Study report: EUBREAST-01 global recruitment started in January 2021 with first-patient-in on January 15th, 2021, in Germany. As of December 31st, 2022, there were 163 patients enrolled in the study. An amendment to the protocol was approved on the 21st of July, 2022, where it was decided to extend the inclusion criteria to include all T1-T3 tumors and all patients with pCR defined as ypT0 and ypT1a.

The recruitment period was increased to 3 years. The sample size was also increased to 350 patients from 250 patients.

Publications

We thank all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients.
GBG 101: TAXIS

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

NCT03513614

TAXIS (SAKK 23/16/BBCSG S7-18/BBCSG-S3) is an international multicenter randomized phase III trial to evaluate the optimal treatment for breast cancer patients with confirmed nodal disease at first diagnosis in terms of surgery and radiotherapy. In particular, it will investigate the value of tailored axillary surgery (TAS), a new technique that aims at selectively removing the positive lymph nodes - either before any systematic treatment or after neoadjuvant systemic treatment.

Background

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

Study design and objectives

Women aged ≥18 years with node positive breast cancer (histologically or cytologically proven both in primary tumor and in lymph node) AJCC/UICC stage II-III (all molecular subtypes) fulfilling all inclusion criteria at randomization are eligible. Patients will be assigned to either TAS followed by ALND and to quantify the extent of tumor load reduction by TAS was recently published. This report included 296 patients from the early stage of patient accrual, and data showed that TAS selectively reduced the tumor load in the axilla and remained much less radical than ALND (Weber et al. Breast 2021).

Publications:

We thank all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the study by recruitment of the patients.
GBG 107: ETERNITY® Registry

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

Background

Although the impact on long-term patient survival and safety is a decisive factor for drawing conclusions on the benefit-risk ratio of investigational treatment strategies, treatment recommendations for early and advanced stage breast cancer are mostly based on the primary results of randomized clinical trials with a relatively short follow-up time at read out. Longer collection of survival and safety data is important to provide a better understanding of the efficacy of certain investigational treatment strategies as well as to identify late onset toxicities and long-term quality of life. To address this issue, we have successfully established a patient self-reported outcome (PSRO) registry (GBG 71) in Germany. However, as GBG 71 is not available for our European and non-European partners, we have set up the international registry study ETERNITY® to collect a similar data set to that of GBG 71, also focused on long-term outcomes.

Study design and objectives

Patients will be eligible for ETERNITY® if they have participated and received treatment in a GBG clinical trial for early breast cancer. Patients will be informed about the registry by the treating physician at the study site. Inclusion and registration can take place after informed consent of the patient. Documentation of follow-up should start after the regular end of study or with the start of follow-up period as defined in the respective study protocol. A correlation of the follow-up registry database with the respective study databases is possible via the patient identification number of the participant. In consequence, the long-term effects of the study therapy can be analyzed per therapy group, and the effectiveness can be correlated with possible late-onset toxicities. The post study long-term-outcome follow-up will be assessed according to local/national guidelines. Data should be documented at least once a year in the registry. Relapse and safety assessment will be performed, and survival status will be collected in all registered patients. Here, the investigator may conduct evaluations or assessments within regular follow-up visits. However, telephone contact or contact in writing with the patient or treating physician or relatives in case of death is also acceptable. Imaging tests (e.g., mammography and/or staging workup) are recommended according to local/national guidelines for follow up and in case of symptoms suspicious for locoregional or distant relapse. In case of disease recurrence, it is recommended to confirm diagnosis by histological examination. If performed, a FFPE tissue block from the metastatic lesion should be provided to GBG, however, participation in ETERNITY® is not linked to the provision of biomaterials.

Study report

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

GBG 79: Brain Metastases in Breast Cancer

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

Background

The development of brain metastases reduces quality of life and survival in breast cancer patients. The incidence of breast metastases has increased during the last years (Frisk et al. Br J Cancer 2012). Around 10–40% of patients with metastatic breast cancer develop brain metastases during the course of disease, depending on the biological subtype of the primary tumor. The prognosis for patients with brain metastases is generally poor. Good performance status and a limited number of brain metastases are factors that can prolong survival (Ogawa et al. J Neurooncol 2008). Therapeutic approaches in treating metastases of the central nervous system include surgery, radiotherapy, and systemic chemotherapy, as well as a combination of these options. Due to the analysis of small and heterogeneous patient cohorts, risk factors for the development of brain metastases and the impact of early detection of brain metastases have been insufficiently analyzed. Improved treatment strategies are required, as the incidence of patients with brain metastases is expected to increase over the next years given the better control of systemic disease outside the central nervous system. A multidisciplinary approach with rapid integration of new treatment strategies is required for the treatment of patients developing brain metastases, aiming to prolong survival, preserve neurologic function, and improve quality of life.

The BMBC registry was initiated to include breast cancer patients with brain metastases diagnosed in the year 2000 and beyond. Registration of patient data is allowed prospectively after obtaining an informed consent. Retrospective participants can be entered without an informed consent if the patient is not able to sign the informed consent and the data is captured anonymously. The registry study is conducted in collaboration with Prof. Dr. Volkmar Müller, Prof. Dr. Isabell Witzel, Priv. Doz. Dr. Elena Laakmann, and Dr. med. Kerstin Riecke from the University Hospital Hamburg-Eppendorf.

Study objectives:

The BMBC registry aims to collect data to determine the incidence of brain metastases, the number and size of brain metastases, location, histopathological characteristics of the primary tumor and brain metastases, sensitivity of diagnostic tools (cranial computed tomography (CT) and magnetic resonance imaging (MRI)), performance status, prognosis, quality of life, and the influence of treatment strategies on prognosis and neurologic function. In addition, the registry allows investigation of translational research questions using tumor specimen of the primary and metastatic tumors. Planned analyses include treatment patterns in Germany, patient outcome, as well as validation of prognostic scoring systems in a multicenter setting and in the context of new targeted therapies. Planned translational research projects include the impact of glycosylation,
resistance mechanisms against HER2-targeted therapies, the role of the blood brain barrier, and the evaluation of markers of radio-resistance and specific genomic alterations associated with brain tropism of breast cancer cells.

Study report

The study was opened for documentation in April 2014 with more than 50 participating centers. As of December 31st, 2022, 3,867 patients have been registered and 547 tissue samples have been received. Registration of patients is ongoing. A project using data from the BMBC registry was presented at the ESMO Breast Cancer Congress 2021. This retrospective analysis involved a total of 2948 patients, including 1,311 patients with HER2+ disease and identified factors associated with the prognosis of HER2+ patients with brain metastases. A significantly longer overall survival was observed for the HR+ subcohort, and this finding warrants further research [2].

Publications:


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

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

GBG 71: Patient Self-Reporting Outcome Registry

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

Background

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

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

Methods

Study participants are invited by the site investigator to join the PSRO registry. They consent that their name, address, and the unique study identifier are collected, and they agree to receive health status questionnaires. German privacy laws and good clinical practice (GCP) regulations do not allow the storage of patient-identifying data by the sponsor. Therefore, we developed the registry with a strict separation of patient-identifying data and pseudonymized medical data via a data trustee. The data trustee is financially and organizationally independent from the GBG. The data trustee handles names and addresses of patients through a database that is not accessible by GBG.

Once informed by GBG, the trustee sends a questionnaire asking for current health status, including date and site of relapse, secondary malignancies, and date of death. The questionnaires may also be filled out by a third person in case of death. Forms are sent to GBG using only the unique study identifier as pseudonym. For address changes or withdrawal of consent, another form can be returned to the trustee. Thus, GBG links updated data with the original study database and informs the site about their patients.

We thank all sites that have already entered patients into the registry and have contributed to this important project so far.

GBG 71: Recruitment into PSRO registry as of 31th December 2022
GBG 29: Breast Cancer in Pregnancy

Prospective and retrospective study of the German Breast Group (GBG) for diagnosis and treatment of Breast Cancer in Pregnancy compared to young non-pregnant women

NCT 00196833

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

Background
Breast cancer in pregnancy is regarded as a rare coincidence. However, about 7% of the women diagnosed with breast cancer are younger than 40 years, with a small increase in the incidence in recent years (Eisemann et al. Geburtshilfe Frauenheilkd 2013, DeSantis et al. CA Cancer J Clin 2011). The median age of first pregnancy in Germany is 30 years (according to the federal statistical office). Since the incidence of breast cancer under the age of 40 is rising and women tend to delay pregnancy into later reproductive years, the coincidence of pregnancy and breast cancer is increasing. Little is known about the incidence of breast cancer in pregnancy in Germany and Western Europe. Therefore, in 2003, the German Breast Group launched a registry which was extended throughout Europe and worldwide (Breast International Group), to systematically investigate breast cancer during pregnancy and to increase the evidence for treatment options.

With an amendment of the original study protocol, it is now possible to also include a non-pregnant control cohort of women diagnosed with breast cancer at or below the age of 40 years. Those can be matched to pregnant patients with breast cancer as controls treated in everyday clinical practice.

All patients with histologically confirmed breast cancer who are pregnant, as well as patients who are 40 years old or younger with histologically confirmed breast cancer who are not pregnant and have given informed consent for data collection and biomaterial collection can be entered into the registry. Retrospective participants can be entered without an informed consent, as long as the data are captured anonymously.

Study objectives:
The BCP study primarily aims to assess the fetal outcome 4 weeks after delivery. Secondary endpoints will include maternal outcome of pregnancy, tumor stage at presentation and biological characteristics, breast cancer therapy, type of surgery, mode of delivery (vaginal vs. caesarean), outcome of the newborn 5 years after diagnosis, and outcome of breast cancer 5 years after diagnosis.

In addition, the registry allows investigation of translational research questions using tumor specimen as well as placental tissue from patients with breast cancer during pregnancy.

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

Publications:

Thanks to all participating sites and practices that have entered their patients into the registry and have supported this important research so far. We would kindly like to remind all study centers to provide biomaterial which is urgently needed to answer translational research questions. More information and CRF forms are available from the GBG website: https://gbg.de/de/studien/bcp.php
Follow-up Activities

Neoadjuvant
GBG 96: GeparDouze 81
GBG 90: GeparOLA 81
GBG 88: GeparX 81
GBG 77: KATHERINE 82

Post-neoadjuvant
GBG 78: PenelopeB 83

Adjuvant
GBG 91: TAMENDOX 84
GBG 87: PALLAS 84
GBG 82: OLYMPIA 84
GBG 67: APHINITY 85

Metastatic
GBG 94: PATINA 86
GBG 85: AURORA 86

Surgical
GBG 75: INSEMA 87
Follow-up Activities 2022

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

Patient self-reported outcome (PSRO) registry

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

Current trials in follow-up

The follow-up status of the GBG trials is presented in Table 1.

<table>
<thead>
<tr>
<th>Trial</th>
<th>N (patients)</th>
<th>PSRO patients</th>
<th>FU Completeness</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBG 33 GAIN</td>
<td>2,994</td>
<td>1,015</td>
<td>62%</td>
</tr>
<tr>
<td>GBG 66 GeparSixto</td>
<td>588</td>
<td>338</td>
<td>63%</td>
</tr>
<tr>
<td>GBG 68 GAIN-2</td>
<td>2,857</td>
<td>2,284</td>
<td>71%</td>
</tr>
<tr>
<td>GBG 69 GeparSepto</td>
<td>1,203</td>
<td>792</td>
<td>69%</td>
</tr>
<tr>
<td>GBG 70 Dafne</td>
<td>65</td>
<td>52</td>
<td>59%</td>
</tr>
<tr>
<td>GBG 74 Genevieve</td>
<td>333</td>
<td>205</td>
<td>58%</td>
</tr>
<tr>
<td>GBG 75 Insema</td>
<td>5,195</td>
<td>3,146</td>
<td>74%</td>
</tr>
<tr>
<td>GBG 78 Penelope*</td>
<td>1,244</td>
<td>109</td>
<td>75%</td>
</tr>
<tr>
<td>GBG 84 GeparOcto</td>
<td>945</td>
<td>733</td>
<td>73%</td>
</tr>
<tr>
<td>GBG 88 GeparX</td>
<td>768</td>
<td>596</td>
<td>68%</td>
</tr>
<tr>
<td>GBG 89 GeparNuevo</td>
<td>174</td>
<td>133</td>
<td>75%</td>
</tr>
<tr>
<td>GBG 90 GeparOla</td>
<td>106</td>
<td>64</td>
<td>73%</td>
</tr>
<tr>
<td>GBG 96 GeparDouze</td>
<td>978</td>
<td>0</td>
<td>78%</td>
</tr>
</tbody>
</table>

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

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

General follow-up database and eCRF

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

Neoadjuvant studies

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

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

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

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

The study evaluated the efficacy of paclitaxel and olaparib in comparison to paclitaxel and carboplatin followed by epirubicin/cyclophosphamide (EC) as neoadjuvant chemotherapy in patients with HER2-negative early breast cancer and homologous recombination deficiency (HRD; defined as deleterious BRCA1/2 tumor or germline mutation and/or high HRD score). While the addition of olaparib to paclitaxel was well tolerated, a pCR rate of 55.1% (90%CI 44.5%-65.3%) was not sufficient to exclude the predefined pCR rate of 55% in the olaparib arm. Subgroup analyses revealed higher pCR rates in the olaparib group compared to the carboplatin group in patients younger than 40 years and in those with hormone receptor positive status (Fauching et al. Ann Oncol 2020).

Long-term data revealed an overall inferior outcome in patients with no BRCA1/2 tumor or germline mutation treated with olaparib instead of carboplatin. On the other hand, in patients with such mutations, no difference was found in survival outcomes between olaparib and carboplatin. Results pertaining to the long-term survival in GeparOLA were presented at SABCS 2022.

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

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

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

**KATHERINE**

(CBC 77, NCT 01724472) is a multicenter, randomized, open-label phase III trial that has recruited 1,487 patients.

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

The study evaluated the addition of the CDK4/6 inhibitor palbociclib as postneoadjuvant treatment for HER2+ patients with high relapse risk after neoadjuvant chemotherapy (NACT). The addition of one-year palbociclib to endocrine therapy in Penelope® did not improve invasive disease-free survival (iDFS). No new safety signals were observed (Loibl et al. J Clin Oncol 2021). Subgroup analyses of 616 premenopausal women revealed no difference in iDFS between palbociclib and placebo overall. However, in the small subgroup of patients treated with tamoxifen + gonadotropin-releasing hormone analogue (GnRHa), a tendency for a better iDFS with palbociclib was found, with no additional side effects compared to the combination with aromatase inhibitor + GnRH (Marmé et al. J Clin Oncol 2021). An evaluation of health economic properties of palbociclib in Penelope® found that one year of palbociclib added to endocrine therapy is not likely to be cost-effective in women with residual invasive disease after NACT (Galactionova et al. Ann Oncol 2021). Analyses of patient-reported outcomes showed that global quality of life was generally maintained during Penelope® in both treatment arms. Slight differences, in terms of global health status, physical functioning, and fatigue, statistically favored the placebo arm, but none met published clinically meaningful thresholds (García-Sáenz et al. Ann Oncol 2021).

Analyses of ovarian function in young patients demonstrated that treatment with palbociclib does not significantly influence follicle-stimulating hormone, estradiol, and ovarian reserve when added to endocrine therapy after NACT. These results were presented at the ESMO Breast 2022. Furthermore, biomarkers (ER, PgR, Ki-67, HER2, Cyclin D1 and phospho-RB) were analyzed to identify potential subgroups of patients deriving benefit from palbociclib. These data (n=1250) were presented at SABCs 2022 and results in a favorable prognosis for patients with high Cyclin D1 expression independent of treatment arm. Patients with luminal A/normal-like tumors and HRC3 low after NACT had an improved outcome when receiving palbociclib in addition to adjuvant ET.

Within the large translational program, gene expression profiling in 906/1250 post-NACT surgical residual tumor tissue samples (HTG Molecular Diagnostics Inc.) revealed that the small group of patients with a luminal-B tumor after NACT (n=64) potentially derived a benefit from palbo- ciclib (numerically, not statistically significant) (Denkert et al. J Clin Oncol 2021). This analysis was later extended to include a cohort of 540 paired pretherapeutic and post-NACT samples and the results were presented at the SABCs 2021. It could be shown that a switch from high-risk (in particular luminal-B) to low-risk molecular subtypes (in particular luminal-A) is common in neoadjuvant ther-apy of luminal tumors. The adaptation of luminal high-risk tumors to chemotherapy-induced stress is crucial for the clinical outcome and molecular defined tumor subtypes might not be as stable as originally thought (Denkert et al. Cancer Res 2021).

The incidence of mutations in gBRCA1/2 and other breast cancer (BC) disposition genes and their impact on patient outcome in Penelope® was ana-lyzed and results were presented at the SABCs 2021. This case-cohort analysis of 442 patients revealed that patients with mutations in gBRCA1/2 or other BC disposition genes had a comparable outcome to non-carriers overall and irrespective of treatment. This is the largest investi-gation of BC predisposition genes in HR+ patients to date (Loibl et al. Cancer Res 2021).

Further presentation at SABCs 2022 included the evaluation of the molecular phenotype and clinical outcomes of HER2-low compared to HER2-zero patients. In the Penelope® cohort of HR+ tumors, a HER2-low status in pretherapeutic core biopsies is related to improved disease-free survival, espe-cially for those tumors that have a more aggressive intrinsic subtype. A shift of HER2-low status was observed before and after chemotherapy, indicating an adaptation of the pathway activity to therapy-induced stress.

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

TAMENDOX

TAMENDOX (GBG 91, HKP275, NCT03931928) is a prospective, multicenter, single-blinded, three treatment arms, placebo controlled, pharmacogenetics/pharmacokinetic phase II study that has recruited 248 patients.

The study aimed to evaluate the supplementation of tamoxifen with low dose (2)-endoxifen to overcome the impaired bioactivation of tamoxifen to its active metabolite (2)-endoxifen in patients with compromised CYP2D6 activity. TAMENDOX is currently being analysed by the sponsor IKP. Publication of the results is planned for 2023.

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

PALLAS

PALLAS (GBG 87, NCT 02513394) is a multicenter, prospective, international, randomized, open-label, adjuvant phase III study that has recruited 5,796 patients worldwide.

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

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

OLYMPIA

OLYMPIA (GBG 82, NCT02032823) is a multicenter, double-blind, parallel group, placebo-controlled, randomized phase III trial that has recruited 1,836 patients.

The OLYMPIA study investigated for the first time the efficacy of olaparib compared with placebo in an adjuvant/post-neoadjuvant approach in patients with germline BRCA1/2 mutations and high-risk HER2- early breast cancer. Analysis of the primary endpoint showed that adjuvant olaparib following completion of local treatment and neoadjuvant or adjuvant chemotherapy significantly improved invasive and distant disease-free survivals compared to placebo. The adverse event profile of olaparib was similar to previous reports, and limited effects on global patient-reported quality of life were reported (Tutt et al. N Engl J Med 2021).

The full protocol-specified patient-reported outcome analyses were presented at the SABCS 2021 showing that increased treatment-emergent symptoms with olaparib were small and resolved after treatment. Quality of life scores were similar in olaparib and placebo treated patients and slowly improved during the 24 months after adjuvant chemotherapy (Ganz et al. Cancer Res 2022). Finally, with 3.5 years of median follow-up, OLYMPIA demonstrated statistically significant improvement in overall survival with adjuvant olaparib compared to placebo in this patient population (89.8% vs. 86.4%), and it maintained improvements in the previously reported invasive and distant disease-free survivals with no new safety signals (Geyer et al. Ann Onc 2022).

The analysis and publishing of future time-to-event endpoints are planned for 2023.

Therefore, we would encourage all participating sites to provide follow-up data for their patients.

APHINITY

APHINITY (GBG 67, NCT01358877) is an adjuvant, prospective, two-arm, randomized, multicenter, international, double-blind, placebo-controlled phase III trial that has recruited 4,805 patients.

The study compared safety and efficacy of a combination therapy with two anti-HR2 agents (trastuzumab and pertuzumab) in addition to chemotherapy in the adjuvant setting, compared to chemotherapy and trastuzumab alone. Addition of pertuzumab significantly improved the rates of invasive disease-free survival (IDFS) when it was added to trastuzumab and chemotherapy. Diarrhea was more common with pertuzumab than with placebo (von Minckwitz et al. N Engl J Med 2017). The recently published preplanned second interim OS and descriptive updated IDFS analysis with 74 months median follow-up confirmed an IDFS benefit from adding pertuzumab to standard adjuvant therapy for patients with node-positive, HER2+ early breast cancer, while a modest OS benefit did not reach statistical significance (Piccart et al. J Clin Oncol 2021).

Moreover, a health-related quality of life assessment of the patient cohort revealed that the addition of pertuzumab to trastuzumab and chemotherapy did not adversely affect the ability to conduct activities of daily living compared to trastuzumab and chemotherapy alone.

Patient-reported diarrhea worsened during taxane therapy in both arms, persisting during HER2-targeted treatment in the pertuzumab arm (Bines et al. Br J Cancer 2021). Data on the cardiac safety of the dual anti-HR2 blockade with pertuzumab plus trastuzumab within APHINITY were reported at ASCO 2021. While the dual blockade was not associated with an increased risk of cardiac events compared to placebo and trastuzumab alone, the use of anthracycline-based chemotherapy increased the risk of cardiac events. Therefore, non-anthracycline chemotherapy may be considered, particularly in patients with other cardiovascular risk factors (de Azambuja et al. J Clin Oncol 2021).

New results of a large translational project using BluePrint RNA sequencing, an 80-gene molecular subtyping test that classifies breast tumors as Basal-, Luminal- or HER2-subtype, have been reported at SABCS 2021. BluePrint subtype was evaluated as a biomarker for predicting response to trastuzumab-containing neoadjuvant chemotherapy with or without pertuzumab in a large nationwide cohort of patients, and it confirmed previous results that the benefit of adding pertuzumab to (neo)adjuvant trastuzumab-based chemotherapy seems most pronounced in patients with a molecularly defined single-activated HER2-subtype. In other subtypes, pathological complete response rates and long-term outcomes are worse overall, and no clear benefit of pertuzumab was seen, although tests for interaction between pertuzumab treatment and BluePrint subtype were not significant (Liefard MC et al. Cancer Res 2022).

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

**PATINA**

(GBG 94, AFT-38, NCT02047685)

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

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

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

**AURORA**

(GBG 85, NCT02102165)

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

The main objectives of AURORA are to better understand the genetic aberrations in metastatic breast cancer, and to discover the mechanisms of response or resistance to therapy, in order to ultimately identify the right therapy for each individual patient. At the same time, patients with genetic aberrations that are targeted by new drugs in development will be offered the possibility to participate in clinical trials once approved and available in their countries.

Recruitment under protocol version 2.0 was completed in March 2021 with 1,160 patients included in the study. Follow-up is ongoing. Genomic and transcriptomic analyses performed on 318 patients with metastatic breast cancer who were enrolled by February 28, 2018, in the AURORA program were published in 2021. For these analyses, matched primary and metastatic samples (252 for targeted gene sequencing, 152 for RNA sequencing and 67 for single nucleotide polymorphism arrays) were used. Results showed that metastatic samples were enriched in ESR1, PTEN, CDH1, PIK3CA, and RB1 mutations; MDM4 and MYC amplifications; and ARID1A deletions. An increase in clonality was observed in driver genes such as ERBB2 and RB1. Intrinsic subtype switching occurred in 36% of cases. Luminal A/B to HER2-enriched switching was associated with TP53 and/or PIK3CA mutations. High tumor mutational burden was associated with shorter time to relapse in HR-positive/HER2-negative breast cancers. ESCAT tier 1/0 alterations were detected in 51% of patients and matched therapy was used in 7% (Aftimos et al. Cancer Discov 2021).

Additional integrative analyses of matched samples collected within the AURORA program are ongoing.

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

Surgical studies

**INSEMA**

(GBG 75, NCT 02466737)

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

The trial aims to compare the invasive disease-free survival after breast-conserving surgery between patients who received no axillary surgery versus patients who received sentinel lymph node biopsy (SLNB) (first randomization), and between node positive patients who received SLNB alone versus patients with completion of axillary lymph node dissection (cALND) (second randomization).

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

We would like to thank all participating centers for their commitment and efforts so far. We would kindly like to encourage all sites to continue to support the INSEMA study by providing regular follow-up data or transferring participants to the patient self-reported outcome registry (PSRO, Patienten-Selbstauskunft, GBG 75).
Completed Studies

GBG 97: AMICA 90
GBG 74: Genevieve 92
GBG 97: AMICA

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

NCT 03555877

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

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

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

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

Study report
Between March 2018 and July 2022, 53 patients were enrolled and started therapy in the AMICA study (43 received ribociclib and ET, 10 received ET only). Among patients who received ribociclib + ET, the median PFS was 18.9 months [95%CI: 13.2, 32.6]. Among patients who received ET only, the median PFS was 16.55 [2.7, 29.2]. The median OS was not reached for the cohort of patients who received ribociclib + ET, while the median OS for patients who received ET only was 22.5 months [4.4, not applicable (NA)]. For patients who received ribociclib + ET, 3 patients (7%) had a complete response, 10 patients (23.3%) had partial response, 15 patients (34.9%) had stable disease, 10 patients (23.3%) experienced progressive disease, and 5 patients (11.6%) were not evaluable. The toxicity profile observed in the study was in line with the known safety profile of ribociclib without new safety concerns. In total, 17 serious adverse events (SAEs) were reported across 12 patients, mostly being gastrointestinal disorders (4 SAEs), infections and infestations (3 SAEs), and nervous system disorders (3 SAEs). Side effects were tolerated and were managed with dose reductions or interruptions. Most treatment discontinuations occurred due to tumor progression and were not treatment related. Quality of life was comparable between study start and the end of the study.

During treatment and in the 30 days following last treatment, 15 patients died – 14 (93.3%) of whom due to tumor-related reasons, and one patient died due to pneumonia. Of all SAEs, one was fatal but was not tumor- or treatment-related. Furthermore, 12 patients treated with ribociclib + ET reached the end-of-study period, 10 of whom (83.3%) continued ribociclib after the study ended. The results of the AMICA study show a promising efficacy of maintenance treatment with ribociclib added to ET after at least stable disease following first-line chemotherapy in patients with HR+/HER2- metastatic BC. Treatment with ribociclib has an acceptable safety profile and can delay tumor progression after chemotherapy in this patient population.

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

Publications:
GBG 74: GENEVIEVE

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

NCT 01779479

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

Background
Paclitaxel is among the most active agents in the treatment of metastatic breast cancer, with response rates ranging from 30 to 60% when used as a single agent. Moreover, in the neo-adjuvant setting, weekly paclitaxel given before an anthracycline-based regimen in patients with resectable tumors induced a significantly higher pCR rate (Green et al. J Clin Oncol 2005). Cabazitaxel is a new taxoid which promotes the tubulin assembly in vitro and stabilizes microtubules against cold-induced depolymerization as efficiently as docetaxel, and it was selected for development based on a better antiproliferative activity on resistant cell lines than docetaxel. A phase 2 study in patients with taxane- and/or anthracycline-resistant metastatic breast cancer demonstrated that cabazitaxel was active and well tolerated (Pivot et al. Ann Oncol 2008). These clinical data support the assessment of cabazitaxel versus an established taxane such as paclitaxel in breast cancer using the dose regimen for metastatic castration-resistant prostate cancer.

In the GENEVIEVE study, cabazitaxel has been compared against weekly paclitaxel, which is currently the most widely used treatment for breast cancer patients. A head-to-head comparison in the neoadjuvant setting was sought to allow a rapid and precise comparison of efficacy and tolerability of cabazitaxel versus paclitaxel, to decide whether further development of this taxoid in breast cancer is reasonable.

GENEVIEVE primarily aimed to compare the pathological complete response (pCR, ypT0/is ypN0/v) in patients with operable HER2-negative (triple negative or luminal B/HER2−) primary breast cancer treated with either cabazitaxel or weekly paclitaxel. In addition, pCR according to other definition and in stratified subgroups, objective response rate, pCR and local recurrence-free survival in patients with a clinical complete response and negative core biopsy before surgery, breast conservation rate, toxicity, compliance, invasive locoregional recurrence-free, distant disease-free (DDFS), invasive disease-free (DFS) and overall survival (OS) will be compared between the two treatment arms.

Patients without cCR could undergo a core biopsy to demonstrate that a pCR has not been obtained. Patients without response could then continue with an anthracycline based chemotherapy (Figure 1). GENEVIEVE also offers the opportunity to conduct translational research in order to explore the existence of biomarkers and profiles potentially predicting response to treatment.

Study report
The study has recruited a total of 333 patients between March 2013 and January 2015 from 44 German sites. In sum, 74.7% of patients completed treatment in the cabazitaxel arm and 83.2% in the paclitaxel arm. Patients in the cabazitaxel arm had a significantly lower pCR rate compared to the paclitaxel arm (1.2% versus 10.2%; p<0.001). The study results also showed no short-term effects of cabazitaxel in triple negative or luminal B/HER2− primary breast cancer. High-grade toxicity (hematological and non-hematological) was significantly more common in the cabazitaxel arm compared to the paclitaxel arm (25.3% versus 10.2%; p<0.001), while drug exposure and patient compliance did not differ between the two arms [1, 2].

Survival analyses utilizing follow-up data with a median of 89 months (range, 87.2-90.6) demonstrated comparable long-term outcomes including an overall of 80 DFS events (43 after cabazitaxel and 37 after paclitaxel) and 47 deaths (23 after cabazitaxel and 24 after paclitaxel). There were no significant differences in the DFS, DDFS, and OS rates between the two arms after 3 and 5 years. Patients with HER2− primary breast cancer treated with neoadjuvant cabazitaxel showed significantly lower pCR rate, however, that did not negatively impact survival rates.

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

We thank all participating centers for their commitment and efforts.

Figure 1: GENEVIEVE Study Design (Amendment 2)

<table>
<thead>
<tr>
<th>STUDY GROUPS:</th>
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<tbody>
<tr>
<td>COLLABORATING STUDY GROUPS:</td>
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<tr>
<td>PD Dr. Sherko Kümmel, Clinics Essen-Mitte</td>
<td>G</td>
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<td>G</td>
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<tr>
<td>STUDY CHAIR:</td>
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<tr>
<td>Prof. Dr. Gunter von Minckwitz, Luisenkrankenhaus, Düsseldorf</td>
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<td>STUDY CO-CHAIRS:</td>
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<tr>
<td>Dr. Stefan Paepke, Technical University Munich, Munich</td>
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<td>SPONSOR:</td>
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<tr>
<td>German Breast Group</td>
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<tr>
<td>CONTACT:</td>
<td>G</td>
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<td>B</td>
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<tr>
<td>Jan Steffen Clinical Project Management <a href="mailto:genevieve@GBG.de">genevieve@GBG.de</a></td>
<td>G</td>
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Translational Research & Biobanking

Central Pathology and GBG Tumor Bank 96
New Research Activities 96
Update on ongoing projects 97
Translational Research & Biobanking

Central Pathology and GBG Tumor Bank

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

New Research Activities

**SATURN3**

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

SATURN3 stands for “Spatial and Temporal Resolution of Intratumoral Heterogeneity in 3 hard-to-treat Cancers” (breast cancer, colorectal cancer, and pancreatic cancer). The German Federal Ministry of Education and Research (BMBF) is funding SATURN3 for 5 years as part of the initiative “Nationale Dekade gegen Krebs”. The aim of the SATURN3 consortium is to address intratumoral heterogeneity (ITH), which may be the cause for therapy resistance and the development of metastatic clones. For this purpose, it is first necessary to characterize ITH in patients using innovative tissue sampling schemes, then to functionally explore the underlying mechanisms driving therapy resistance and metastasis, and eventually to validate biomarkers and novel therapeutic strategies within clinical settings.

Nine subprojects will organize recruitment of patients and biomaterial sampling, multi-omics analyses, data modeling, data management, and clinical translation to validate emerging results. Prof. Dr. Sibylle Loibl as the lead of subproject “Clinical Translation” will bring in GBG’s longstanding expertise on clinical study protocols, biomaterial collection, and biomarker validation.

Update on ongoing projects

**Gut microbiome analyses within the “ONCOBIOME” project**

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

The GBG participates with sample collections (tumor tissue and stool samples) as well as expertise in clinical translational research. Collection of stool samples was successfully introduced in the study protocol of CancerTox. Starting with amendment 1, it will also be implemented in the SASCIA study. Feces are collected in a special conservation medium and stored frozen at -20°C. Next generation sequencing of the stool samples to identify cancer-relevant microbial species is conducted at the University of Trento, Italy (Prof. Nicola Segata).

An expression analysis of pre-therapeutic FFPE tumor samples by HTG EdgeSeq is performed at the Institute of Pathology at the University of Marburg (Prof. Denkert), as well as evaluation of stromal TILs (tumor infiltrating lymphocytes).

The rationale for harnessing the gut microbiome in support of cancer therapy and the progress of clinical trials testing this new therapeutic paradigm in cancer patients were highlighted in a recent publication (Dallaire et al. Oncoimmunology 2020).

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

Prof. Andrew Tutt and his team at the ICR, London, and GBG are cooperating on a translational research project aiming to understand the mechanisms of resistance to platinum-based therapy and PARP inhibitors in breast cancer with homologous recombination deficiency (HRD). Cancers with defects in HR-based DNA repair have characteristic chromosomal changes reflecting the use of alternative error-prone repair pathways, thus promoting the growth of cancer cells by inducing de novo driver mutations, generating tumor heterogeneity, and evading apoptosis. Triple negative breast cancer (TNBC) may have diverse defects in HR-based DNA repair through germline mutations in BRCA1, BRCA2 and PALB2, promoter methylation of BRCA1 and RAD51C, and other yet to be identified mechanisms.

The use of PARP inhibitors and platinum-containing chemotherapy regimens is now well-established in advanced breast cancers with germline BRCA1/2 mutation. The GeparOLa, GeparOceto, and GeparSixto trials are among those that have investigated these agents in the neoadjuvant setting, and also in gBRCA1/2 wild type but HRD-positive (homologous recombination deficient tumors). Residual tumors collected within these trials will be analyzed (whole exome/RNA sequencing) to identify genomic and transcriptomic features that may have led to therapy resistance.

Update on ongoing projects

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

https://www.gbg.de/de/forschung/trafo.php

Figure 2: Saturn3 flowchart

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

Update on ongoing projects

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https://www.gbg.de/de/forschung/trafo.php

Figure 2: Saturn3 flowchart
**GBG Study Finder 2023**

### Early Breast Cancer

**Operative Studies (M0)**

<table>
<thead>
<tr>
<th>Operable node-positive breast cancer:</th>
<th>GBG 101: TAXIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Most suspicious lymph node clipped</td>
<td>Tailored axillary surgery with or without axillary lymph node dissection</td>
</tr>
<tr>
<td>• AJCC/UICC stage II-III</td>
<td>followed by radiotherapy. All patients will receive breast/chest wall</td>
</tr>
<tr>
<td>• Eligible for primary axillary lymph node dissection or sentinel lymph node biopsy procedure</td>
<td>and regional nodal irradiation. Patients without axillary lymph node dissection</td>
</tr>
<tr>
<td></td>
<td>will receive additional irradiation of the axilla.</td>
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<table>
<thead>
<tr>
<th>Operable HER2-positive or triple-negative breast cancer:</th>
<th>GBG 104: EUBREAST-01</th>
</tr>
</thead>
<tbody>
<tr>
<td>• cT1c-T3 prior to neoadjuvant treatment and non-pCR</td>
<td>Omission of sentinel lymph node biopsy in patients with radiologic</td>
</tr>
<tr>
<td>• cN0/iN0</td>
<td>and pathologic complete response in the breast after neoadjuvant</td>
</tr>
<tr>
<td>• Standard NAST with radiological complete response</td>
<td>systemic therapy. All patients with confirmed pCR after lpectomy will be</td>
</tr>
<tr>
<td></td>
<td>selected for the single study arm leading to omission of any axillary</td>
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<thead>
<tr>
<th>Neo-adjuvant Studies (M0)</th>
<th>GBG 105: CeparPIPPa</th>
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</thead>
<tbody>
<tr>
<td>HER2-positive, HR-positive breast cancer:</td>
<td>Arm A: Endocrine therapy in combination with ready-to-use fixed-dose</td>
</tr>
<tr>
<td>• cT1c-T3 prior to neoadjuvant treatment</td>
<td>combination of pertuzumab and trastuzumab s.c. (PH-FDC SC) q3w and</td>
</tr>
<tr>
<td>• Centrally confirmed PIK3CA mutation (tumor)</td>
<td>inavobil (6 cycles)</td>
</tr>
<tr>
<td>• BMI ≤30</td>
<td>Arm B: Endocrine therapy and PH-FDC SC q3w (6 cycles)</td>
</tr>
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<thead>
<tr>
<th>Post-neoadjuvant Studies (M0)</th>
<th>GBG 102: SASCIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-negative breast cancer, non-pCR after NACT:</td>
<td>Arm A: Sacituzumab govitecan 8 cycles d1,8 q3w</td>
</tr>
<tr>
<td>• HR-negative (TNBC)</td>
<td>Arm B: Treatment of physician’s choice (8 cycles capcitabine or</td>
</tr>
<tr>
<td>or</td>
<td>platinum-based chemotherapy or observation)</td>
</tr>
<tr>
<td>• HR-positive with CPS-EG score x3 or 2 and ypN+</td>
<td>In patients with HR-positive breast cancer, endocrine therapy will be</td>
</tr>
<tr>
<td>At least 16 weeks of taxane-based chemotherapy</td>
<td>administered according to local guidelines.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HER2-positive breast cancer, non-pCR after NACT:</th>
<th>GBG 103: TruDy/DESTINY-B05</th>
</tr>
</thead>
<tbody>
<tr>
<td>• cT4a, cN0-3 or cT1-3, cN2-3 at first diagnosis of prevention of metastases of the breast</td>
<td>Arm A: Trastuzumab-deruxtecan 14 cycles d1 q3w</td>
</tr>
<tr>
<td>or</td>
<td>Arm B: Trastuzumab-entanetin (T-DMT) 14 cycles d1 q3w</td>
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</table>

### Adjuvant Studies (M0)

<table>
<thead>
<tr>
<th>HR-positive / HER2-negative breast cancer:</th>
<th>GBG 110: CAMBRIA-1**</th>
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</thead>
<tbody>
<tr>
<td>• Intermediate/high risk of relapse</td>
<td>Arm A: Camizelstrant 150mg 3x1/d over 5 years with or</td>
</tr>
<tr>
<td>• 2 - 5 years endocrine therapy (ET)</td>
<td>without LHHRH agonist</td>
</tr>
<tr>
<td>Adequate surgical and systemic pretreatment</td>
<td>Arm B: Continue the standard ET of investigator’s choice</td>
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<tr>
<td></td>
<td>(At or tamoxifen with or without LHHRH agonist)</td>
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<tr>
<th>HER2-positive breast cancer:</th>
<th>GBG 111: Flamingo-01**</th>
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</thead>
<tbody>
<tr>
<td>• Stage I, II or III prior to neoadjuvant treatment and non-pCR</td>
<td>HLA-A*02 subjects will be randomized to GLSI-100 or placebo.</td>
</tr>
<tr>
<td>or Stage III and pCR</td>
<td>Arm A: 11 intradermal doses of placebo (NaCl 0 9%) over 3 years</td>
</tr>
<tr>
<td>• Neoadjuvant chemotherapy (CT) with at least 4 cycles of a taxane-based CT and anti-HER2 therapy</td>
<td>Arm B: 11 intradermal doses of GLSI-100 (blinded) over 3 years</td>
</tr>
<tr>
<td>• Start of study treatment within 90 days after completion of adjuvant trastuzumab</td>
<td>A third open-label arm will explore GLSI-100 in non-HLA-A*02 positive patients</td>
</tr>
<tr>
<td></td>
<td>(11 intradermal doses of GLSI-100 over 3 years)</td>
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### Metastatic Breast Cancer

**All subtypes**

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<tr>
<th>Brain metastases of breast cancer</th>
<th>GBG 79: Brain Metastases in Breast Cancer (BMBC)</th>
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<tbody>
<tr>
<td></td>
<td>Retrospective and prospective registry designed to collect tumor</td>
</tr>
<tr>
<td></td>
<td>characteristics of the primary and metastatic tumor as well as</td>
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<tr>
<td></td>
<td>treatment data and biomaterial from patients diagnosed with breast</td>
</tr>
<tr>
<td></td>
<td>metastases of breast cancer.</td>
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**HER2-negative Breast Cancer**

<table>
<thead>
<tr>
<th>HER2-negative and HR-positive metastatic breast cancer:</th>
<th>GBG 93: PADMIA</th>
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</thead>
<tbody>
<tr>
<td>• 1° systemic therapy for the treatment of metastatic breast cancer</td>
<td>Endocrine therapy + palbociclib versus mono-chemotherapy</td>
</tr>
<tr>
<td>• Patients with asymptomatic oligometastases of the bone as the only site of metastastic disease are</td>
<td>+/- endocrine maintenance therapy</td>
</tr>
<tr>
<td>excluded</td>
<td>Possible mono-chemotherapies (Physician’s choice):</td>
</tr>
<tr>
<td></td>
<td>• Capecitabine p.o.</td>
</tr>
<tr>
<td></td>
<td>• Epirubicin i.v.</td>
</tr>
<tr>
<td></td>
<td>• Paclitaxel i.v.</td>
</tr>
<tr>
<td></td>
<td>• Vinorelbine i.v.</td>
</tr>
</tbody>
</table>

### Breast Cancer in Special Situations

**Pregnancy and Young Women**

<table>
<thead>
<tr>
<th>Patients with breast cancer during pregnancy</th>
<th>GBG 29: BCP</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Non-pregnant women with breast cancer &lt; 40 years</td>
<td>Prospective and retrospective registry study for the diagnosis</td>
</tr>
<tr>
<td>• M1 possible</td>
<td>and treatment of breast cancer in pregnancy compared to young non-pregnant</td>
</tr>
<tr>
<td>women.</td>
<td>women.</td>
</tr>
</tbody>
</table>

**Prophylaxis**

<table>
<thead>
<tr>
<th>Women with a confirmed or likely deleterious BRCA1 germline mutation</th>
<th>GBG 106: BRCA-1**</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Age ≥25 years and ≤55 years</td>
<td>Study to determine the preventive effect of denosumab on metastases of</td>
</tr>
<tr>
<td>• No evidence of breast cancer</td>
<td>breast cancer in women carrying a BRCA1 germline mutation.</td>
</tr>
<tr>
<td>• No preventive breast surgery planned</td>
<td>Denosumab 120mg s.c. every 6 months vs placebo s.c.</td>
</tr>
<tr>
<td>• No previous history of breast or ovarian cancer</td>
<td>every 6 months</td>
</tr>
</tbody>
</table>

### Follow-up

**Long-term Safety and Efficacy**

<table>
<thead>
<tr>
<th>Former GBG study participants from prospective clinical trials. Data reporting by the patient</th>
<th>GBG 71: Patient self-reported outcome registry (PSRO)</th>
</tr>
</thead>
<tbody>
<tr>
<td>via questionnaire.</td>
<td>Collection of long-term safety and efficacy parameters of former GBG</td>
</tr>
<tr>
<td>study participants from prospective clinical trials. Data reporting by the patient via questionnaire.</td>
<td>study participants from prospective clinical trials. Data reporting by the</td>
</tr>
<tr>
<td></td>
<td>patient via questionnaire.</td>
</tr>
</tbody>
</table>

**Former GBG study participants in other countries**

<table>
<thead>
<tr>
<th>GBG 29: BCP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Former GBG study participants from prospective clinical trials. Data reporting by the patient</td>
<td></td>
</tr>
<tr>
<td>via questionnaire.</td>
<td>via questionnaire.</td>
</tr>
</tbody>
</table>

**GBG 71: Patient self-reported outcome registry (PSRO)**

<table>
<thead>
<tr>
<th>GBG 107: ETERNITY**</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Registry for collection of long-term safety and efficacy parameters of former GBG study participants</td>
<td></td>
</tr>
<tr>
<td>from prospective clinical trials. Data collection and documentation is performed study site.</td>
<td></td>
</tr>
</tbody>
</table>

* Further studies are currently in planning. Please refer to [www.gbg.de](http://www.gbg.de)

** Planned start of recruitment QII-III/2023