Article published online: 2025-04-10

COGNITION-GUIDE – Genomics-Guided Targeted Post-Neoadjuvant Therapy in Patients with Early Breast Cancer: Study Design of a Multicenter, Open-Label, Umbrella Phase II Study

COGNITION-GUIDE – Molekulare Diagnostik zur Stratifizierung der post-neoadjuvanten Therapie bei Patientinnen mit Brustkrebs im Frühstadium: Studiendesign einer multizentrischen Open-Label-Umbrella-Phase-II-Studie

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Keywords

precision oncology, early breast cancer, clinical trial in progress, targeted therapy

Schlüsselwörter

Präzisionsonkologie, Brustkrebs im Frühstadium, laufende klinische Studie, zielgerichtete Therapie

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received 23.10.2024
accepted after revision 1.3.2025
published online 10.4.2025

Bibliography
Geburtsh Frauenheilk 2025; 85: 611–619
DOI 10.1055/a-2557-1876
ISSN 0016-5751

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Supplementary Material is available at https://doi.org/10.1055/a-2557-1876

ABSTRACT

Background As part of the COGNITION diagnostic registry program, residual tumor material after neoadjuvant therapy (NAT) of patients with early breast cancer (eBC), who are still at high-risk for relapse after NAT, is analyzed by next generation sequencing to identify biomarkers and actionable alterations. This strategy aims to stratify patients for subsequent genomics-guided therapies to reduce the significant risk of metastatic dissemination and hence to improve disease-free survival.

Patients and Methods COGNITION-GUIDE is a multicenter umbrella phase-II-trial to translate molecular biomarker profiles generated in the COGNITION platform into six molecular-guided post-neoadjuvant therapeutic options in addition to standard-of-care treatment. Patients can be allocated to

1. immune checkpoint inhibition (PD-L1-antibody),
2. PI3K inhibition,
3. AKT inhibition,
4. PARP inhibition,
5. anti-Trop-2 antibody-drug-conjugate,
6. HER2 inhibition or, in case of missing biomarkers, to observation for 12 months.

The primary endpoint is invasive disease-free survival (IDFS) four years after surgery. Secondary endpoints include IDFS in each study arm separately, distant disease-free survival, overall survival and safety. 240 patients will be enrolled within four years.

Conclusions The COGNITION-GUIDE trial, which was activated in June 2023 and will recruit in different centers in Germany, empowers a risk-adapted, biomarker-guided therapy escalation algorithm in eBC patients who are still at high risk of metastasis.

ZUSAMMENFASSUNG

Hintergrund Im Rahmen der COGNITION-Diagnostik-Studie wird verbleibendes Tumorgewebe nach neoadjuvanter Therapie (NAT) von Patientinnen mit Brustkrebs im Frühstadium (eBC), die nach NAT ein erhöhtes Rückfallrisiko haben, mithilfe von Next Generation Sequencing analysiert, um Biomarker sowie aktionsfähige genomische Alterationen zu identifizieren. Das Ziel ist eine Stratifizierung der Patientinnen für nachfolgende genomikgeleitete Therapien, um das erhebliche Risiko einer metastatischen Disseminierung zu reduzieren und dadurch das krankheitsfreie Überleben zu verbessern.

Patientinnen und Methoden COGNITION-GUIDE ist eine multizentrische, übergreifende Phase-II-Studie zur Umsetzung von molekularen Biomarkerprofilen, die mit der COGNITION-Plattform erstellt wurden, in 6 molekular geleitete post-neoadjuvante Therapieoptionen zusätzlich zur Standardbehandlung. Die Patientinnen werden einer Behandlung mit

1. Immuncheckpoint-Inhibitor (PD-L1-Antikörper),
2. PI3K-Inhibitor,
3. AKT-Inhibitor,
4. PARP-Inhibitor,
5. Anti-Trop-2 Antikörper-Wirkstoff-Konjugat,
6. HER2-Inhibitor oder, im Falle fehlender Biomarker, einer Beobachtung über 12 Monate hinweg zugeführt.

Der primäre Endpunkt der Studie ist das invasive krankheitsfreie Überleben (IDFS) 4 Jahre nach dem operativen Eingriff. Zu den sekundären Endpunkten gehören das IDFS für jeden Studienarm, das fernmetastasenfreie Überleben, das Gesamtüberleben und die Sicherheit. Über einen Zeitraum von 4 Jahren werden 240 Patientinnen in die Studie aufgenommen.

Schlussfolgerungen Die im Juni 2023 aktivierte COGNITION-GUIDE-Studie wird bundesweit in verschiedenen Zentren Patientinnen rekrutieren. Die Studie soll die Grundlage für einen risikoadaptierten, biomarkergeleiteten Algorithmus zur Therapieeskalation bei eBC-Patientinnen mit einem hohen Metastasenrisiko schaffen.

Introduction

In early breast cancer (eBC), pathologically evaluated response status after neoadjuvant therapy and surgical resection and the CPS-EG-Score (incorporating pretreatment clinical stage and post-treatment pathologic stage as well as estrogen receptor status and tumor grade) are precise surrogate parameters for risk of relapse and overall survival (OS) helping to discriminate potential high-risk patients which might benefit from additional post-neoadjuvant therapy [1 – 5]. Several randomized phase III studies have shown that adjuvant therapy intensification following surgery in patients at high risk for recurrence with standard of care treatment substantially improves outcome. Capecitabine as adjuvant treatment in patients with triple-negative breast cancer (TNBC)

and residual disease after neoadjuvant treatment (NAT) was associated with improved disease-free (DFS) and OS within the CREATE-X trial [6] (see ▶ **Fig. 1 b**). An adjuvant therapy with olaparib for one year is recommended as standard of care per international guidelines for high-risk patients with human epidermal growth factor receptor 2-negative (HER2−) eBC and a pathogenic germline *BRCA* mutation according to the significant invasive disease-free survival (IDFS) and OS within the OlympiA trial. Within this trial eligible patients after neoadjuvant chemotherapy had a non-pCR in case of TNBC and a non-pCR and a CPS-EG-Score ≥ 3 (see Supplementary Table **S1**) in case of hormone receptor-positive (HR+)/HER2− eBC [7, 8] (see ▶ **Fig. 1 b**). Following the positive results of the monarchE trial, abemaciclib is considered standard of care as adjuvant treatment in patients with high-risk, HR+/HER2− eBC [9, 10]. Ribociclib – tested in a broader population of patients with HR+/HER2− eBC also improves the outcome and is now approved [11]. For HER2-positive (HER2+) eBC, trastuzumab emtansine is the standard post-neoadjuvant treatment in patients with a non-pathological complete response (non-pCR) following neoadjuvant, HER2-directed treatment according to the KATHERINE trial [12, 13] (see ▶ **Fig. 1 b**). However, molecular profiling in the sense of next generation sequencing (NGS-)based whole genome and transcriptome sequencing does not currently play a role in determining molecularly driven therapies in the context of eBC. While gene specific diagnostics, including DNA-sequencing of restricted gene panels, have been used for patient stratification in analogous trials addressing advanced cancer, the benefit of comprehensive molecular analyses including the whole genome and transcriptome to identify additional markers for the same stratification or even novel biomarkers, has rarely been exploited. This multiomics approach seems to be particularly advantageous for the early cancer situation, where genome-guided cellular evolution is not yet governed by therapy-induced selection processes.

The COGNITION (comprehensive assessment of clinical features, genomics and further molecular markers to identify patients with eBC for enrolment on marker driven trials) diagnostic registry program (NCT05852522) was established in 2019 within the existing infrastructure of the National Center for Tumor Diseases (NCT) Heidelberg with a standardized streamlined workflow for whole-genome and transcriptome-sequencing [14]. At present, > 750 patients have been enrolled in the COGNITION diagnostic registry platform.

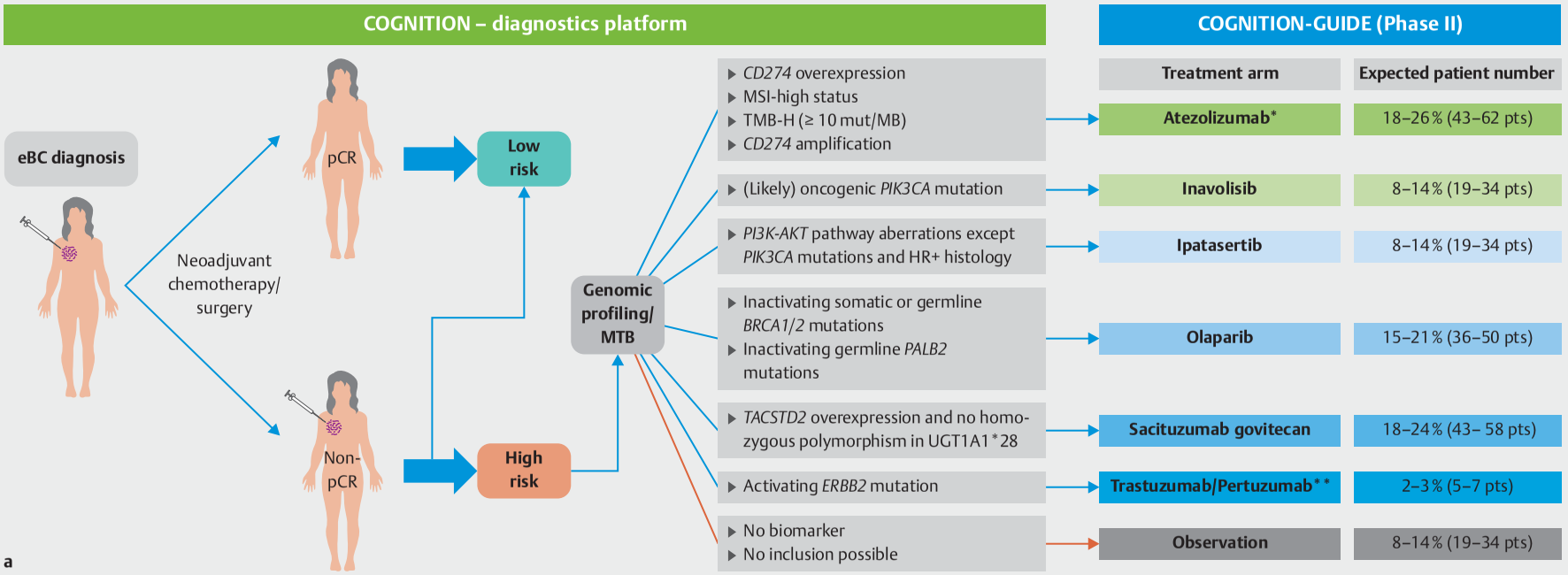
In order to avoid overtreatment in patients with a favorable prognosis, a therapy escalation strategy is exploited in a risk-adapted manner. Within COGNITION, patients with high-risk eBC defined by the existence of a non-pCR for TNBC or HER2+ BC or a high CPS-EG-Score (≥ 3 or, in case of ypN+ disease, ≥ 2) for patients with HR+/HER2− BC are identified. Since the residual tumor burden after NAT presumably reflects the genomic drivers in the periphery, which might give rise to metastasis, the molecular landscape of the treatment-resistant residual tumor is inferred by whole genome and transcriptome sequencing in order to identify molecular alterations that might drive recurrence. Methods of analysis have been previously described [14]. Briefly, fresh tumor tissue of the residual tumor is the preferred material for analysis. In case of insufficient tumor cell content of the fresh tissue (cut-off tumor cell content ≥ 20 %) formalin-fixed, paraffin-embedded (FFPE) material from the tumor specimen resected at surgery is used in case of sufficient tumor cell content of this material. Isolation of DNA and RNA and preparation of the respective libraries for sequencing are carried out. Sequencing data are processed and analyzed using in-house computational pipelines as previously described [14]. The identified molecular targets are used to drive treatment allocation within COGNITION-GUIDE (Genomics guided targeted post-neoadjuvant therapy in patients with early breast cancer), a multicenter, open-label, umbrella phase II study. Within COGNITION-GUIDE (EudraCT: 2019 2020-002606-22, ClinicalTrials.gov: NCT04551521) eligible patients are assigned to one of seven arms after post-neoadjuvant standard-of-care treatment. Arm allocation is determined by the cross-site molecular tumor board (MTB). The primary endpoint is IDFS four years after surgery.

Methods

COGNITION-GUIDE is a multicenter, open-label, umbrella phase II trial investigating the impact of an additional omics-guided post-neoadjuvant therapy in high-risk patients according to tumor response, following standard-of-care NAT, surgery and post-neoadjuvant treatment. The trial will be active for recruitment at different NCT sites in Germany (so far Augsburg, Berlin, Dresden, Heidelberg, Ulm, Tübingen, Erlangen). The first patient in was in Q2/2023.

Patients

Eligible patients are identified within the COGNITION registry platform (NCT05332561) considering pCR-status and CPS-EG-score following NAT and surgery. Within COGNITION pre-therapeutic (baseline prior to NAT) tumor tissue and in particular tumor residues following NAT of patients at high-risk are collected and biobanked. Following individualized prognosis assessment according to the pathological response to NAT, high-risk patients are subjected to whole-genome or whole-exome and RNA sequencing (see ▶ **Fig. 1 a**) to infer clinically-relevant biomarker profiles. High-risk patients are defined as follows: patients with TNBC or HER2+ BC with non-pCR and patients with HR+/HER2− BC with non-pCR and a CPS-EG-score ≥ 3 or ≥ 2 in case of a nodal involvement following NAT (ypN+). Blood-derived non-tumor DNA is profiled to account for germline variants that depict intolerance to specific drugs (pharmacogenomics) and to discriminate germline from true somatic variants in tumor cells. Patients eligible for COGNITION-GUIDE must have previously received NAT, surgery, radiotherapy (if indicated) and standard post-neoadjuvant systemic treatment (capecitabine in case of TNBC or trastuzumab emtansine in case of HER2+ BC) and/or adjuvant treatment with pembrolizumab (in case of TNBC). In case of HR+ disease, endocrine treatment is administered according to standard-of-care guidelines and will be continued as a combination partner for genomic-guided treatment within COGNITION-GUIDE. Patients with an indication for a CDK4/6 inhibitor as part of adjuvant treatment are not eligible. The timeline of COGNITION-GUIDE within the context of the standard therapy is shown in ▶ **Fig. 1 b**. ▶ **Table 1** illustrates the main in- and exclusion criteria for COGNITION-GUIDE.



* Patients that have received prior pembrolizumab in the postneoadjuvant setting cannot be included.
** Patients are supposed to be HER2−.
*** Depending on standard of care PNAT (14 cycles T-DM1 q21d in case of HER2+ histology, 6–8 cycles capecitabine q21d in case HER2− and TNBC).
**** T1 = Biopsy before NAT.
***** T2 = Biopsy after NAT; in case of no available fresh tumor tissue after biopsy, FFPE from surgery is used.
****** According to German guidelines.

▶ **Fig. 1** Trial design of COGNITION-GUIDE. **a** shows the COGNITION-diagnostics workflow (left) in which patients with high-risk eBC are identified and tumor residues after NAT are molecularly profiled. Depending on the molecular findings, patients in COGNITION-GUIDE (right) receive personalized, intensified post-neoadjuvant therapy. Biomarkers, that are determined by whole genome/exome and RNA sequencing, are validated in a certified/accredited laboratory. In this setting, *CD274*-overexpression is defined as PD-L1 positivity (≥ 1% on immune cells) by immunohistochemistry (IHC) and *TACSTD2*-overexpresssion as Trop-2-positivity (H-score ≥ 100) by IHC. The timeline of COGNITION-GUIDE within the context of the COGNITION diagnostics platform and standard-of-care therapy is shown in **b**. Abbreviations: approx.: approximately; eBC: early breast cancer; EOS: end of study; EOT: end of treatment; FFPE: formalin fixed paraffin embedded; FU: follow-up; HR: hormone receptor; IC: informed consent; IMP: investigational medicinal product; max.: maximum; MB: megabase; MSI: microsatellite; mo: months; MTB: molecular tumor board; NAT: neoadjuvant treatment; non-pCR: non-pathological complete response; PNAT: post-neoadjuvant therapy; pts: patients; RT: radiotherapy; TB: tumor board; TMB: tumor mutational burden; T1: 1st/baseline biopsy; T2: 2nd biopsy.

Pixberg C et al. COGNITION-GUIDE – Genomics-guided… Geburtsh Frauenheilk 2025; 85: 611–619 | © 2025. The Author(s).

Trial design and treatment

Molecular eligibility is evaluated in the COGNITION diagnostics platform within the NCT MTB. Decision making within the MTB is based on the NCT and/or ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) level of evidence classification [15–17]. Only predictive biomarkers for which published evidence m1a (positive prospective data within the same entity), m1b (positive retrospective data within the same entity), m2a (positive prospective data within a different entity) or m2b (positive retrospective data within a different entity) according to NCT classification and/or tier I (association with improved outcome in clinical trials), tier II (association with anti-tumor activity, but magnitude of benefit is unknown), or tier III (suspicion to improve outcome based on clinical trial data in other tumor types) according to ESCAT is available are taken into consideration (see ▶ **Fig. 1 a**). Treatment recommendation is based only on biomarkers detected in the post-neoadjuvant tumor tissue (even though pre-NAT tissue, if available, will be also analyzed and compared to post-NAT tissue and the detected tumor evolution will be taken into consideration). Enrolment of eligible patients occurs one to three months after completion of standard post-neoadjuvant therapy. Patients will be assigned to the following treatment arms based on individual biomarker profiles:

1. atezolizumab (anti-PD-L1-antibody, intravenous, 1200 mg every 3 weeks);
2. inavolisib (PI3K inhibitor, oral, 9 mg once daily);
3. ipatasertib (AKT inhibitor, oral, 400 mg once daily);
4. olaparib (PARP inhibitor, oral, 300 mg twice daily);
5. sacituzumab govitecan (anti-Trop-2-antibody-drug-conjugate, intravenous, 10 mg per kilogram of body weight on day 1 and 8 every three weeks);
6. trastuzumab/pertuzumab (anti-HER2-antibodies, subcutaneous, trastuzumab 600 mg plus pertuzumab 1200 mg as a loading dose, followed by trastuzumab 600 mg plus pertuzumab 600 mg every three weeks).

A list of the evidence for each biomarker is presented in Supplementary Table **S2**. Patients that received pembrolizumab according to KEYNOTE 522 are not eligible for the atezolizumab arm. Only patients with HER2− disease will be included in arm 6 in case of an activating HER2-mutation. Patients who fulfil general inclusion criteria but are biomarker negative or do not fulfil inclusion criteria of the recommended treatment arm will be allocated to an observational arm. Treatment period is intended to be 12 months. The investigational medicinal products used in COGNITION-GUIDE are either approved for patients with BC (atezolizumab, olaparib, trastuzumab/pertuzumab, sacituzumab govitecan) or are in late clinical development in patients with BC (inavolisib, ipatasertib). Thus, side effects and management of these investigational medicinal products are characterized. Due to the overall sufficiently favorable pharmacokinetic and pharmacodynamic profiles of endocrine therapies, the combinations with endocrine therapy in the COGNITION-GUIDE study are supposed to be safe

▶ **Table 1** Key eligibility criteria of COGNITION-GUIDE.

General key inclusion criteria[a]
1. Female and male patients with non-metastatic eBC aged ≥ 18 years
2. Either patients with TNBC or HER2+ BC and ▪ Non-pCR defined as other than ypT0/is ypN0 or Patients with initially HR+ and HER2− BC and ▪ Non-pCR and CPS-EG score – ≥ 3 and ypN0, or – ≥ 2 and ypN+
3. Eastern Cooperative Oncology Group Performance Status ≤ 1
4. Conducted NAT, surgery and standard post-neoadjuvant treatment +/− radiotherapy (standard according to German guidelines except a CDK4/6 inhibitor and olaparib)
5. Acute effects of any prior therapy resolved to baseline severity or NCI CTCAE v5.0 grade ≤ 1 except for adverse effects not constituting a safety risk by investigator judgement
General key exclusion criteria[a]
1. Other malignancy within the last 5 years except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, ductal carcinoma in situ, stage 1 grade 1 endometrial carcinoma, or other solid tumors including lymphomas (without bone marrow involvement) curatively treated with no evidence of disease for ≥ 5 year
2. Concurrent severe, uncontrolled systemic disease that would place patient at undue risk or interfere with planned treatment
3. Concurrent or previous treatment within 30 days in another interventional clinical trial with an investigational anticancer therapy
4. Persistent toxicity (≥ grade 2 according to NCI CTCAE v5.0 caused by previous cancer therapy, excluding alopecia)
5. Clinical signs of active infection (> grade 2 according to NCI CTCAE v5.0)
6. History of or newly diagnosed human immunodeficiency virus infection and immunocompromised patients
7. Active hepatitis A, B and/or C virus infection
8. Pregnancy and breast feeding
9. Inability to take oral medication and gastrointestinal disorders likely to interfere with absorption of study medication
10. Major surgery within 4 weeks before screening
11. Heart failure classified as NYHA II/III/IV

[a] refers to the general in- and exclusion criteria of COGNITION-GUIDE. Each treatment arm has separate in- and exclusion criteria that need to be fulfilled within 4 weeks after general inclusion of the patient into COGNITION-GUIDE. For complete eligibility criteria of COGNITION-GUIDE, please visit www.clinicaltrials.gov/study/NCT05332561.

Abbreviations: BC: breast cancer; CPS-EG: pre-treatment clinical stage (CS), final pathological stage (PS), estrogen receptor (E), nuclear grade (G); eBC: early breast cancer; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; MTB: molecular tumor board; NCI CTCAE v5.0: National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0; NCT: National Center for Tumor Diseases; non-pCR: non-pathological complete response; NYHA: New York Heart Association; TNBC: triple-negative breast cancer.

and tolerable. COGNITION-GUIDE is conducted in accordance with the current version of the Declaration of Helsinki, and the protocol is approved (AFmu-741/2022). All patients provide written informed consent prior to participation in COGNITION and COGNITION-GUIDE.

Assessment of endpoints

The primary endpoint of the COGNITION-GUIDE trial is IDFS four years after surgery in the overall cohort. IDFS is defined as the time from surgery to whatever comes first

1. ipsilateral invasive breast tumor recurrence,
2. local/regional invasive breast cancer recurrence,
3. distant recurrence,
4. death attributable to any cause,
5. contralateral invasive breast cancer or
6. second primary non-breast invasive cancer.

Patients without event are censored at the last date of follow-up with tumor assessment. Secondary endpoints include IDFS separately in each study arm, distant disease-free survival, OS and safety. All endpoints are defined according to Hudis et al. [18] and are calculated from time of surgery onwards. Safety is assessed according to Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v5.0). Exploratory endpoints include patient-reported outcomes (PRO) as assessed by the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30), the EORTC BC-specific and fatigue module (EORTC QLC-BR45 and QLQ-FA12, respectively), the Pittsburgh Sleep Quality Index, the Patient Health Questionnaire for Anxiety and Depression (PHQ-4), the Functional Assessment of Cancer Therapy-Cognitive Function questionnaire (FACT-coq), the distress barometer, and the Patient Satisfaction Questionnaire Short Form (PSQ-18).

The clinical value of liquid biopsies is assessed as a further exploratory endpoint. Follow-up is carried out according to German guidelines, i.e. clinical assessment takes place every 3 months in the first 3 years after the end of treatment, followed by every 6 months in years 4 and 5 and annually thereafter. Breast imaging is done on an annual basis.

Statistical analysis

Based on historical data, disease-free survival in high-risk patients with eBC following NAT defined by non-pCR and a high CPS-EG-score (>/3 and ypN0 or >/2 and ypN+), respectively at 4 years after surgery is in the range of 60% to 70% [1, 2, 5, 6, 19]. The outcome of patients with HER2+ eBC and a non-pCR treated with T-DM1 in the KATHERINE trial is increased with an IDFS of 80.8% after 7 years [12]. The IDFS within the CREATE-X trial was 69.8% after 4 years for patients with TNBC and a non-pCR treated with capecitabine [6]. In KEYNOTE-522, the event-free survival after 5 years in patients with TNBC and a non-pCR who were treated with pembrolizumab was 62.6% [19]. Therefore, we test the one-sided null hypothesis H0: IDFS (4-year) ≤ 70%. Assuming exponential survival, uniform accrual over 4 years and a follow-up of 2 years after inclusion of the last patient, sample size is calculated to achieve a power of 90% to reject the null hypothesis at a significance level of 5% given an IDFS rate of ≥ 80% at 4 years. A hypothesis test based on Kaplan-Meier estimator is used. To reach this, 215 patients have to be eligible for the statistical analysis. To account for up to 10% loss to follow-up, 240 patients have to be recruited in total within 4 years. A secondary comparative analysis is planned with patients treated at the same time in a standard of care cohort matching the general characteristics of the study population. The data are provided by the German Breast Group.

Results und Discussion

In contrast to most traditional precision oncology strategies, which exploit the benefits of precision oncology in the management of advanced-stage metastatic BC, to the best of our knowledge COGNITION-GUIDE is one of the first phase II trials evaluating the efficacy, safety, tolerability of molecular driven therapies in an intensified post-neoadjuvant setting in addition to standard of care therapy for patients with high-risk eBC. All drugs were selected with regard to an appropriate risk of toxicity taking the curative setting into account. The specific potential severe side effects include hyperglycaemia (inavolisib, ipatasertib), autoimmune disorders (atezolizumab), cardiotoxicity (trastuzumab/pertuzumab) and/or bone marrow suppression (sacituzumab govitecan).

Antibody-drug-conjugates are being investigated in patients with eBC and a non-pCR following neoadjuvant treatment. SASCIA and ASCENT-05 evaluate sacituzumab govitecan (+ pembrolizumab in ASCENT-05) in patients with HER2− eBC and TNBC, respectively. DESTINY Breast05/TruDy evaluate trastuzumab deruxtecan versus T-DM1 in patients with HER2+ eBC and residual disease after neoadjuvant chemotherapy. In contrast to these trials, COGNITION-GUIDE evaluates a targeted treatment approach in addition to standard-of-care postneoadjuvant therapy.

One limitation of the design is that patients with an indication for a CDK4/6 inhibitor cannot be enrolled in COGNITION-GUIDE. Since treatment with a CDK4/6 inhibitor, after which genomic-guided treatment would have to start, is at least 2 years, we would expect a considerable lead time bias, considering the other, standard post-surgery systemic treatments (capecitabine, pembrolizumab, trastuzumab emtansine), which are administered in a much shorter time window. This will inevitably lead to reduced inclusion of HR+/HER2− BC patients. Considering the results of the OlympiA trial, treatment with olaparib within COGNITION-GUIDE represents the established standard-of-care approach for patients with high-risk eBC and a germline *BRCA* mutation. In addition, supported by results in the metastatic BC setting also patients with a somatic *BRCA* mutation or a germline *PALB2* mutation can be treated with olaparib within COGNITION-GUIDE [20, 21].

The BRE12-158 study tested the concept of a genomically directed treatment approach based on next generation sequencing not in addition to but against treatment of physician's choice (mostly capecitabine) in the post-neoadjuvant setting of patients with TNBC and a non-pCR after NAT [22]. The trial did not meet its primary end-point since no disease-free survival difference was found 2 years after randomization. However, COGNITION-GUIDE and BRE12-158 differ significantly in terms of study design including the comprehensive molecular profiling approach, eligible BC subtypes, start of genomically directed treatment, duration of

treatment, time-point of primary endpoint assessment, and the drugs selected. Most importantly, within COGNITION-GUIDE the genomically guided post-neoadjuvant therapy is given in addition to and not instead of the standard-of-care post-neoadjuvant treatment.

To the best of our knowledge, there are currently no study data or running studies in other entities in which molecular therapies are based on a molecular individual biomarker profile analyzed by omics analysis and that have been applied in the curative setting. In contrast, COGNITION Guide might contribute to a general paradigm shift if molecular therapy selection based on the individual biomarker profile by omics approaches is shown to be feasible and useful in the curative setting.

Supplementary Material

- Supplementary Table **S1:** CPS-EG-Score.
- Supplementary Table **S2:** Biomarker selection for each arm including most relevant evidence in literature.

Trial Registration Numbers

EudraCT: 2020-002606-22; ClinicalTrials.gov: NCT05332561.

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Acknowledgements

We highly appreciate the excellent study nurse support by Annette Sattler, Tina Bausewein, Inan Merve, Sibylle Klessen and Sabine Knothe. Additionally, we are very grateful for the strong support of the Breast Care Team of the Gynecological Department of the University Hospital Heidelberg. Moreover, we would like to thank the Data Management NCT Trial Center (especially Agnes Roth, Angelika Freitag and Marlene Diewald), the NCT Tissue Bank (Alexander Brobeil) as well as the Sample Processing Lab (SPL; Katrin Pfütze) and the Genomics High-Throughput Sequencing facility (Stephan Wolf) at the DKFZ for excellent organizational and/or technical support and the DKFZ Omics IT and Data Management Core Facility (ODCF; Ivo Buchhalter) for data management and data processing. Blood samples were processed and provided by NCT Cell and Liquid Biobank (Anne Merbach), a member of BioMaterialBank Heidelberg. The authors would like to further sincerely thank the patients and their families for study participation. This study was funded by the German Federal Ministry of Education and Research (BMBF) (grant 01EK2202A). Study drugs are provided free of charge by AstraZeneca PLC, Gilead Sciences Inc. and Roche Pharma AG. We also thank the Molecular Precision Oncology Program (MPOP) and the Proof-of-Concept Program of the NCT Heidelberg for supporting the core workflow.

Conflict of Interest

Constantin Pixberg has received speaker's fee from Merck Sharp & Dohme (MSD). **Christian Maurer** declares travel grants from Novartis, Mundipharma, Amgen, Servier Deutschland GmbH, Abbvie, and consulting fees from Daiichi Sankyo, Novartis, Abbvie, Celgene/BMS, Pfizer. **Katharina Smetanay** has received consulting fees from Lilly and honoraria for lectures from Lilly, Pfizer and Gilead, support for attending meetings and/or travel from Lilly, MSD, Daiichi Sankyo and Gilead and is participating on a Data Safety Monitoring Board or Advisory Board from Gilead and Roche. **Mario Hlevnjak** has received speaker's fee from Merck Sharp & Dohme (MSD) and holds stocks from AbbVie, Agilent Technologies, Amgen, AstraZeneca, Eli Lilly, Exact Sciences, Gilead Sciences, Guardant Health, Illumina, Merck Sharp & Dohme (MSD), Novartis, Organon, Veracyte. **Celina V. Wagner** reports support for attending meetings from AstraZeneca. **Laura Michel** has received consulting fees from Lilly and honoraria for lectures from Lilly, Pfizer and Gilead, support for attending meetings and/or travel from Lilly, MSD, Daiichi Sankyo and Gilead and is participating on a Data Safety Monitoring Board or Advisory Board from Gilead and Roche. **Sabine Heublein** received research funding from Novartis, speakers fee from Clovis, AstraZeneca and Pfizer, travel grants from MSD and participates on a data safety monitoring board or advisory board from MSD and Novartis. **Carlo Fremd** received grants from Roche/Genentech and personal fees from Roche/Genentech, AstraZeneca, Gilead, MSD, Novartis, Eisai, Pfizer, GSK and Veracyte. **Peter Sinn** reports a grant from Veracyte and personal fees from Daiichi Sankyo, AstraZeneca and Exact Sciences outside the submitted work. **Nina Ditsch** is part of the advisory boards from Gilead, Lilly, MSD, Novartis, Pfizer, Roche, Seagen. She received honoraria for lectures (personal) from AstraZeneca, Exact Sciences, Pierre Fabre, I-Med-Institute, Merit-Medical, pfm medical ag, Medi-Seminar GmbH, Roche, Lilly, Pfizer, Gilead, Novartis, Daiichi Sankyo and manuscript support (per-

Thieme

sonal) from pfm Medical. She also received trial funding from Gilead, BZKF (institutional). Other COIs (personal): Onkowissen. **Sibylle Loibl** received grants and/or honorarium for adboards and/or contracts from the following entities/all paid to institution: AZ, Abbvie, Agendia, Amgen, BionTech, Celgene/BMS, Cellcuity, DSI, Exact Science, Gilead, GSK, Incyte, Lilly, Medscape, Molecular Health, MSD, Novartis, Pierre Fabre, Pfizer, Relay, Roche, Sanofi, Seagen, Stemline/Menarini, Olema, Bayer, Bicycle, JAZZ Pharma and support for attending meetings and/or travel from DSI, ESMO, SGBCC, ASCO, AGO Kommission Mamma as well as royalties from VM Scope. Following patents are planned, issued or pending: EP14153692.0/EP21152186.9/EP15702464.7. **Stefan Fröhling** reports consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Illumina, Roche and support for attending meetings and/or travel from Roche. **Theresa Link** reports payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events from Amgen, Roche, MSD, Novartis, Pfizer, Lilly, GSK, Gilead, AstraZeneca, Daiichi Sankyo, Stemline, Seagen; support for attending meetings and/or travel from Pfizer, Astra Zeneca, Gilead, Daiichi Sankyo, Stemline; participation on an Advisory Board from MSD, Roche, Pfizer, Lilly, Myriad, Esai, GSK, Gilead, Daiichi Sankyo, Roche, AstraZeneca. **Pauline Wimberger** has received research funding from Amgen, AstraZeneca, MSD, GlaxoSmithKline, Novartis, Pfizer, Roche Pharma, Clovis, Lilly, honoraria from Amgen, AstraZeneca, MSD, GlaxoSmithKline, Novartis, Pfizer, Roche Pharma, Clovis, Teva, Eisai, Lilly, Gilead, Daichii Sankyo and participates at advisory boards from Amgen, AstraZeneca, MSD, GlaxoSmithKline, Novartis, Pfizer, Roche Pharma, Clovis, Teva, Eisai, Lilly, Gilead and Daichii Sankyo. **Jens Uwe Blohmer** reports payment for presentations at satellite symposia: AstraZeneca, Daiichi Sankyo, Eisai, Gilead, MSD, Lilly, Novartis, Pfizer, Roche, Seagen; support for attending meetings and/or travel from AstraZeneca, Daiichi Sankyo, Gilead, Pfizer, Roche; participation on a Data Safety Monitoring Board or Advisory Board from AstraZeneca, Daiichi Sankyo, Eisai, Gilead, MSD, Lilly, Novartis, Pfizer, Roche, Seagen. **Hanna Huebner** is receiving grants or contracts from Novartis Pharma GmbH, payment from Lilly Germany, Novartis Pharma GmbH and Leo Pharma GmbH. **Wolfgang Janni** reports grants or contracts from any entity, consulting fees, payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, payment for expert testimony and/or support for attending meetings and/or travel from AstraZeneca, Cellgene, Chugai, Daiichi Sankyo, Eisai, ExactScience, GSK, Janssen, Lilly, Menarini, MSD, Novartis, Sanofi-Aventis, Roche, Pfizer, Seagen, Gilead, Inivata and Guardant Health. He is participating on a Data Safety Monitoring Board or Advisory Board from AstraZeneca, Cellgene, Chugai, Daiichi Sankyo, Eisai, ExactScience, GSK, Janssen, Lilly, Menarini, MSD, Novartis, Sanofi-Aventis, Roche, Pfizer, Seagen, Gilead, Inivata and Guardant Health. **Richard F. Schlenk** reports consulting fees for advisory board/data safety monitoring board from AbbVie, Daiichi Sankyo, Jazz, and Pfizer; participation on data safety monitoring board: BerGenBio, Novartis; consulting fees for steering committee/expert; testimony from Daiichi Sankyo; honoraria for lectures/speakers bureaus from AstraZeneca, Daiichi Sankyo, Novartis, and Pfizer; receipt of equipment from AbbVie, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, PharmaMar, Pfizer, Roche, Recordati and support for attending meetings and/or travel from Daiichi Sankyo. **Verena Thewes** reports a travel grant from Gilead Sciences. **Andreas Schneeweiss** reports grants from Celgene, Roche and AbbVie, personal fees from Celgene, Roche, Pfizer, AstraZeneca, Novartis, MSD, Tesaro, Lilly, Pfizer, Seagen, Gilead, GSK, Bayer, Amgen, Pierre Fabre, AstraZeneca outside the submitted work.

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