DEUTSCHES KREBSFORSCHUNGSZENTRUM IN DER HELMHOLTZ-GEMEINSCHAFT
Forschen für ein Leben ohne Krebs

NCT NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

getragen von:
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Deutsche Krebshilfe

Clinical Trial Protocol

Genomics guided targeted post-neoadjuvant therapy in patients with early breast cancer – a multicenter, open-label, umbrella phase-II study

COGNITION-GUIDE

Clinical Trial Code:	DKFZ-2019-008
EudraCT No.:	2020-002606-22
Clinicaltrials.gov:	NCT05332561
Clinical Phase:	Phase II
Version and date:	Version 1.1, 12.04.2023
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Abbreviations

Ab	Antibody
ADC	Antibody-drug conjugate
ADL	Activities of Daily life
ADR	Adverse Drug Reaction
AE	Adverse Events
AESI(s)	Adverse Event(s) of Special Interest
AGO	German Society of Gynecological Oncology
AKT	AKT Serine/Threonine Kinase, Proteinkinase B
ANC	Absolute Neutrophil Count
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AMG	*Arzneimittelgesetz,* German Drug Law
AML	Acute Myeloid Leukemia
AST	Aspartate Aminotransferase
ARR	Administration-Related Reactions
AUC	Area under the Curve
BID	Bis in die/ twice a day
BP	Blood Pressure
BC	Breast Cancer
BRCA	Breast Cancer
BUN	Blood Urea Nitrogen
CATCH	Comprehensive Assessment of Clinical Features and Biomarkers To Identify Patients with Advanced or Metastatic Breast Cancer for Marker Driven Trials in Humans
CBP	Child Bearing Potential
CDK	Cyclin-dependent Kinase
CI	Coordinating Investigator
CI (stat.)	Confidence Interval
CHO	Chinese Hamster Ovary (cells)
COGNITION	Molecular diagnostic registry platform: Comprehensive assessment of clinical features, genomics and further molecular markers to identify patients with early breast cancer for enrolment on marker driven trials
COGNITION-GUIDE	Clinical Trial: Genomics guided targeted post-neoadjuvant maintenance therapy in patients with early breast cancer
COGNITION-MOMENT	Registry study of German Breast Group with focus on residual tumors and metastases: A MOMENT (Molecular Mechanisms of Therapy Resistant Breast Cancer) of Cognition. Genomic profiling is conducted in collaboration by NCT / DKFZ along the lines of COGNITION.
CPK	Creatine Phosphokinase

CPS-EG	Pre-treatment clinical stage (CS), post-treatment pathologic stage (PS), pre-treatment estrogen receptor status E and grade (G)
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computed tomograpy
(NCI) CTCAE	(National Cancer Institute) Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCIS	Ductal carcinoma in situ
DCR	Disease Control Rate
DDFS	Distant Disease Free Survival
DDI	Drug-Drug Interaction
DFS	Disease-Free Survival
DILI	Drug-induced liver injury
DNA	Deoxyribonucleic acid
DKFZ	*Deutsches Krebsforschungszentrum,* German Cancer Research Center
DKTK	*Deutsches Konsortium für Translationale Krebsforschung,* German Cancer Consortium
DSGVO	Datenschutz-Grundverordnung (Verordnung (EU) 2016/679)
DSUR	Development Safety Update Report
eBC	Early Breast Cancer
EC	Ethics Committee
ECG	Electrocardiogram
EF	Ejection Fraction
EGFR	Epidermal Growth Factor Receptor (HER1)
ECHO	Echocardiogram
eCRF	Electronic case report form
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of Study
EOT	End of Treatment
ER	Estrogen Receptor
FACT-Cog	Functional Assessment of Cancer Therapy-Cognitive ability scale
FAP	Full Analysis Population
FPI	First patient in, *beginning of the clinical phase*
FSH	Follicle stimulating hormone
fT3 / fT4	Free triiodothyronine / free thyroxine
GBG	German Breast Group
GCP	Good Clinical Practice
Gamma GT	Gamma glutamyltransferase
GMP	Good Manufacturing Practice
Hb	Hemoglobin

HbA1C	Glycosylate Hemoglobin
HBcAb	Hepatitis B core antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HER(2)	Human Epidermal Growth Factor Receptor (2), (ERBB2, erb-b2 receptor tyrosine kinase (2))
HIV	Human Immunodeficiency Virus
HR+	Hormone-Receptor positive
HR (statistics)	Hazard Ratio
I	Inhibitor
IB	Investigator's Brochure
IC	Informed Consent
ICs	Immune cell(s)
IDFS	Invasive Disease-Free Survival
IDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
IHC	Immunohistochemistry
IIT	Investigator Initiated Study
IMP	Investigational medicinal product
INF	Interferon
INFORM	Individualized Therapy For Relapsed Malignancies in Childhood
INR	International normalized ratio
ITT	Intention-To-Treat
IV / i.v.	Intravenous
LDH	Lactate dehydrogenase
LPLV	Last Patient Last Visit
ISF	Investigator Site File
ITT	Intention to treat
LVEF	Left ventricular ejection fraction
KKS	Koordinierungszentrum Klinische Studien
m	Metastatic
MAPK	Mitogen-activated Protein Kinase
MDS	Myelodysplastic Syndrome
MEDRA	Medical Dictionary for Regulatory Activities
MTB	Molecular Tumor Board
mTOR	Mammalian Target of Rapamycin
NACT	Neoadjuvant Chemotherapy
NCT	National Center for Tumor Diseases
NCT DKTK/MASTER	Molecularly Aided Stratification for Tumor Eradication Research
NSCLC	Non-small cell lung carcinoma
NYHA	New York Heart Association

OFS	Ovarian Function suppression
ORR	Overall Response Rate
OS	Overall Survival
P-gp	P-glycoprotein
PARP	Polyadenosine 5'Diphosphoribose [poly (ADP Ribose)] Polymerase
pCR	pathological Complete Response
PCR	Polymerase chain reaction
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand-1
PFS	Progression Free Survival
PHQ-4	Patient Health Questionnaire for Anxiety and Depression
PIK3CA	Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha
PI3K	Phosphatidylinositol 3-kinase
PK	Pharmacokinetic
PIP 2/3	Phosphatidylinositol 4,5-bis/tri phosphate
PLT	Platelet Count
PR	Partial Response
PNACT	Post-Neoadjuvant (Chemo)Standardtherapy (+/- Radiotherapy)
PO / p.o.	Per Os, oral
PRO	Patient Reported Outcome
~~PT~~	Prothrombin Time
(a)PTT	(activated) Partial Thromboplastin Time
PTEN	Phosphatase and Tensin Homolog
PTS	Patients
PSQI	Pittsburgh Sleep Quality Index
QD	Quaque Die/ every day
QoL	Quality of Life
RBC	Red Blood Count
RNA	Ribonucleic acid
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Steering Committee
SC / s.c.	Subcutaneous
SD	Stable Disease
SERD	Selective Estrogen Receptor Downregulator
SOP	Standard Operating Procedures
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TNBC	Triple-Negative Breast Cancer

TROP-2	Trophoblast cell surface antigen-2
TSH	Thyroid stimulating hormone
UGT1A1	UDP-Glucuronosyltransferase 1 Polypeptid A1
ULN	Upper Limit of Normal
WBC	White blood cells/ count
WES	Whole-Exome Sequencing
WGS	Whole-Genome Sequencing
WHO	World Health Organization

Summary

In early breast cancer (eBC), pathological complete response (pCR) after neoadjuvant therapy acts as surrogate marker for metastasis and overall survival. Therapy intensification by adding an adjuvant therapy line (post-neoadjuvant treatment) substantially lowers the risk of relapse in high-risk breast cancer patients with residual disease after neoadjuvant treatment (non-pCR). While this approach was exemplified in two phase III trials without biomarker-stratification (CREATE-X, KATHERINE), even higher efficiency might be achieved by individualized genomic-guided post-neoadjuvant therapies.

To date, prospective whole genomic and transcriptomic sequencing in the framework of precision oncology concepts is predominantly conducted in advanced-stage cancer, limiting the overall benefit mainly to prolongation of progression-free survival rather than cure.

In contrast, the implementation of precision oncology in an early disease stage may empower targeted intervention based on high throughput sequencing at a time point with low tumor burden and limited clonal complexity, harbouring the prospect to substantially improve cure rates by prohibition of incurable metastasis.
Whole-genome (WGS), whole exome (WES), gene panel and transcriptome sequencing in the molecular diagnostic registry platform COGNITION (neoadjuvant-treated eBC patients) revealed relevant diagnostic information on molecular-druggable alterations in a substantial proportion of patients in different molecular pathways (e.g. phosphatidylinositol 3-kinase (PI3K)/ serine/threonine kinase (AKT), apoptosis, DNA-repair, immune escape etc.).

Within the seven-arm umbrella phase-II clinical trial COGNITION-GUIDE, we aim to deliver molecularly-tailored cancer care by implementing an additional response- and genomics-guided post-neoadjuvant therapy after finishing the guideline-compliant post-neoadjuvant treatment in high-risk breast cancer patients with residual cancer burden after neoadjuvant therapy to reduce the substantial risk of local and distant relapse.

The trial evaluates not a single drug but rather a general strategy of precision oncology in the curative setting and provides the basis for future confirmatory biomarker-driven trials.

Eligible patients are identified considering pCR-status and clinical stage estrogen receptor status grade (CPS-EG)-score following surgery after neoadjuvant therapy. Allocation to the therapy-arms is conducted by a molecular tumor board based on in depth molecular characterization of tumors within the COGNITION registry program. Recruitment of adequate patient numbers in well-defined molecular subgroups is achieved in a multicenter approach.

The study aims to show an overall benefit of the precision medicine approach in high-risk eBC patients and to allow for secondary exploratory evaluation of each study-arm.

The primary endpoint of the study is invasive Disease-Free Survival (IDFS) after 4 years measured from surgery to local or distant relapse or death. The sample size of the entire trial is 240 eligible patients.

Zusammenfassung

Beim frühen, potentiell kurativ behandelbaren Brustkrebs (eBC) ist das pathologische evaluierte Ansprechen auf neoadjuvante Therapie (pCR Status) ein Surrogat-Parameter für Metastasierung und Gesamtüberleben. Die Therapie-Intensivierung in Form einer zusätzlichen adjuvanten Therapielinie (post-neoadjuvante Therapie) reduziert substanziell das Rezidivrisiko bei Patientinnen mit Hochrisiko eBC mit Resttumor nach neoadjuvanter Chemotherapie (non-pCR). Dies konnte in zwei randomisierten Phase III Studien ohne Biomarker-Stratifikation (CREATE-X, KATHERINE) gezeigt werden. Basierend auf diesen Ergebnissen ist die Hypothese der vorliegenden Studie, dass mit einer durch das individuelle genetische Profil geleiteten zielgerichteten zusätzlichen post-neoadjuvanten Therapie nach Abschluss der leitliniengerechten post-neoadjuvanten Therapie eine weitere Verbesserung der Wirksamkeit erreicht werden kann.

Molekular-stratifizierte Präzisionsonkologie-Konzepte, welche die prospektive Sequenzierung des gesamten Genoms und des Transkriptoms umfassen, werden gegenwärtig meist bei fortgeschrittenen Krebserkrankungen eingesetzt, bei denen der Nutzen sich vor allem auf die Verlängerung des progressionsfreien Überlebens beschränkt und weniger auf die Verbesserung der Heilungsraten ausgerichtet ist.

Im Gegensatz dazu eröffnet der Einsatz der Sequenzierung des gesamten Genoms und des Transkriptoms in einem frühen Erkrankungsstadium zu einem Zeitpunkt mit geringer Tumorlast und geringer genetischer Komplexität die Möglichkeit, die Heilungsrate mit zielgerichteten Therapien wesentlich zu steigern und das Auftreten einer Metastasierung zu verhindern.

Innerhalb der Molekulardiagnostik Registerplattform COGNITION (eBC Patient:innen mit Indikation für Neoadjuvanz) hat die Hochdurchsatzsequenzierung des Genoms und des Transkriptoms relevante diagnostische Informationen über molekulare Angriffspunkte bei einem beträchtlichen Anteil der Patient:innen in verschiedenen molekularen Signalwegen aufgezeigt (z.B. Phosphatidylinositol 3-Kinase (PI3K)/ Serin-/Threoninkinase (AKT)-, DNA-Reparatur, Apoptose, Immunevasion etc.).

Die sieben-armige COGNITION-GUIDE Phase II-Studie hat das Ziel, im Rahmen der Präzisionsonkologie im frühen, potentiell kurativ behandelbaren Krankheitsstadium durch eine zusätzliche, molekular stratifizierte post-neoadjuvante Therapie die Behandlung von Brustkrebspatientinnen mit hohem Rezidiv- und Metastasierungsrisiko zu verbessern.

Die Studie prüft den Nutzen der Präzisionsonkologie mit Translation in molekular zielgerichteten Therapieansätzen in einem potentiell kurativen Krankheitsstadium als Grundlage für zukünftige konfirmatorische Biomarker-basierte randomisierte interventionelle Studien.

Geeignete Patientinnen und Patienten werden mittels pathologischer Evaluation nach OP und CPS-EG-Score nach neoadjuvanter Therapie und Operation identifiziert und nach eingehender molekularer Charakterisierung der Tumoren im Rahmen des COGNITION-Register-Programms von einem molekularen Tumorboard verschiedenen Behandlungsarmen zugeteilt. Die Rekrutierung adäquater Fallzahlen in klar definierten molekularen Untergruppen wird in einem multizentrischen Ansatz erreicht.

Die Studie prüft, ob ein Gesamtnutzen des präzisionsmedizinischen Ansatzes bei Hochrisiko-eBC-Patient:innen erreicht werden kann und ermöglicht eine explorative Evaluation der einzelnen Studienarme.

Primärer Endpunkt der Studie ist das invasive krankheitsfreie Überleben (Invasive Disease Free Survival, IDFS) nach 4 Jahren (von der Operation bis zum lokalen Rezidiv, Metastasierung oder Tod). Die Fallzahl der gesamten Studie beträgt 240 eingeschlossene Patient:innen.

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Protocol Synopsis

Title

Genomics **guid**ed targeted post-neoadjuvant therapy in patients with **e**arly breast cancer – a multicenter, open-label, umbrella phase-II study (COGNITION-GUIDE)

Trial Phase

Phase II

Sponsor

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Financing/ Status of the Sponsor

The trial is financed by funds of National Center for Tumor Diseases / German Cancer Research Center Heidelberg and the Federal Ministry of Education and Research (BMBF). Study drugs are provided free of charge by Roche Pharma AG, Astra Zeneca and Gilead Sciences.

Number of Sites

Five oncological hospitals in Germany.

Number of Patients

240 eligible patients are enrolled in the study.

Indication

Patients with early breast cancer and high-risk for relapse following neoadjuvant chemotherapy and surgery.

Trial Population

High-risk early breast cancer patients, defined as

- Triple negative breast cancer (TNBC) or human epidermal growth factor receptor 2 (HER2)+ breast cancer (BC) with residual cancer burden (non-pCR, defined as other than ypT0/is ypN0), or
- Hormone-receptor positive (HR+)/HER2- BC with non-pCR and
    - CPS-EG score ≥ 3, or
    - ypN+ and a CPS-EG score ≥ 2

after neoadjuvant therapy, surgery and standard post-neoadjuvant therapy according to current German guidelines.

Patients identified within COGNITION (or COGNITION-MOMENT) as high-risk-patients and who are admitted to and discussed in the NCT molecular tumor board (MTB) are allocated to one of the different therapy-arms of COGNITION-GUIDE in case of druggable genetic/transcriptomic alterations meeting the respective biomarker criteria. High-risk patients who are marker-negative or with failure to conduct molecular profiling are allocated into the observational arm of COGNITION-GUIDE.

General Inclusion Criteria

General inclusion criteria are relevant for all patients at screening and at baseline. Arm-specific inclusion criteria are outlined in the corresponding sub-protocol and are evaluated at baseline.

Patients meeting all of the following criteria are considered for enrollment into the trial:

1. Provision of written informed consent

2. Female and male patients with non-metastatic early (stage I-III) breast cancer aged ≥ 18 years

3. Conducted neoadjuvant chemotherapy and surgery as well as conducted standard post-neoadjuvant treatment +/- radiotherapy (standard according to German guidelines except Abemaciclib and Olaparib)

4. For patients with initially triple negative (TNBC) or HER2-positive breast cancer:

- Non-pCR defined as other than ypT0/is ypN0

5. For patients with initially hormone receptor positive and HER2-negative breast cancer: Non-pCR and CPS-EG score

- ≥ 3 and ypN0, or
- ≥ 2 and ypN+

6. ECOG Performance Status ≤ 1

7. Acute effects of any prior therapy resolved to baseline severity or National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) Grade ≤ 1 except for adverse effects not constituting a safety risk by investigator judgement

8. Postmenopausal or evidence of non-childbearing status. For women of childbearing potential negative urine pregnancy test at post-operative screening and baseline as well as highly effective forms of contraception have to be in place thereafter

- Evidence of childbearing potential is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile
- Postmenopausal or evidence of non-childbearing status is defined as:
    - Amenorrhea for 1 year or more without an alternative medical cause following cessation of exogenous hormonal treatments plus follicle stimulating hormone

(FSH) levels in the postmenopausal range in women not using hormonal contraception or hormonal replacement therapy
    - Chemotherapy-induced menopause
    - Surgical sterilisation (bilateral oophorectomy, bilateral salpingectomy, total hysterectomy or tubal ligation at least 6 weeks before IMP treatment)
    - Female patients with age ≥ 60 years
- A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy

9. Female patients of childbearing potential and male patients with partners of childbearing potential who are sexually active must agree to the use of two forms of contraception in combination (male condom and one highly effective method). These should be started immediately after signing the informed consent form and continued throughout the period of study treatment plus a substance-depending time period (see respective sub-protocol) for female patients and a substance-depending time period for male patients. Details on contraception and pregnancy testing for male and female patients (and if indicated their partners) under IMP treatment are described within the respective sub-protocol

10. Ability of patient to understand and comply with the protocol for the duration of the study, including treatment and scheduled visits and examinations

11. Adequate bone marrow, renal, and hepatic function defined by laboratory tests*

* Arm-specific laboratory parameters and reference values to be met at baseline within 14 days prior to experimental study treatment are described within the respective sub-protocol.

General Exclusion Criteria

General exclusion criteria are relevant for all patients at screening and at baseline. Arm-specific exclusion criteria are outlined in the corresponding sub-protocol and are evaluated at baseline.

Patients presenting any of the following criteria are not included in the trial:

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 (DCIS), Stage 1 grade 1 endometrial carcinoma, or other solid tumours 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 NCI CTCAE v5.0)

6. History of or newly diagnosed human immunodeficiency virus (HIV) infection and immunocompromised patients

7. Active Hepatitis A virus infection

8. Active hepatitis B virus (HBV) infection, defined as having a positive hepatitis B surface antigen (HBsAg) test. Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening , are eligible for the study if active HBV infection is ruled out on the basis of HBV DNA viral load per local guidelines

9. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test at screening confirmed by a polymerase chain reaction (PCR) positive for HCV RNA

10. Dementia or significant impairment of cognitive state

11. Epilepsy requiring pharmacologic treatment

12. Pregnancy and breast feeding

13. Inability to take oral medication and gastrointestinal disorders likely to interfere with absorption of study medication

14. Major surgery (any invasive operative procedure in which a more extensive resection is performed, e.g. a body cavity is entered, organs are removed, or normal anatomy is altered) within four weeks before screening and baseline excluding breast-tumor resection after neoadjuvant chemotherapy. Patients must have recovered from any effects of any major surgery

15. Systemic chemotherapy or radiotherapy within four weeks or a longer period depending on the characteristics of the agents used

16. Heart failure classified as New York Heart Association (NYHA) II/III/IV

17. Severe obstructive or restrictive ventilation disorder

18. Patients with clinically active tuberculosis

19. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug

20. Is taking or requiring the continued use of any of the prohibited concomitant medications listed in the respective subprotocols at baseline

21. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder or non-malignant systemic disease. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, unstable spinal cord compression or, superior vena cava syndrome.

Trial Objectives and Endpoints

Primary Objective

- to improve clinical outcome in early high-risk breast cancer by biomarker-guided post-neoadjuvant therapy (systemic treatment in the adjuvant setting following neoadjuvant therapy, surgery and post-neoadjuvant standard therapy)

Secondary Objectives

- To assess Invasive Disease-free Survival (IDFS) as defined by Hudis et al*,[1] four years after surgery in each study arm separately

To assess

- Distant Disease-free Survival (DDFS) as defined by Hudis et al**,[1] four years after surgery
- overall survival (OS)
- Safety and tolerability of biomarker-guided post-neoadjuvant treatment

in each study arm separately and overall

- To evaluate feasibility of biomarker-guided post-neoadjuvant treatment

Explorative Objectives

- Subjective tolerability, feasibility and quality of life of biomarker-guided post-neoadjuvant treatment evaluated by patient-reported outcomes (PROs) (see chapter 10.2) in each study arm separately and overall
- To assess the clinical value of liquid biopsies in the study context

Primary Endpoint

- IDFS* of patients four years after surgery overall (definition chapter 10.2)

Secondary Endpoints

- OS (definition chapter 10.2)
- IDFS* in each study arm separately (definition chapter 10.2)
- DDFS** (definition chapter 10.2)
- Safety including incidence of adverse events (definition chapter 10.2)

Explorative Endpoints

- Patient reported outcomes (definition chapter 10.2)
- To assess the clinical value of liquid biopsies in the study context

***IDFS: time from surgery to whatever comes first a) ipsilateral invasive breast tumor recurrence, b) local/regional invasive breast cancer recurrence, c) distant recurrence, d) death attributable to any cause incl. breast cancer, e) contralateral invasive breast cancer or f) Second primary non-breast invasive cancer.**

****DDFS: time from surgery to whatever comes first a) distant recurrence, b) death attributable to any cause incl. breast cancer or c) second primary non-breast invasive cancer.**

Trial Design

Multicenter, open-label, multi-arm, umbrella phase-II study

Patients are screened and enrolled earliest 1 month and latest 3 months after completion of post-neoadjuvant standard therapy (including radiotherapy, if indicated). In case of existing exclusion criteria estimated by the investigator as transient a rescreening can be performed within this time frame. The arm-allocation takes place after the interdisciplinary molecular tumor board of the NCT between general inclusion and start of the study-medication. Further arm-specific in- and exclusion criteria are evaluated by the investigator before the start of experimental study treatment (baseline). Study treatment starts within 14 days after the baseline visit. The IMP treatment duration for each patient is expected to be 12 months followed by a substance-depending safety follow-up (observational arm: 12 months).

Visit schedule and assessments are summarized in the trial schedule overview and the trial schedules for each treatment arm in the applicable sub-protocol.

Investigational Medicinal Products and Dosage Overview

Arm 1	Immune Evasion*	Atezolizumab (anti-PD-L1 antibody), i.v.: 1200 mg d1, q21d
Arm 2	PI3K*	Inavolisib (PI3K inhibitor): 9mg, d1-d28, q28d
Arm 3	AKT*	Ipatasertib (AKT inhibitor): 400 mg d1-d28 q28d
Arm 4	DNA Repair*	Olaparib (PARP inhibitor): 300 mg bid d1-d28, q28d
Arm 5	TROP-2*	Sacituzumab Govitecan (TROP-2 antibody), i.v.: 10mg /kg BW, d1, d8, q21d
Arm 6	ERBB2*	Trastuzumab/Pertuzumab (anti-HER2 antibody), s.c.: initial dose: Trastuzumab 600 mg, Pertuzumab 1200 mg, 30 000 units hyaluronidase maintainance dose: Trastuzumab 600 mg, Pertuzumab 600 mg, 20 000 units hyaluronidase; d1, q21d
Arm 7	N/A*	Observational Arm (Biomarker-negative or inability to conduct molecular profiling)

*if hormone-receptor positive (HR+) concurrently to standard-of-care adjuvant endocrine therapy. For specific therapy regimen refer to corresponding sub-protocol.

Sample Size

Based on historical data disease-free survival (DFS) in high risk patients with early breast cancers following neoadjuvant chemotherapy defined by no pathological complete response (for TNBC and HER2+ BC) and a high CPS-EG-score (for HR+HER2- BC) at 4 years after surgery is in the range of 60% to 70% [2-5]. Therefore, we test the one-sided null hypothesis H0: IDFS (4-year) ≤70%. Assuming exponential survival, uniform accrual over 3 year 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. To show this, 215 patients have to be eligible for the statistical analysis. To account for up to 10% loss to follow-up, 240 patients (pts) have to be recruited in total.

The following patient allocation to the respective study-arms is expected:

- Arm 1 Atezolizumab (Immune Evasion) 18-26% (43-62 patients (pts))
- Arm 2 Inavolisb (PI3K) 4-9% (10-22 pts)
- Arm 3 Ipatasertib (AKT) 8-14% (19-34 pts)
- Arm 4 Olaparib (PARP, DNA-Repair) 15-21% (36-50 pts)
- Arm 5 Sacituzumab Govitecan (TROP-2) 18-24% (43-58 pts)
- Arm 6 Trastuzumab / Pertuzumab (ERBBB) 2-3% (5-7 pts)
- Arm 7 Observation* 8-14% (19-34 pts)
  (*Biomarker-negative or inability to conduct molecular profiling)

Statistical Analysis.

The primary endpoint IDFS is analyzed according to the Kaplan-Meier method and confidence interval (CI) estimation for IDFS is based on the cumulative hazard function using Greenwood's formula for variance estimation. All secondary endpoints are analyzed in an explorative manner. After the overall assessment of the primary hypothesis explorative subgroup analyses in the different treatment arms are performed. Interim safety analyses are performed in all arms after 24 and 36 months.

Trial Duration and Dates

Total trial duration:	90 months
Recruitment period:	48months
Minimum endpoint follow-up:	48 months after surgery
Duration of clinical phase:	84 months (FPFV – LPLV)
First patient first visit (FPFV)	Q2/2023
Last patient first visit (LPFV):	Q1/2027 (FPFV + 48 months recruitment)
Last patient last visit (LPLV):	Q1/2030 (FPFV + 84 months clinical phase)
Trial Report Completed:	Q4/2030 (LPLV + 6 months)

Trial Schedule - Overview

Overview of trial design, **general assessments for all study arms** regarding screening, baseline and follow-up period and schedule for observational arm.
A detailed **trial schedule** for **each treatment arm** (baseline, study treatment, end of treatment, safety follow-up) is specified in the **applicable sub-protocol**.

		Screening[1]	Baseline[2,3] Arm-Specific: see Sub-Protocols	Study Treatment (Arms 1 - 6)[2] Treatment Cycles dependent on IMP (+/- 2 days) Treatment Arms 1-6: See Sub-Protocols			End of Treat-ment	Safety Follow-up[5,6]	Follow-up Period
			Baseline[2,3] General / Arm Allocation[17]	Observation (Arm 7) Visits every 3 months after Baseline (+/- 7 days)			End of Observation[4]		
	Cycle and visit description	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6		
		1 - 3 months after end of standard therapy[3]	≤ 28 days after enrollment	Month 3	Month 6	Month 9	12 months after treatment start or Baseline		FU every 3 month for 3 years and then all 6 month until EOS
	Clinical Assessments								
	Informed consent	X	X (IMP)[5,7]						
	Demographics	X							
	Medical/ oncologic history	X							
	Inclusion/ Exclusion	X[1]	X[8]						
	Signs/ symptoms	X	X						
	Vital signs	X	X	X	X	X	X		
	Physical examination	X	X	X	X	X	X		
	ECOG	X	X				X		
	ECHO		X				(X)		
	ECG	X	X	(X)	(X)	(X)	(X)		
	Enrollment	X							
	Arm allocation		X[18]						

		Screening[1]	Baseline	Observation (Arm 7)				Follow-up
				Month 3	Month 6	Month 9	Observation End	
	Laboratory Assessments							
	Hematology (local lab)	X	X	X	X	X	X	
	Blood chemistry (local lab)	X	X	X	X	X	X	
	Coagulation (local lab)	X	X					
	Urinanalysis (local lab)	X	X				X	
	HAV, HBV, HCV, HIV-1 (local lab)	X						
	Pregnancy test (if CBP, local lab)	X	X				X	
	Biobanking Blood samples (central lab)[9, 10]		X[11]	X			X	X[12]
	Breast Cancer Status[13]							
	Clinical exam. (breast)		X	X	X	X	X	X
	Sonography		X				X	X
	Mammography		X				X	X
	Further Assessments							
	Background medication	X	X	X	X	X	X	X
	Concomitant medication	X	X	X	X	X	X	
	PRO[14, 15]		X[11]	X	X		X	X[12]
	SADRs background medication	X	X	X	X	X	X	X
	AESIs / SADRs of IMP during FU[5,16]							X
	Status / survival patients							X

Description of footnotes:

1. Assessment of general in- and exclusion criteria; in case existing exclusion criteria are estimated as transient by the investigator, a re-screening can be performed within the time frame of screening.

2. Refer to sub-protocols for baseline assessments of treatment arms 1-6. Additional arm-specific assessments are required.

3. In treatment arms, baseline assessments can be performed 14 days prior to start of study treatment until day 1 before administration of IMP.

4. also referred to as “end of treatment” (EOT)

5. Not applicable for the observational arm.

6. Plus 28 days except for study arm 1 (atezolizumab) and study arm 6 (trastuzumab/pertuzumab): plus 10 weeks.

7. Informed consent form for the applicable arm-specific IMP treatment is obtained.

8. Assessment of general and arm-specific in- and exclusion criteria; in case not meeting of in- or existing exclusion criteria are estimated as transient by the investigator, a re-evaluation can be performed within the time frame for baseline.

9. For detailed blood draw schedule please refer to chapter 7.2.2.5.

10. In case of temporary discontinuation (cycle delay) or premature discontinuation of IMP blood draws for biobanking should be taken as close as possible to the 3 month and 12 month point in time after therapy start (+/- 4 weeks).

11. At baseline visit (all arms) or arms 1-6: day 14 to day 1 prior to IMP administration.

12. Every 6 month until end of year four after surgery.

13. Breast cancer status and FU according to S3- and German Society of Gynecological Oncology (AGO)-Guidelines. Assessments are performed within the clinical standard routine of breast cancer follow up care, results of the last assessment are documented.

14. Please refer to chapter 7.2.4 Further Assessments.

15. PRO-Assessments are performed at baseline, 3 and 6 months after baseline, EOT and then every 6 month until end of year four after surgery. Refer to chapter 7.2.4.

16. Within the follow-up period, only SADRs and AESIs are collected and are reported to the pharmaceutical company as well as to the NCT trial center in copy (refer to chapter 9.8).

17. Patients are allocated to the therapy arms according to the report of the NCT molecular tumor board. At baseline, after (re-)assessment of arm-specific and general in- and exclusion criteria by the investigator, arm allocation is completed.

1 Introduction

1.1 *Scientific Background*

Despite high cure-rates for early breast cancer patients (about 421.000 new diagnoses / per year in Europe), annually about 129.000 patients die of the disease. Thus, breast cancer is a major cause of tumor-related deaths, which is predominantly attributed to tumor progression with metastatic dissemination [6-8].

In the past, conventional treatment decisions in breast cancer were largely guided by standard clinical-pathological prognostic and predictive biomarkers such as hormone-receptor, human epidermal growth factor receptor 2 (HER2)-status and proliferation markers like KI-67 as well as grading. In the last decade, the extensive application of high-throughput genomic and transcriptomic sequencing facilitated therapy stratification by deep molecular profiling [9-13]. Nowadays large-scale initiatives such as the MOSCATO-01 trial across all entities have demonstrated the feasibility and the clinical benefit (objective response 11% (95%, confidence interval (CI) 7%-17%) of prospective integrative implementation of deep sequencing into the clinical routine [14].

In Heidelberg, the precision oncology platforms NCT DKTK/MASTER for young adults with advanced-stage or rare cancers as well as the INFORM registry for recurrent pediatric tumors enable multidimensional genomic-profiling (whole-genome/exome and transcriptome sequencing) for unbiased detection of drug targets and biomarkers [15,16,17].

While these approaches allow cross-entity enrolment, a similar dedicated structure specifically for advanced-stage/metastatic breast cancer (CATCH) was implemented at the NCT Heidelberg enrolling approximately 120 patients per year [18].

All programs share a streamlined, standardized workflow for the identification of acquired genomic and transcriptomic aberrations following clinical evaluation within an interdisciplinary molecular tumor board, which prioritize and rank evidence-based therapeutic options *in-* and *off-label* and in particular assign patients to omics-guided interventional clinical trials. The power of pre-defined individual biomarkers is categorized by a reproducible evidence-built scoring system based on published data [16,19].

Despite advances in sequencing reliability and cost reductions, these omics-based precision oncology concepts have been predominantly focused on advanced-stage and metastatic cancers, limiting the overall benefit mainly to prolongation of progression-free survival in the palliative setting rather than of increasing cure rates.

Efficacy data for personalized-driven treatment based on molecular profiling for patients with early breast cancer are so far not available. Standard therapy in the curative setting is mostly not driven by specific biomarkers and cannot address the individual genetic tumor landscape of each patient.

The molecular stratification of an extended post-neoadjuvant treatment for high risk early breast cancer (eBC) patients provides an excellent opportunity to test the benefit of precision oncology in a clinical curative situation.

In eBC standard treatment for high-risk molecular subtypes such as Luminal B, HER2-positive and Triple-Negative Breast Cancers (TNBC) conventionally comprises cytotoxic chemotherapy, which is nowadays predominantly administered as a neoadjuvant (pre-operative) treatment regimen. It has been demonstrated that neoadjuvant chemotherapy (NACT) and adjuvant chemotherapy have similar rates for distant recurrence (1.02 [95% CI 0.92-1.14]; p=0.66) breast cancer mortality (1.06 [0.95-1.18]; p=0.31) and death from any cause (1.04 [0.94-1.15]; p=0.45) vs. adjuvant chemotherapy in the long-term analyses (15 years) [20]. However, beyond the initial intention to downsize locally advanced tumors for surgical purposes, these neoadjuvant treatment schemes outperform traditional adjuvant therapies for various reasons:

Most importantly, given the tight correlation between the extent of residual cancer burden and overall survival, neoadjuvant therapies harbour the advantage to identify high-risk patients

requiring treatment escalation very early in the course of their disease before developing frank metastatic disease[2].

Two standard-classifiers can be used to identify high-risk early breast cancer patients after NACT[3,21-23]:

a) In TNBC and HER2+ BC: non pathological complete response (non-pCR)
b) In HR+, -HER2- BC: non-pCR plus CPS-EG score ≥ 3 in ypN0 or a CPS-EG score ≥ 2 in ypN+ (CPS-EG: pre-treatment clinical stage (CS), post-treatment pathologic stage (PS), pre-treatment estrogen receptor status E and grade (G) according to).

Hence, the residual local cancer burden after neoadjuvant therapy acts as a surrogate marker for the systemic tumor burden, which might give rise to metastatic dissemination [3,21-23].

While for a large proportion of neoadjuvant-treated patients, no detectable tumor material is left, about 20-30 % of the patients present with highly therapy-resistant residual bulk tumors at the time point of surgery. This initial lack of response tightly correlates with an increased risk of relapse and metastasis as, depending on the molecular subtype, 30-50% of the patients with residual invasive disease after neoadjuvant therapy (non-pCR) relapse within the first 5-years[21,24,25].

In summary, the tumor burden after tumor resection and thereby the assessment of the high risk state can identify patients with a substantial risk of relapse who require further treatment intensification to improve outcome.

1.2 *Trial Rationale/ Benefit- Risk Assessment*

To reduce the considerable risk of relapse in high-risk eBC patients with residual invasive disease after neoadjuvant therapy (non-pCR), intensification of treatment by adding an adjuvant therapy line after neoadjuvant intervention (post-neoadjuvant treatment) harbours the prospect to substantially lower the risk of relapse, which has been emphasized in two randomized phase III trials. The addition of adjuvant capecitabine in the CREATE-X trial in HER2-negative residual invasive breast cancers despite neoadjuvant treatment with anthracyclines and taxanes (n=910) resulted in an improved disease-free survival (DFS) of 74.1% *vs.* 67.6% after 5-years (hazard ratio (HR) 0.7, 95%, CI 0.53 to 0.92; p=0.01) as well as an extended overall survival (89.2% *vs.* 83.6%, HR 0.59; 95% CI, 0.39 to 0.90; p=0.01) [26]. Recently, the phase III KATHERINE trial further confirmed that the substitution of trastuzumab by T-DM1 (ado-trastuzumab ematansine) in patients with residual HER2-positive disease after neoadjuvant chemotherapy and trastuzumab substantially lowered the risk of invasive recurrence (DFS events: 12.2% of patients in the T-DM1 arm, compared to 22% in the trastuzumab arm; HR 0.50; 95% CI, 0.39 to 0.64; p<0.001) highlighting the advantages of post-neoadjuvant treatment regimens [27].

These post-neoadjuvant interventions in early breast cancer already demonstrated significant outcome improvements despite lack of biomarker-guided stratification.

Omics-matched therapeutic intervention according to the unique omic tumor profile at an early time point in the disease course possesses the advantage of limited overall tumor burden, corresponding lower tumor heterogeneity as which may result in a higher therapeutic efficacy in the eradication of pre-metastatic cell clones in the circulation.

Consequently, the major goal of the strategy is to eliminate cell clones resistant to standard neoadjuvant treatment at an early stage, thereby liberating patients from their high risk of local and distant relapse.

The COGNITION molecular diagnostic registry platform of the National Center for Tumor Diseases (NCT) has been implemented in April 2019 and enrols eBC patients with an indication for neoadjuvant standard therapy. The platform integrates systematic collection of clinical data and biomaterial (tissue and blood) as treatment-naïve baseline biopsies and from residual tumors after neoadjuvant therapy along with corresponding blood samples (Figure 1).

Samples from high-risk patients with treatment-resistant residual tumors after neoadjuvant pre-operative therapy will be subjected to comprehensive genomic-profiling. Fresh-frozen or formalin-fixed paraffin embedded (FFPE) breast tissue from residual bulk tumors is obtained after neoadjuvant therapy by fine-needle biopsies or during surgery and analyzed by genomic high-throughput sequencing and evaluated by the interdisciplinary molecular tumor board of the NCT. Genomic aberrations and transcriptomic changes (e.g. mutations, copy number alterations, mutational signatures, expression patterns) are analysed and discussed in the clinical context using an evidence-based biomarker scoring system in an interdisciplinary molecular tumor board by the combined expertise of clinicians, bioinformaticians, molecular biologists, pathologists and human geneticists in order to delineate potential routes for treatment intensification and to assign patients to respective biomarker-guided treatments[16,19].

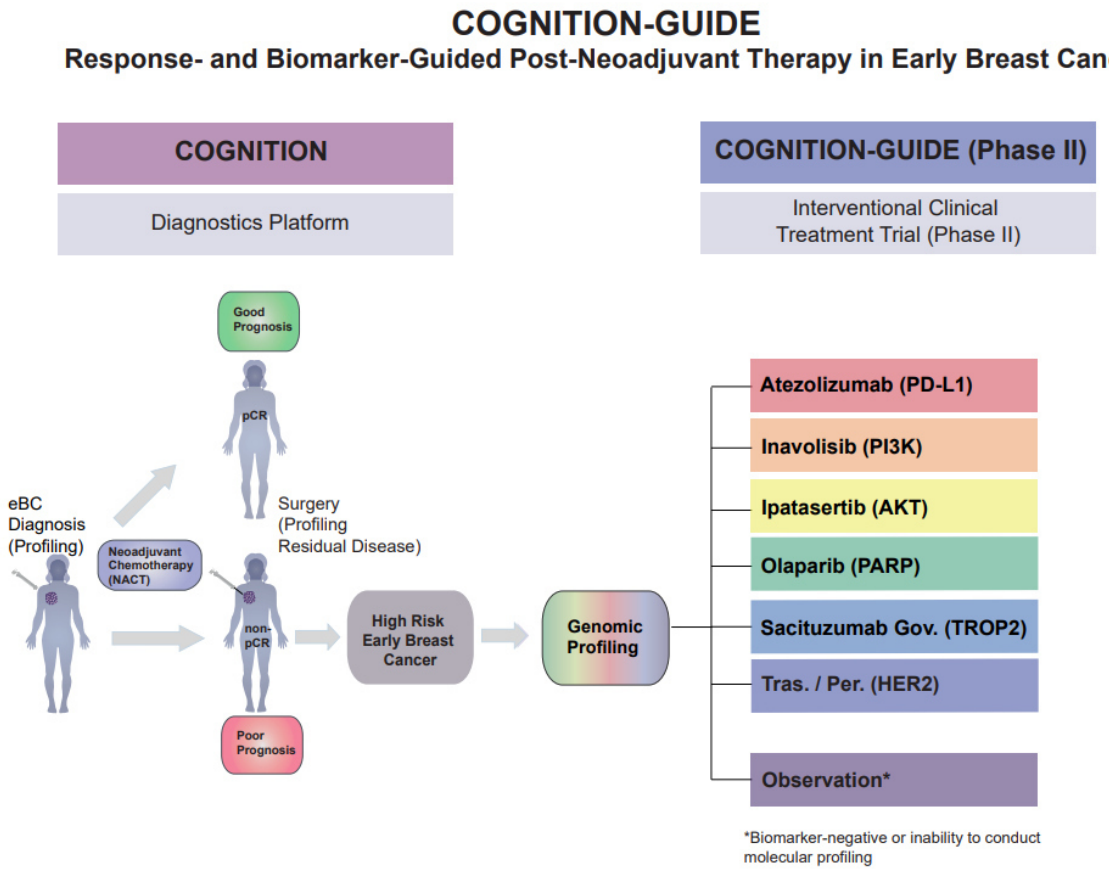

Figure 1. Design of molecular diagnostic registry platform COGNITION and clinical trial COGNITION-GUIDE

Due to lack of existing biomarker-guided targeted post-neoadjuvant interventional trials and ethical constraints in the early curative setting, which prohibit *off- label* treatment, therapy administration has to be accomplished in an interventional clinical trial (COGNITION-GUIDE).
Importantly the benefit of individualized treatment within precision oncology frameworks in the early disease stage, has to be assessed in a rigorous clinical trial with standardized assessments and a hypothesis driven statistical analysis[28]. Based on the success of non-stratified post-neoadjuvant treatment intensification in eBC and the overall benefit of precision oncology trials in advanced-stage disease, one can envisage that additional genomic-matched post-neoadjuvant treatment harbours the prospect to achieve further clinical benefit for individual patients.

The investigational medicinal products (IMPs) used in COGNITION-GUIDE are either approved for breast cancer or other indications (atezolizumab, olaparib, trastuzumab/pertuzumab, sacituzumab govitecan) or are in late clinical development in advanced breast cancer with an expected approval (inavolisib, ipatasertib). Thus, side effects and their management of these IMPs are already characterized.

In case of HR+ positive disease (ER ≥1%), patients receive standard-of-care endocrine therapy backbone according to German “S3-guideline” and AGO guidelines [Tamoxifen or aromatase inhibitor (exemestane, letrozole or anastrozole) -/+ ovarian function suppression (OFS), i.e. with zoladex]. Adjuvant bone targeted therapy with bisphosphonates or denosumab is allowed according to German guidelines.

Due to the overall sufficiently favourable pharmacokinetic and -dynamic profiles of endocrine therapies, the combinations with endocrine therapy in the COGNITION-GUIDE study are supposed to be safe and tolerable [29]. In addition, upcoming safety signals in published studies and within the COGNITION-GUIDE study are communicated on a regular basis with short turn-around times according to German and European law.

Given the tremendous risk of generalized metastasis in this high-risk study cohort with relapse rates between 30-50% within 5 years following surgery [21,25] without further therapeutic intervention and/or standard post-neoadjuvant treatment, we expect a highly favorable risk/benefit ratio in the COGNITION-GUIDE study.

Short- and long-term toxicities that have been described and are expected for the specific agents are described within the corresponding sub-protocols.

1.3 *Reference Committee*

1.3.1 Independent Data Monitoring Committee (IDMC)

The IDMC is composed of three independent experts, assessing the progress and safety data. The mission of the IDMC is to ensure the ethical conduct of the trial and to protect the safety interests of patients in this trial.

Meetings of the IDMC are planned after 24 and 36 months after FPI (when results of the safety interim-analyses for these timepoints are available). Additionally, safety monitoring is performed separately in each treatment arm after 6 and 12 patients have finished at least one cycle of the study treatment. This arm-specific safety analysis is reviewed by the IDMC via e-mail discussion. Based on its review, the IDMC will provide the sponsor with recommendations for the conduct of the trial, modifications and further IDMC meetings, if applicable. Further details including IDMC members are specified in the IDMC charter.

1.3.2 Steering Committee (SC)

COGNITION-GUIDE is steered in regular intervals by the scientific steering committee including all principle site investigators, the scientific leads of the study (CI, Co-CI, scientific program coordination, clinical counselor) and patient´s representatives. The SC members meet virtually every 6 months from time of first site initiation. The mission of the SC is to ensure the scientific basis for decisions on trial modifications and to provide expertise in study conduct, analyses of data and the scientific quality of the final study report.

2 Trial Objectives and Endpoints

2.1 Primary Objective

- to improve clinical outcome in early high-risk breast cancer by biomarker-guided post-neoadjuvant therapy (systemic treatment in the adjuvant setting following neoadjuvant therapy, surgery and post-neoadjuvant standard therapy)

2.2 Secondary Objectives

- To assess Invasive Disease-free Survival (IDFS) as defined by Hudis et al*,[1] four years after surgery in each study arm separately

To assess

- Distant Disease-free Survival (DDFS) as defined by Hudis et al**,[1] four years after surgery
- Overall Survival (OS)
- Safety and tolerability of biomarker-guided post-neoadjuvant treatment

in each study arm separately and overall

- To evaluate feasibility of biomarker-guided post-neoadjuvant treatment

2.3 *Explorative Objectives*

- Subjective tolerability, feasibility and quality of life of biomarker-guided post-neoadjuvant treatment evaluated by patient-reported outcomes (PROs) (see chapter 10.2) in each study arm separately and overall
- To assess the clinical value of liquid biopsies in the study context

2.4 Primary Endpoint

IDFS* of patients four years after surgery overall (definition chapter 10.2)

2.5 Secondary Endpoints

- IDFS* in each study arm separately (definition chapter 10.2)
- DDFS** (definition chapter 10.2) in each study arm separately and overall
- OS (definition chapter 10.2) in each study arm separately and overall
- Safety including incidence of adverse events (definition chapter 10.2) in each study arm separately and overall

2.6 *Explorative Endpoints*

- Patient reported outcomes (definition chapter 10.2) in each study arm separately and overall
- To assess the clinical value of liquid biopsies in the study context

***IDFS: time from surgery to whatever comes first a) ipsilateral invasive breast tumor recurrence, b) local/regional invasive breast cancer recurrence, c) distant recurrence, d) death attributable to any cause incl. breast cancer, e) contralateral invasive breast cancer or f) Second primary non-breast invasive cancer.**

****DDFS: time from surgery to whatever comes first a) distant recurrence, b) death attributable to any cause incl. breast cancer or c) second primary non-breast invasive cancer.**

3 Trial Design

Multicenter, open-label, multi-arm, umbrella phase II study.

4 Trial Duration and Schedule

High-risk patients defined by non-pCR-state and CPS-EG-score will be screened and enrolled in COGNITION-GUIDE earliest 1 month and latest 3 months after completion of post-neoadjuvant standard therapy (including radiotherapy, if indicated). In case of existing exclusion criteria estimated by the investigator being potentially transient, a rescreening can be performed within this time frame. The arm-allocation takes place after the interdisciplinary molecular tumor board of the NCT between general inclusion and start of the study-medication. Further arm-specific in- and exclusion criteria are evaluated by the investigator before the start of experimental study treatment (baseline) and are specified in the applicable sub-protocol. Study treatment starts within 14 days after the baseline visit.

The IMP treatment duration for each patient is expected to be 12 months followed by a substance-depending safety follow-up (observational arm: 12 months). In the follow-up period breast cancer status and survival will be continuously followed according to standard S3- and AGO guidelines every 3 months for 3 years and every 6 months from year 4 on until end of study (EOS).

Conditions leading to patient withdrawal from the study are detailed in Section 5.6 Criteria for Withdrawal. In case of relapse, study therapy is stopped.

A recruitment period of 4 years and an overall study duration of 7.5 years (incl. completion of trial report) is anticipated. Start of patient recruitment is planned for the second quarter of 2023.

The clinical phase of the trial ends, when the last patient has completed endpoint follow-up 4 years after surgery (LPLV / end of study).

After finishing all study-relevant procedures, therapy, and follow-up period, the patient will be followed in terms of routine care and treated if necessary by the primary responsible oncology center.

Trial Duration and Dates

Total trial duration:	90 months
Recruitment period:	48months
Minimum endpoint follow-up:	48 months after surgery
Duration of clinical phase:	84 months (FPFV – LPLV)
First patient first visit (FPFV)	Q2/2023
Last patient first visit (LPFV):	Q1/2027 (FPFV + 48 months recruitment)
Last patient last visit (LPLV):	Q1/2030 (FPFV + 84 months clinical phase)
Trial Report Completed:	Q4/2030 (LPLV + 6 months)

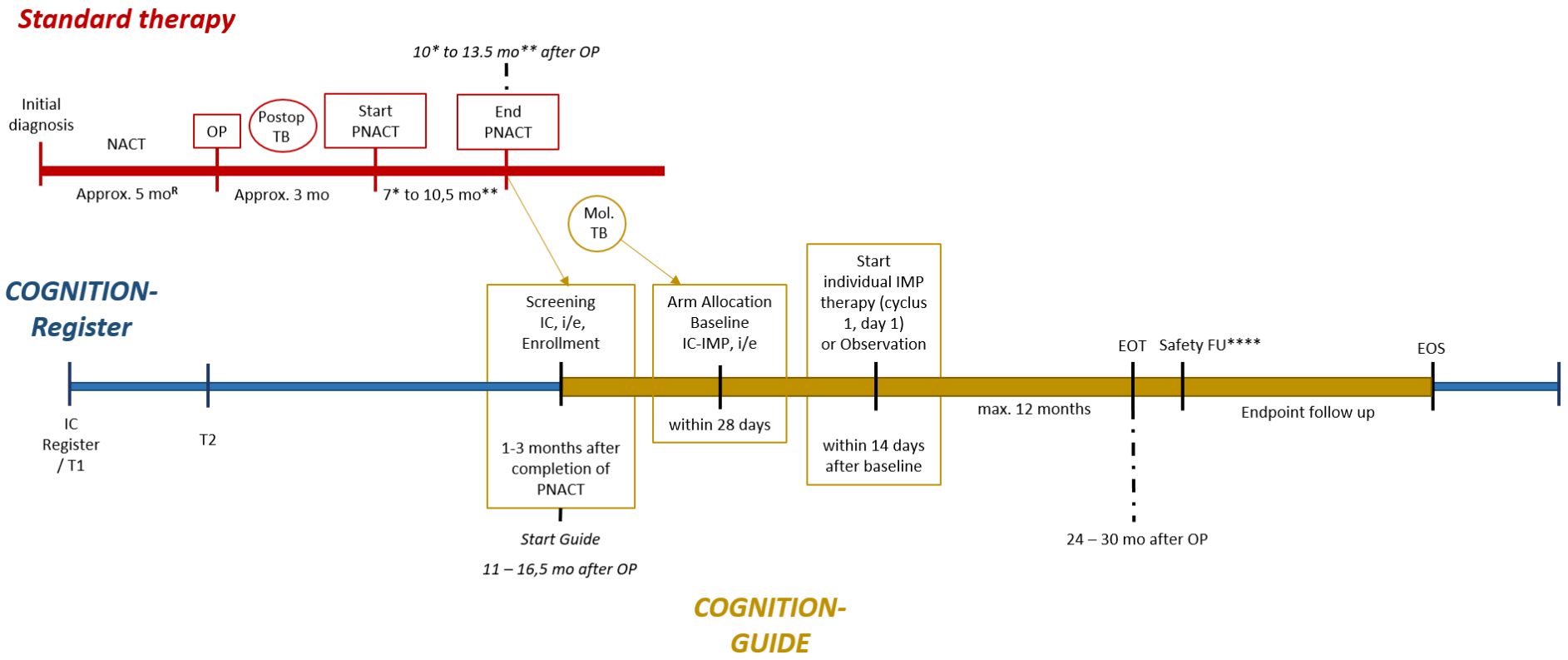

Figure 2: Timeline for COGNITION-GUIDE in the context of standard therapy and COGNITION

* Depending on standard therapy. In case of capecitabine (approx. 7 months including 18 weeks capecitabine plus 6-7 weeks RT).

** In case of T-DM1 (10.5 months inclusive RT).

*** In case of existing exclusion criteria estimated by the investigator as transient, a rescreening can be performed within the time frame of screening.

OP = surgery, IC = informed consent, i/e = inclusion / exclusion criteria, TB = tumor board, T1 = 1. Baseline biopsy COGNITION, T2 = 2. Biopsy COGNITION, NACT = standard neoadjuvant chemotherapy, PNACT = standard post-neoadjuvant (chemo)therapy, RT= radiotherapy, IMP = investigational medicinal product, EOT = end of treatment, EOS = end of study.

****Safety follow up for IMP arms (28 days, for study arms 1 and 6: 10 weeks).

5 Selection of Patients

5.1 *Number of Patients and Recruitment*

During a recruitment period of 4 years, 240 patients are enrolled in the clinical trial. Details on patient numbers and sample size calculation are depicted in chapter 10.3. Recruitment and treatment of patients are performed in five trial centers. 48 pts are recruited in average per site.

Based on experience within the molecular diagnostic registry platform COGNITION, the following patient allocation to the respective study arms is expected:

- Arm 1 Atezolizumab (Immune Evasion) 18-26% (43-62 patients (pts))
- Arm 2 Inavolisib (PI3K) 4-9% (10-22 pts)
- Arm 3 Ipatasertib (AKT) 8-14% (19-34 pts)
- Arm 4 Olaparib (PARP, DNA-Repair) 15-21% (36-50 pts)
- Arm 5 Sacituzumab Govitecan (TROP-2) 18-24% (43-58 pts)
- Arm 6 Trastuzumab / Pertuzumab (ERBBB) 2-3% (5-7 pts)
- Arm 7 Observation* 8-14% (19-34 pts)
  (*Biomarker-negative or inability to conduct molecular profiling)

5.2 *General Criteria for Patients' Selection*

High-risk early breast cancer patients, defined as

- Triple negative breast cancer (TNBC) or human epidermal growth factor receptor 2 (HER2)+ BC with residual cancer burden (non-pCR, defined as other than ypT0/is ypN0 after surgery), or
- Hormone-receptor positive (HR+)/HER2- BC with non-pCR after surgery and
  - CPS-EG score ≥ 3, or
  - ypN+ and a CPS-EG score ≥ 2

after neoadjuvant therapy, surgery and standard post-neoadjuvant therapy according to current German guidelines.

Patients identified within COGNITION (or COGNITION-MOMENT, see below) as high-risk-patients and who are admitted to and discussed in the NCT molecular tumor board (MTB) are allocated to one of the different therapy-arms of COGNITION-GUIDE in case of druggable genetic/transcriptomic alterations meeting the biomarker criteria of the different therapy arms (please refer to 5.3 for the specific molecular inclusion criteria). High-risk patients who are marker-negative or with failure to conduct molecular profiling are allocated into the observational arm of COGNITION-GUIDE.

5.3 *Arm-Specific Criteria for Patients' Selection*

The biomarker-guided eligibility for the respective study arm is evaluated and determined exclusively by the NCT molecular tumor board on the basis of results of the COGNITION molecular diagnostic registry platform or of results from other molecular studies, when genomic profiling is performed according to the streamlined end-to-end workflow of the NCT (e.g., COGNITION-MOMENT, where genomic profiling is conducted in collaboration by NCT / DKFZ along the lines of COGNITION). Decision making of the tumor board is based on the validated evidence levels of ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) published by Leichsenberg et al.[19]. Only those predictive biomarkers for which published evidence m1a, m1b, m2a or m2b is available are taken into consideration. In addition, the following conditions are applied: 1) Patients with PIK3CA-mutations eligible for inclusion in arm 2 (inavolisib) are not allocated in arm 3 (ipatasertib); 2) Patients eligible for inclusion in study arms 1, 2, 3, 4 and 6 are not considered for inclusion in arm 5 (sacituzumab govitecan).

Further arm-specific in- and exclusion criteria are evaluated by the investigator before the start of study treatment and are specified in the applicable sub-protocol.

Biomarkers, that are determined by whole genome sequencing and RNA sequencing within COGNITION (refer to chapter 1.2), are validated or identified in a certified/accredited laboratory (see specifications in footnotes 1-3. Biomarkers that allow inclusion in the respective arm are:

- **Arm 1 (Atezolizumab, Immune Evasion)** [1]:
  - PD-L1 positivity measure by IHC (≥1% on immune cells within the tumor)
  - MSI-high status (validated by PCR)
  - TMB-H (≥10mut/MB)
  - CD274 amplification
- **Arm 2 (Inavolisib, PI3K)** [2]**:**
  - Known/reported oncogenic mutation in PIK3CA
- **Arm 3 (Ipatasertib, AKT)** [2]**:**
  - Aberrations predicting increased PI3K-AKT pathway activity except PI3K-mutations
  - HR positive histology
- **Arm 4 (Olaparib, PARP, DNA-Repair)** [2]**:**
  - Inactivating somatic or germline BRCA1/2 mutations, including homozygous deletions
  - Inactivating germline PALB2 mutations
- **Arm 5 (Sacituzumab Govitecan, TROP-2)** [3]**:**
  - Trop-2-overexpression (with IHC and except known/reported homozygous polymorphism in UGT1A1*28)
- **Arm 6 (Trastuzumab / Pertuzumab, ERBBB)** [2]:
  - HER2 exon-20 insertion
  - Activating HER2-mutation

In case of more than one MTB-recommendation, the allocation to treatment arms is performed according the MTB priority listing, in that higher priority is preferable but patient´s eligibility regarding further specified arm-specific in- and exclusion criteria of the applicable sub-protocol has to be considered.

[1].PD-L1 positivity will be determined/confirmed using a validated immunohistochemistry assay in a certified pathology laboratory according to IMpassion130 trial criteria (see sub-protocol arm 1, reference no. 8) which is PD-L1 expression on ≥1% tumor-infiltrating immune cells expressed as a percentage of tumor area.
MSI status will be determined/confirmed according to criteria and cutoffs used in a validated assay performed by a certified pathology laboratory.
TMB status will be determined/confirmed in a validated assay or analysis workflow performed by a certified/accredited laboratory with the cutoff for TMB-H defined as ≥10 mutations per megabase.
CD274 amplification status will be determined/confirmed according to criteria and cutoffs used in a validated assay or analysis workflow performed by a certified/accredited laboratory.

[2].Biomarker positivity will be determined/confirmed by gene panel according to criteria and cutoffs used in a validated assay or analysis workflow performed by a certified/accredited laboratory.

[3].Trop2 expression will be determined/confirmed using a validated immunohistochemistry assay and histochemical scoring in a certified pathology laboratory. Trop2 positivity is defined as H-score ≥100, which corresponds to intermediate or high Trop2 expression levels based on the biomarker analysis of the ASCENT trial (see sub-protocol arm 5, reference no. 4).

5.4 *General Inclusion Criteria*

General inclusion criteria are relevant for all patients at screening and at baseline. Arm-specific inclusion criteria are outlined in the corresponding sub-protocol and are evaluated at baseline.

Patients meeting all of the following criteria are considered for enrollment into the trial:

1. Provision of written informed consent
2. Female and male patients with non-metastatic early (stage I-III) breast cancer aged ≥ 18 years
3. Conducted neoadjuvant chemotherapy and surgery as well as conducted standard post-neoadjuvant treatment +/- radiotherapy (standard according to German guidelines except Abemaciclib and Olaparib)
4. For patients with initially triple negative (TNBC) or HER2-positive breast cancer:
    - Non-pCR defined as other than ypT0/is ypN0
5. For patients with initially hormone receptor positive and HER2-negative breast cancer: Non-pCR and CPS-EG score
    - ≥ 3 and ypN0, or
    - ≥ 2 and ypN+
6. ECOG Performance Status ≤ 1
7. Acute effects of any prior therapy resolved to baseline severity or National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0) Grade ≤ 1 except for adverse effects not constituting a safety risk by investigator judgement
8. Postmenopausal or evidence of non-childbearing status. For women of childbearing potential negative urine pregnancy test at post-operative screening and baseline as well as highly effective forms of contraception have to be in place thereafter
    - Evidence of childbearing potential is defined as fertile, following menarche and until becoming post-menopausal unless permanently sterile
    - Postmenopausal or evidence of non-childbearing status is defined as:
        - Amenorrhea for 1 year or more without an alternative medical cause following cessation of exogenous hormonal treatments plus follicle stimulating hormone (FSH) levels in the postmenopausal range in women not using hormonal contraception or hormonal replacement therapy
        - Chemotherapy-induced menopause
        - Surgical sterilisation (bilateral oophorectomy, bilateral salpingectomy, total hysterectomy or tubal ligation at least 6 weeks before IMP treatment)
        - Female patients with age ≥ 60 years
    - A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy
9. Female patients of childbearing potential and male patients with partners of childbearing potential who are sexually active must agree to the use of two forms of contraception in combination (male condom and one highly effective method). These should be started immediately after signing the informed consent form and continued throughout the period of study treatment plus a substance-depending time period (see respective sub-protocol) for female patients and a substance-depending time period for male patients. Details on contraception and pregnancy testing for male and female patients (and if indicated their partners) under IMP treatment are described within the respective sub-protocol
10. Ability of patient to understand and comply with the protocol for the duration of the study, including treatment and scheduled visits and examinations
11. Adequate bone marrow, renal, and hepatic function defined by laboratory tests*

* Arm-specific laboratory parameters and reference values to be met at baseline within 14 days prior to experimental study treatment are described within the respective sub-protocol.

5.5 *General Exclusion Criteria*

General exclusion criteria are relevant for all patients at screening and at baseline. Arm-specific exclusion criteria are outlined in the corresponding sub-protocol and are evaluated at baseline.

Patients presenting any of the following criteria are not included in the trial:

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* (DCIS), Stage 1 grade 1 endometrial carcinoma, or other solid tumours 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 participation or previous treatment within 30 days in another interventional clinical trial
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 NCI CTCAE v5.0)
6. History of or newly diagnosed human immunodeficiency virus (HIV) infection and immunocompromised patients
7. Active Hepatitis A virus infection
8. Active hepatitis B virus (HBV) infection, defined as having a positive hepatitis B surface antigen (HBsAg) test. Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study if active HBV infection is ruled out on the basis of HBV DNA viral load per local guidelines
9. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test at screening confirmed by a polymerase chain reaction (PCR) positive for HCV RNA
10. Dementia or significant impairment of cognitive state
11. Epilepsy requiring pharmacologic treatment
12. Pregnancy and breast feeding
13. Inability to take oral medication and gastrointestinal disorders likely to interfere with absorption of study medication
14. Major surgery (any invasive operative procedure in which a more extensive resection is performed, e.g. a body cavity is entered, organs are removed, or normal anatomy is altered) within four weeks before screening and baseline excluding breast-tumor resection after neoadjuvant chemotherapy. Patients must have recovered from any effects of any major surgery
15. Systemic chemotherapy or radiotherapy within four weeks or a longer period depending on the characteristics of the agents used
16. Heart failure classified as New York Heart Association (NYHA) II/III/IV
17. Severe obstructive or restrictive ventilation disorder
18. Patients with clinically active tuberculosis
19. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug
20. Is taking or requiring the continued use of any of the prohibited concomitant medications listed in the respective subprotocols at baseline
21. Patients considered a poor medical risk due to a serious, uncontrolled medical disorder or non-malignant systemic disease. Examples include, but are not limited to, uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, unstable spinal cord compression or, superior vena cava syndrome.

5.6 *Criteria for Withdrawal*

5.6.1 Withdrawal of Patients

A patient may be withdrawn from the trial treatment or/and all trial-related procedures for the following reasons:

- At any time at their own request or at request of the legal representative, withdrawal of patient's consent to start or to continue therapy. The patient is at any time free to discontinue treatment, without prejudice to further treatment.
    - In case of treatment discontinuation the patient is followed up according to the regular study procedures (safety follow up, endpoint follow up)
    - In case of withdrawal of informed consent the patient is withdrawn from further trial related procedures. If informed consent is withdrawn before start of experimental study therapy, the patient is replaced, see 5.6.3).
- Pregnancy
- Non-compliance by the patient with protocol requirements
- Patients are withdrawn from the trial treatment in case of unacceptable toxicity or progressive disease
- Patients who were not admitted to or discussed in a molecular tumor board (e.g. no tumor tissue available) are withdrawn from further trial related procedures (and are replaced, see 5.6.3).
- Patient is lost to follow-up. If a patient does not return for scheduled visits, every effort should be made to re-establish contact. In any circumstance, every effort should be made to document patient outcome if possible

5.6.2 Handling of Withdrawals

In all cases, the reason for withdrawal must be recorded in the CRF and in the patient's medical records. In case of withdrawal of informed consent, the reason should be asked for as extensively as possible and documented. Patients should be specifically asked if they are withdrawing informed consent to further participation in the study including any further follow up (e.g. status, survival), to the use of their study generated data or to the use of any samples collected.

If the patient withdraws informed consent, no further evaluations are allowed to be performed and no additional data can be collected. The sponsor may retain and continue to use data collected before such withdrawal of consent according to regulatory requirements and guidelines.

Patients withdrawn from the trial retain their identification codes (e.g. allocation number or Patient ID, if already given).

All ongoing AEs/ Serious Adverse Events (SAEs) of withdrawn patients have to be followed up until no more signs and symptoms are verifiable or the patient is on stable condition.

5.6.3 Replacement of Patients

Patients are replaced in the following cases:

- Patients who withdraw informed consent before start of experimental therapy
- Patients who were not admitted to or discussed in a molecular tumor board

Further replacement of patients is not performed.

5.6.4 Premature Closure of the Clinical Trial or a Single Center

The trial or single study arms can be prematurely closed or suspended by the sponsor after consulting the coordinating investigator. The Ethics Committee (EC) and the Competent Regulatory Authorities must then be informed. Furthermore, the Ethics Committee(s) and Competent Regulatory Authorities themselves may decide to stop or suspend the trial.

Should the trial be closed prematurely, all trial material (investigational medicinal product and other material) must be returned to the sponsor or treated according to sponsor's notice.

All involved investigators have to be informed immediately about a cessation/suspension of the trial or a single arm. The decision is binding to all trial centers and investigators.

The trial or single study arms may be prematurely closed, if

- New risks to patients become known which lead to a change of the risk-benefit assessment
- Unfavourable side effect profile (high amount of SAEs/ suspected unexpected serious adverse reactions (SUSARs))
- Slow accrual
- New scientific results rendering the research questions addressed overall no longer sound and innovative

in the trial or in a single arm, respectively.

The sponsor after consulting the coordinating investigator has the right to close a center, at any time, in case of:

- Non-compliance with the protocol
- Poor data quality
- No or slow recruitment

5.7 *Prior and Concomitant Illnesses*

Relevant additional illnesses present at the time of informed consent and/or baseline are regarded as concomitant illnesses and are documented on the appropriate pages of the eCRF. Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities which appear for the first time or worsen (intensity, frequency) during experimental study treatment (incl. safety follow up) are adverse events (AEs) and must be documented on the appropriate pages of the eCRF.

5.8 *Background Medication*

Background medication is used according to the different sub-protocols of the different treatment arms.

Endocrine anti-cancer therapy, if applicable, is captured in the eCRF.

5.9 *Prior and Concomitant Medication / Non-Drug Treatment*

Relevant additional treatments administered to the patients on entry to the trial or at any time during experimental study treatment are regarded as concomitant treatments and must be documented on the appropriate pages of the CRF. Every given drug is checked for possible cross-reactions with treatment medication from COGNITION-GUIDE. Concomitant treatments not permitted during or prior to experimental study treatment are specified for each sub-protocol individually.

6 Investigational Medicinal Product/-s

For further details refer to individual sub-protocols.

6.1 *General Information about Investigational Medicinal Product/-s*

Refer to sub-protocols.

6.2 *Therapeutic/ Diagnostic Effects*

Refer to sub-protocols.

6.3 *Known Side Effects*

Refer to sub-protocols.

6.4 *Dosage Schedule*

Each patient is intended to remain on experimental study treatment for 12 months. In case of intolerability to study treatment or disease progression / relapse study therapy is stopped.

The investigator may temporarily suspend IMP dosing due to IMP related toxicity or an unanticipated medical event not associated with study treatment toxicity or with disease progression. Dose interruptions for any component of study treatment should not exceed 28 days. If the interruption is any longer, the clinical counselor must be informed, if continuation of study treatment is intended by the investigator. Patients withheld from treatment beyond 28 continuous days are expected to stop study treatment unless confirmation of extension for extenuating circumstances received from the NCT study team.

Administration of IMP and dosage adjustments / toxicity management are specified in the sub-protocols.

6.5 *Contraception*

Female patients of child bearing potential and male patients with partners of child bearing potential, who are sexually active, must agree to the use of 2 forms of contraception in combination (male condom plus one of the highly effective methods listed below) or must totally/truly abstain from any form of sexual intercourse (see below), throughout their participation in the study from the signing of the informed consent and for a substance-depending time period after last dose (see respective sub-protocol).

Acceptable non-hormonal birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly:

- Total/True abstinence: When the patient refrains from any form of sexual intercourse and this is in line with their usual and/or preferred lifestyle; [Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods, or declaration of abstinence solely for the duration of a trial) and withdrawal are not acceptable methods of contraception]
- Vasectomised sexual partner PLUS male condom. With participant assurance that partner received post-vasectomy confirmation of azoospermia.
- Tubal occlusion PLUS male condom
- Intrauterine device (IUD) PLUS male condom. Provided coils are copper-banded
- Hormonal methods are not acceptable for breast cancer patients

Regarding IMP-arms, details on contraception are specified in the respective sub-protocol.

Contraception within the observational arm will be conducted according to standard S3- and AGO-Guidelines.

6.6 *Overdose*

Refer to sub-protocols.

6.7 *Treatment Assignment*

The trial medication is administered only to patients enrolled in this trial. It is administered according to the trial schedule (refer to sub-protocols).

The allocation to the biomarker-guided treatment-arms is based on the in depth molecular characterization of tumors and the evaluation of the interdisciplinary molecular tumor board of NCT (refer to chapter 1.2).

The study is open-label.

Assignment to study arms and dosage overview:

Arm 1	Immune Evasion*	Atezolizumab (anti-PD-L1 antibody), i.v.: 1200 mg d1, q21d
Arm 2	PI3K*	Inavolisib (PI3K inhibitor): 9 mg d1-d28, q28d
Arm 3	AKT*	Ipatasertib (AKT inhibitor): 400 mg d1-d28 q28d
Arm 4	DNA Repair*	Olaparib (PARP inhibitor): 300 mg bid d1-d28, q28d
Arm 5	TROP-2*	Sacituzumab Govitecan (TROP-2 antibody) i.v.: 10 mg/kg BW, d1, d8, q21d
Arm 6	ERBB2*	Trastuzumab/Pertuzumab (anti-HER2 antibody), s.c.: initial dose: Trastuzumab 600 mg, Pertuzumab 1200 mg, 30 000 units hyaluronidase maintainance dose: Trastuzumab 600 mg, Pertuzumab 600 mg, 20 000 units hyaluronidase; d1, q21d
Arm 7	N/A*	Observational Arm (Biomarker-negative or inability to conduct molecular profiling)

*if HR+ concurrently to standard-of-care adjuvant endocrine therapy. For specific therapy regimen refer to corresponding sub-protocol.

6.8 *Supplies, Packaging and Labeling*

Refer to each individual sub-protocol.

6.9 *Accountability*

The investigator keeps an account of the trial medication and acknowledges the receipt of all shipments of the trial medication. All trial medication must be kept in a locked area with access restricted to designated trial staff. The investigational medicinal product must be stored dry and in accordance with manufacturer's instructions as specified in each sub-protocol. The investigator keeps accurate records of the quantities of trial medication dispensed, used, and returned by each patient. The documentation has to include date of dispensary, patient identification, batch/ serial numbers or other identification of trial medication. The site monitor checks periodically accountability records and the supplies of trial medication held by the investigator to ensure the correct accountability of all trial medication used. At the end of the trial, all unused trial medication and all medication containers are completely returned or destroyed locally according to sponsor´s instructions. It is assured that a final report of the drug accountability is prepared and maintained by the investigators of the study sites.

6.10 *Compliance*

Trial medication is dispensed/applied to the patients by the investigator or another authorized study personal / physician. In case of IMP (e.g. tablets) is handed out to patients, they are instructed to bring all trial medication to the trial site at every visit. Patients are asked to document the study drug intake on a provided schedule. Compliance is assessed by count of tablets, capsules, vials and so on. Details are recorded on the Drug Accountability Form.

7 Trial Methods

7.1 *Registration and Enrollment*

Patients should be included earliest 1 month and latest 3 months after completion of post-neoadjuvant standard therapy (incl. radiotherapy, if indicated). In case of existing exclusion criteria estimated by the investigator as transient a rescreening can be performed within this time frame.

After the informed consent form has been signed by a patient, the trial site team has to register the patient in the eCRF-system by completion of the respective module immediately. During this registration, a Patient-ID is automatically generated (number of the site plus number of the patient at the site). The Patient-ID is used to identify the patient throughout the clinical study and must be used on all study related documentation. Registration is performed even if the subject is a screening failure.

A patient who signed the informed consent and is fulfilling all of the general inclusion criteria and not meeting any of the general exclusion criteria is considered eligible and is enrolled in the study. Eligibility must be confirmed by the investigator by signing the respective module in the eCRF. A patient who signed the informed consent but does not meet all general in- and exclusion criteria is considered a screening failure.

For eligible patients the pseudonym of the COGNITION molecular diagnostic registry platform or COGNITION-MOMENT has to be entered in the eCRF.

The arm-allocation to a specific study arm according to the recommendation of the NCT molecular tumor board takes place between general inclusion and start of the study medication.

7.2 *Description of Clinical, Laboratory and Therapeutic Measurements*

The trial schedules for each specific therapy arm are depicted in each sub-protocol separately. General study examinations and procedures are described as follows. For design overview please refer to the trial schedule overview.

Clinical status and laboratory parameters are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician, which can involve more frequent testing, especially in neutropenic/aplastic patients. It is expected that enrolled patients are supervised for by physicians experienced in the treatment and supportive care.

7.2.1 Clinical Assessments

- **Informed consent** and patient registration: every patient must date and sign the informed consent to participate in this trial before starting any trial-related procedures. After signature, a patient ID is assigned by the eCRF (refer to 7.1).
  For patients allocated to a therapy arm (arms 1-6), an IMP-specific informed consent is signed before start of study treatment (baseline).

- **Demographics**: Gender, year of birth, ethnicity.

- **General medical and oncologic history**: Date of diagnosis, detailed information on tumor diagnosis, including ICD-0-3 and ICD10 codes, information on tumor subtype (e.g. hormone receptor status, HER2 expression level), information on arm allocation according to recommendation of the NCT molecular tumor board, date and outcome of breast cancer surgery, detailed information on pre-treatment including type and composition of prior therapy as well as response to prior therapy, family history, additional medical history on concomitant diseases, prior exposure to toxic agents, prior malignancy including therapy, information on smoking.

- **Inclusion / exclusion criteria:** general inclusion/exclusion criteria as defined in chapters 5.4 and 5.5 are assessed at screening and before start of study treatment (baseline); at baseline, for patients allocated to a therapy arm according to recommendation of the molecular tumor board, arm-specific inclusion/exclusion are assessed and must be met as specified in the applicable sub-protocol.

- **Signs / symptoms:** Tumor-related and unrelated signs and symptoms at screening and baseline.

- **Vital signs:** Height, weight, temperature (°C), and heart rate and blood pressure (after 5 minutes in a sitting position) are collected at screening and every study visit from baseline until safety follow up. Height (in cm) is measured at screening only.

- **Physical examination:** inspection, abdominal, cardiac and lung auscultation, palpation of the abdomen and lymph node sites, neurological examination. Physical examination is conducted at screening and every study visit from baseline until safety follow up.

- **Echocardiography (ECHO):** at baseline and thereafter at investigator's discretion or if specified in the applicable sub-protocol. If abnormal at baseline, ejection fraction (EF) has to be quantified, and thereafter in case of abnormal findings. EF has to be specified according to Simpson.

- **Electrocardiogram (ECG):** Twelve-lead ECGs is obtained after the patient has been rested in a supine position for at least 5 minutes in each case. The Investigator or designated physician reviews the paper copies of each of the timed 12-lead ECGs on each of the study days when they are collected. ECG is performed at screening, baseline and thereafter at investigator's discretion or if specified in the applicable sub-protocol.

  ECGs is recorded at 25 mm/sec. All ECGs are assessed by the investigator as to whether they are clinically significantly abnormal / not clinically significantly abnormal. If there is a clinically significant abnormal finding after the baseline visit, the Investigator records it as an AE on the eCRF or as SAE if applicable. The original ECG traces must be stored in the patient medical record as source data.

  For the purpose of this study, QTc intervals are calculated according to the formula of Bazett:

$$QTc = \frac{\overline{QT}\,(ms)}{\sqrt{RR\,(sec)}}$$

  For QTc intervals >500 ms and ≤470 ms, check magnesium and potassium levels and correct any abnormalities. If possible, stop any medication that may prolong the QTc interval. Continue/discontinue or reduce study medication according the respective sub-protocol.

- **ECOG Performance Status** is performed at screening, baseline and EOT.

- Further arm-specific clinical assessments are specified in the respective sub-protocol.

7.2.2 Laboratory Assessments

7.2.2.1 Safety Assessment

- **Hematology (local lab):** Hemoglobin (Hb), red blood count (RBC), MCV/MCH/MCHC, PLT, white blood cells/ count (WBC). Differential cell counts (among others: absolute lymphocyte counts and neutrophil count) should be performed at screening and every study visit from baseline until safety follow up.

- **Blood chemistry (local lab):** Serum cholesterol, triglycerides, blood urea nitrogen (BUN) or urea, creatinine, total protein, albumin, aspartate aminotransferase (AST)/SGOT, alanine aminotransferase (ALT)/SGPT, gamma glutamyltransferase (gamma GT), total bilirubin, ALP, lactate dehydrogenase (LDH), sodium, potassium, magnesium, calcium, serum uric acid, creatinine phosphokinase (CPK) and creatinine clearance (CrCl) according to Cockcroft-Gault formula: at screening and every study visit from baseline until safety follow up using individual institutional guidelines and the best clinical judgment of the responsible physician, which can involve more frequent testing.

- **Coagulation (local lab):** INR and aPTT are measured at screening and baseline and at investigator's discretion during treatment.

- **Urinalysis (local lab):** Urinalysis by dipstick should be performed at screening, baseline and EOT and if clinically indicated at investigator's discretion or if specified in the applicable sub-protocol. Microscopic analysis should be performed by the hospital's local laboratory if required. Parameters: pH, glucose, proteins (qualitative, dipstick accepted).

- Further arm-specific safety assessments are specified in the respective sub-protocol.

These laboratory tests are performed by the hospital's local laboratory. Additional analyses may be performed if clinically indicated. Safety laboratory assessments have to be dated and signed by the investigator.

Any clinically significant abnormal laboratory values should be repeated as clinically indicated and recorded on the eCRF as AE after experimental treatment start.

In case a subject shows an AST or ALT ≥3xULN, AST/ALT elevations combined with total bilirubin ≥ 2xULN without findings of cholestasis (defined as serum alkaline phosphatase activity less than 2× the upper limit of normal) and no other reason can be found to explain the combination of increased AST/ALT and serum total bilirubin, such as viral hepatitis, alcohol abuse, ischemia, pre-existing liver disease, or another drug capable of causing the observed injury (Hy's Law) immediate actions are required:

1) AST/ALT ≥ 3x ULN:
   - repetition of serum liver testing within 48–72 h

   In case AST/ALT remain ≥ 3x ULN:
   - continuation of liver testing 2–3x per week until normalisation/resolution

2) a) AST/ALT ≥ 8x ULN or
   b) 5x ULN over 2 weeks or
   c) 3x ULN and total bilirubin 2x ULN or INR > 1.5 or
   d) 3x ULN with symptoms (e.g. fatigue, nausea and vomiting, right upper quadrant pain, fever, rash) or eosinophilia:
   - immediately stop of the study drug

Cases of potential drug-induced liver injury (DILI) as defined by Hy's Law have to be reported as adverse event of special interest (AESI) within 24 hrs after knowledge using the SAE form (refer to 9.3 and 9.12).

7.2.2.2 Pregnancy Tests

on blood or urine samples are performed for pre-menopausal women as defined in 5.4, criterion 8 of childbearing potential (CBP) at screening, baseline (within 14 days), day 1 prior to the start

of experimental study treatment, EOT and safety follow up. Within the IMP-arms, pregnancy tests for patients of CBP are performed at day 1 of each treatment cycle.

Tests are performed by the hospital's local laboratory. If results are positive the patient is ineligible/must be discontinued from the study. In the event of a suspected pregnancy during the study, the test should be repeated. Details of the pregnancy tests must be recorded in the patient's medical records. Further contraception and pregnancy testing for male and female patients (and potential their partners) is described within the respective sub-protocol.

7.2.2.3 HAV, HBV, HCV, and HIV-1 Testing

at screening and thereafter at investigator's discretion (local lab).

7.2.2.4 Quantiferon Test

is performed at screening, if clinically active tuberculosis is suspected by the investigator and thereafter at investigator´s discretion.

7.2.2.5 Exploratory Assessments / Blood Draws

Multi-analyte blood sample draw (for biobanking and exploratory liquid biopsy assessment) is conducted dependent on study site:

Table 1 Analyte Types Biobanking Blood Samples

Analyte Types			
No. Vials	Analyte Type	Volume (ml)	Analyte Type
All Study Sites Except NCT Heidelberg			
4	CPT Vials or PAX Gene	à 8/ 10	ctDNA / PBMCs
1	Serum	à 7,5	Humoral immune response
NCT Heidelberg			
4	CPT Vials or PAX Gene	à 8/ 10	ctDNA / PBMCs
1	Serum	à 7,5	Humoral immune response
1	Cell Safe*	à 10	CTC Quantification

*Schedule for Cell Safe:

Start IMP (Baseline Visit).

Stop IMP (last day of administration or EOT Visit).

Follow up: every 12 months after IMP treatment phase until four years of follow-up after surgery or local or distant relapse, if earlier; in case of relapse, an additional blood draw is performed timely after knowledge.

Table 2 Schedule Blood Draws

Schedule Blood Draws (except for Cell Safe)	
• Baseline Visit	Day -14 to d1 IMP: prior infusion / oral drug administration
• After 90 d IMP[1] (experimental therapy)	d90 IMP[3,4]: prior infusion, oral drug administration
• Stop IMP[1,2,3] (experimental therapy)	last day IMP administration: prior infusion / oral drug administration or at the end of treatment visit
Follow up-Period:	
• every 6 months after IMP treatment phase[1] until four years of follow-up after surgery or local or distant relapse, if earlier; in case of relapse, an additional blood draw is performed timely after knowledge (unscheduled study visit).	

1: Observational arm: Baseline, 3 and 12 month after Baseline and every 6 month thereafter until end of year four after surgery or relapse, if earlier.

2: In case of premature therapy discontinuation an additional blood draw should be performed at 12 month after IMP start. Other blood draws are aligned according to above outlined scheme.

3: In case of temporary discontinuation (incl. cycle delay) or premature discontinuation of IMP blood draws for biobanking should be taken as close as possible to the 3 month and 12 month point in time after therapy start (+/- 4 weeks).

4: In the trial schedules, the trial visit next to day 90 is marked and intended for blood draw.

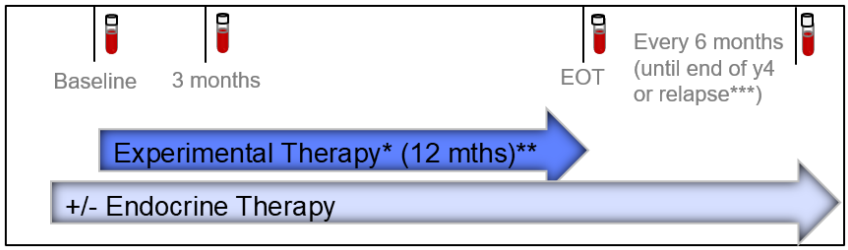

Figure 3: Blood draw sampling scheme

*or observation.

**In case of premature therapy discontinuation an additional blood draw should be performed at 12 months after IMP start.

***if earlier. In case of relapse at any time, an additional blood draw is performed timely after knowledge (unscheduled study visit).

7.2.3 Measurement of Efficacy Parameters

Breast Cancer Status

Breast cancer status is assessed according to standard S3- and AGO Guidelines (clinical breast examination, sonography, mammography, other assessments as applicable). Assessments are performed within the clinical standard routine of breast cancer follow-up care, the existing time schedule can be retained.

Results of the last mammography / sonography are documented at baseline and at end of treatment (EOT) (and additionally, if applicable). Last results of other assessments are documented at baseline, EOT and at the study visit of or following the examination performed every 3 months during the treatment or observation period according to S3- and AGO-guidelines.

In case breast cancer assessments (e.g. mammography) are not performed at the site, the patient has to be instructed, to bring the examination reports / doctor´s letters to the next study visit. A copy is collected for the patients´ file.

Documentation of breast cancer assessments are depicted in the trial schedule overview and the respective sub-protocol trial schedules.

In the follow-up period, IDFS- and DDFS-state (definition see chapter 10.2) are assessed according to standard S3- and AGO guidelines every 3 months for 3 years after EOT and then every 6 months from year 4 on until end of study (EOS) or IDFS and DDFS have occurred (if earlier). Breast cancer assessments are performed within the clinical standard routine of breast cancer follow-up care as described above. Results of all breast cancer assessments are documented at the follow up study visits.

Overall Survival Status

Overall survival status is collected until EOS (or death, if earlier).

7.2.4 Further Assessments

IMP-Treatment, Background medication, concomitant medications and non-drug-treatments should be reported at every study visit from Cycle 1 Day 1 until EOT (IMP) or screening and every study visit from baseline until safety follow up (other treatments) and documented in the relevant eCRF pages. This includes endocrine anti-cancer therapy, supportive care drugs, prophylaxis with antiemetics, and drugs used for treating AEs or chronic diseases. Additionally, the status of endocrine anti-cancer therapy is collected during the follow up-period.

AE assessments: refer to chapter 9.2.

Adverse events should be documented and recorded continuously from signing the informed consent form for experimental study treatment until 28 days/ 10 weeks after end of treatment (substance-depending Safety Follow up).

AE assessment is performed for patients treated with IMP (Arms 1-6). AEs will not be collected for patients of the observational arm (Arm 7).

Patient Reported Outcomes (PROs) including Quality of Life (QoL):

assessed by questionnaires of the EORTC Quality of Life Item Library (core questionnaire QLQ-C30, breast-cancer specific module QLQ-BR45, fatigue module QLQ-FA12, and selected symptom items), as well as the Pittsburgh Sleep Quality Index (PSQI), the Patient Health Questionnaire for Anxiety and Depression (PHQ-4), the distress barometer, the Functional Assessment of Cancer Therapy - cognitive ability scale (FACT-cog), and the Patient Satisfaction Questionnaire Short Form (PSQ-18). In addition, the Socio-Economic Questionnaire (SEQ) as well as patient-reported information on personal traits, experiences, and life situation are assessed at baseline.

Assessments are performed at baseline prior to IMP administration or observation, 3 and 6 months after baseline, EOT and then every 6 months until end of year four after surgery (+/- 14 days). In case of premature termination PRO assessment is performed at EOT and then every 6 month until end of year four after surgery.

A Schedule of PRO-Assessments is depicted in Figure 4.

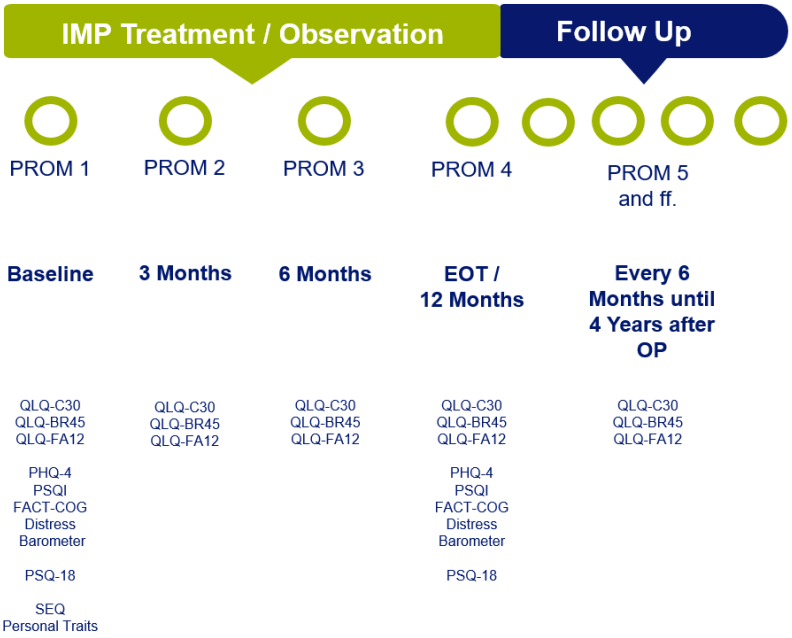

Figure 4: Overview of PRO Measurements and Schedule

PROM = PRO Measurement

7.3 Description of Study Visits

For detailed measurement description, please refer to chapter 7.2.

7.3.1 Screening

Patients are screened earliest 1 month and latest 3 months after completion of post-neoadjuvant standard therapy. In case of existing exclusion criteria estimated by the investigator as transient, a rescreening can be performed within this time frame.

Table 3: Screening

Screening
Clinical assessments: • Informed consent • Assessment of general inclusion and exclusion criteria • Assessment demographics • Assessment of general medical and oncological history • Tumor-related and unrelated signs/symptoms • Assessment of vital signs • Physical examination • ECG • ECOG performance status • Assignment of Patient ID (Pat-ID) and enrollment **Laboratory assessments:** • Hematology (local lab) • Blood chemistry (local lab) • Coagulation (local lab) • Urinalysis (local lab) • HAV, HBV, HCV, and HIV-1 testing (local lab) • Quantiferon test (local lab) in case of clinical suspicion of active tuberculosis

- Assessment of child bearing potential and/or pregnancy test

Further assessments:

- Assessment of concomitant and background medications; check of possible cross-reactions

A patient who signed the informed consent and is fulfilling all of the general inclusion criteria and not meeting any of the general exclusion criteria is considered eligible and may be enrolled in the study.

A patient who signed the informed consent but does not meet all general in- and exclusion criteria is considered as a screening failure. For these patients, reduced documentation in the eCRF is permitted, containing at least the data on informed consent, demographics, inclusion / exclusion criteria and the reason for failing screening.

7.3.2 Arm Allocation

Patients are allocated to the therapy arms according to the report of the molecular tumor board and the clinical context of the patient between initial screening (7.3.1) and start of therapy (7.3.3).

7.3.3 Baseline / Before experimental Treatment Start

The baseline visit should be conducted within 28 days after enrollment and upon availability of the recommendation of the molecular tumor board. Study treatment starts within 14 days after the baseline visit.

Before start of the experimental therapy (day -14 to day 1, Baseline) arm-specific in- and exclusion criteria of the applicable sub-protocol are assessed and general in- and exclusion criteria are reassessed by the investigator. In case of not-fulfilling in- or exclusion criteria estimated by the investigator as transient, a reassessment can be performed within the time frame of baseline (within 28 days after enrollment). IMP is only administered to patients fulfilling all of the inclusion and none of the exclusion criteria. For these patients an additional informed consent form for the applicable arm-specific IMP treatment is obtained and arm allocation is completed.

A patient, who does not meet all in- and exclusion criteria at this point in time is allocated in the observational arm.

Baseline assessments have to be performed latest at cycle 1 day 1 before administration of IMP.

The patient is asked to complete Baseline PROs and receives the corresponding link and individual code.

For further arm-specific baseline assessments (arms 1-6) refer to the respective sub-protocol and trial schedule.

Baseline assessments for the observational arm (arm 7) are depicted in the trial schedule overview.

7.3.4 Trial Visits Treatment Period

Study visits during the treatment or observation phase are conducted depending on the study arm.

7.3.4.1 IMP treatment arms (arms 1-6):

Study visits are scheduled based on IMP treatment in 3- or 4-week cycles starting with weekly visits during the first cycle up to day 1 of each cycle.

In case of intolerabilities visit time ranges can differ for the individual patient. Please note, that in case of temporary or premature discontinuation of IMP blood draws for biobanking should be taken as close as possible to the 3 month and 12 month point in time after therapy start (+/- 4

weeks). An additional blood draw should be performed at 12 month in case of premature discontinuation.

For detailed trial visit assessments and schedule refer to the respective sub-protocol.

7.3.4.2 Observational arm (arm 7):

Study visits are scheduled on a quarterly base: general study examinations are performed at baseline (V2) and 3 (V3), 6 (V4), 9 (V5) and 12 months (V6, EOT) after baseline (+/- 7 days). Visit assessments are depicted in the trial schedule overview within this protocol.

AE assessment and safety FU are not applicable within this arm. SADRs of endocrine anti-cancer therapy, if applicable, are collected and documented in the eCRF.

7.3.5 End of Treatment (EOT) Visit

The end of treatment visit is performed at the last day of the last cycle or latest within 7 days after permanent discontinuation of study treatment, if not specified otherwise in the applicable sub-protocol. In case of premature discontinuation, PRO assessment and biomarker schedule are adapted as described in chapter 7.2.
In the observational arm the EOT visit is performed at month12 (visit 6).
For further EOT assessment refer to the respective sub-protocol.

7.3.6 After EOT-Safety Observation

Adverse Events are collected until a substance-depending period (28 days or 10 weeks) after the end of treatment (Safety Follow-up / Safety observation). Further safety assessments are performed according to the respective sub-protocol. Persisting AEs at this time are followed up as described in chapter 9.2.

7.3.7 Follow-up Period

Follow up visits (endpoint follow up) are conducted following standard S3- and AGO guidelines every 3 months for 3 years after EOT and then every 6 months from year 4 on until end of study (EOS). Data about current anti-cancer treatment and patient´s status (including survival) will be collected.

- Breast-Cancer follow-up is conducted according to the current S3- and AGO guidelines as described in chapter 7.2.3. In case breast cancer assessments are not performed at the site, the patient has to be instructed, to bring the examination reports / doctor´s letters to the next follow up study visit. A copy is collected for the patients´ file.
- Endocrine anti-cancer therapy, PRO assessments and blood samples for biobanking are scheduled as described in chapter 7.2 and the trial schedule overview.
- AESIs and SADRs of IMP, if applicable, are reported directly to the pharmaceutical companies (and to the NCT trial center in copy) (refer to 9.8).
- SADRs of endocrine anti-cancer therapy, if applicable, are collected and documented in the eCRF.

Follow up visits can optionally be conducted by phone call, if no blood samples for biobanking have to be collected at the respective visit. However, it must be assured, that doctor´s letters or examination reports of breast cancer follow-up care are obtained in copy from the patient for endpoint follow up.

7.4 *Methods of Data and Sample Collection*

7.4.1 Data Collection and Handling

All protocol required information including clinical and laboratory data are documented by the investigator or an authorized member of the study team in the patient's medical record and in the

eCRFs. The investigator at the clinical site is responsible for ensuring that all sections of the eCRFs are completed accurately and timely and that entries can be verified against source data. The eCRFs has to be filled out according to the specified CRF Completion Guidelines. The correctness of entries in the eCRFs are confirmed by dated signature of the investigator.

PRO data are collected via online questionnaires implemented with LimeSurvey, a DSGVO conform, free and open source software for the implementation of online surveys. The software is supported and hosted by the Information Technology Core Facility (ITCF) at the DKFZ. A list with access codes and the link to the LimeSurvey-Application is provided to the sites. Access to the online questionnaires is provided via the link and an individual access code for the respective study visit PRO assessment and the individual patient by the site personnel. Provided codes are documented in the eCRF for the respective patient and visit, and as a counter-check, the patient's ID will be noted in the list with the provided access codes by the site.

The site personnel is informed about outstanding PRO questionnaires and subsequently reminds the patient of these outstanding PRO questionnaires within 4 days.

All data are reported pseudonymized.

For further processing please refer to chapter 11 (Data Management).

7.4.2 Sample Collection and Handling

Blood samples are taken according to the Trial Schedule for systematic biobanking (7.2.2.5). Blood samples for biobanking are sent to:

NCT Liquid Biobank
Nationales Centrum für Tumorerkrankungen (NCT) Heidelberg
Im Neuenheimer Feld 460
69120 Heidelberg

Please see Laboratory Manual for detailed instructions.

8 Ancillary and Post Trial Care

After EOS patients are routinely followed-up and treated regarding standard of care according to the discretion of the treating physician. Breast-Cancer follow up should be conducted according to the current S3- and AGO guidelines.

9 Assessment of Adverse Events

9.1 *Specification of Adverse Events*

9.1.1 Adverse Events

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Changes of laboratory parameters
- Intercurrent diseases and accidents
- Worsening of medical conditions/ diseases existing before inclusion into the trial
- Recurrence of disease
- Increase of frequency or intensity of episodical diseases.

Surgical procedures themselves are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial.

Events that are clearly consistent with the expected pattern of relapse of the underlying disease are not be recorded as adverse events. These data are captured as efficacy assessment data only. If there is any uncertainty as to whether an event is due to relapse / disease progression, it should be reported as an adverse event.

AEs are classified as "non-serious" or "serious".

Adverse events are coded using the latest version of Medical Dictionary for Regulatory Activities (MedDRA) terminology and are updated once at EOS with the current MedDRA version.

9.1.2 Serious Adverse Event

A serious adverse event (SAE) is any untoward medical occurrence that at any dose meets any of the following criteria:

- Results in death
- Is life-threatening (the term life-threatening refers to an event in which the patient was at risk of death at the time of event and not to an event which hypothetically might have cause death if it was more severe)
- Requires patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/ incapacity or
- Results in a congenital anomaly/ birth defect.
- Is an important medical event
    - Medical and scientific judgement should be exercised in deciding whether other conditions should also be considered as serious, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above. These should usually be considered as serious. Examples of such events include bronchospasm requiring intense treatment in an emergency room or at home, serious blood dyscrasias or seizures/convulsions that do not result in hospitalization, or the development of drug dependence or drug abuse.
    - A diagnosis of (secondary) cancer / malignant tumor during the course of study treatment should always be considered as medically important.

The following events are not considered AEs/SAEs but have to be documented on the AE eCRF page with remark to the following categories:

- Death resulting from relapse/disease progression
- Hospitalisation resulting from relapse/disease progression
- life-threatening resulting from relapse/disease progression
- Hospitalization in accordance with the protocol-required procedures and treatments
- Elective hospitalization

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the CRF.

9.1.3 Adverse Drug Reaction / Serious Adverse Drug Reaction

An adverse drug reaction (ADR) is generally defined as a response to a drug which is noxious and unintended and occurs at doses normally used in humans.

An ADR, that fulfils any of the criteria of seriousness as defined for a serious adverse event (SAE) (refer to 9.1.2) is a serious adverse drug reaction (SADR). Therefore, a SADR is a SAE with a reasonable possibility, that the medicinal product caused the AE (causal relationship).

9.1.4 Expectedness

An 'unexpected' adverse event is one the nature or severity of which is not consistent with the applicable product information, e.g. Investigator's Brochure (IB), Summary of Product Characteristics (SmPC). In this trial the current valid version of the IB of the respective IMP is considered reference safety information. Furthermore, reports which add significant information on specificity or severity of a known adverse reaction are counted as 'unexpected' events.

9.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both suspected, i.e. possibly related to IMP, and 'unexpected', i.e. the nature and/ or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case if either the investigator, who primarily reported the SAE, or the second assessor classify the SAE as 'suspected' and the SAE is also unexpected, it is categorized as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent higher federal authority (BfArM), and to all participating investigators.

9.2 *Period of Observation and Documentation*

All adverse events reported by the patient or detected by the investigator are collected and reported continuously from signing the informed consent form for experimental study treatment until 28 days (study arms 2, 3, 4 and 5) or 10 weeks (study arms 1 and 6) after end of treatment (safety follow-up). Adverse events must be documented on the appropriate pages of the eCRF and must also be documented in the patient's medical records.

AE assessments are performed for patients treated with IMP (Arms 1-6). AEs are not collected for patients of the observational arm (Arm 7).

All patients who have AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the outcome. The clinical course of the AE will be followed up until resolution or normalization of changed laboratory parameters or until it has changed to a "stable" or "chronic" condition as assessed by the investigator (or the patient is lost to follow up). If an event stops and later restarts within the same cycle, all occurrences must be reported.

In case a new anti-cancer treatment starts within the safety follow-up period of either IMP, the observational period of AEs ends with the beginning of the new treatment.

For additional reporting of SADRs of background therapy outside the period of observation and documentation of AEs refer to chapter 9.14.

9.2.1 Grading of AEs

The grading of AEs in this trial will be carried out on the basis of the 5-grade scale defined in the NCI CTCAE v5.0.

Grade 1:	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2:	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3:	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4:	Life-threatening consequences; urgent intervention indicated.
Grade 5:	Death related to AE

A Semi-colon indicates 'or' within the description of the grade.

A single dash (-) indicates a grade is not available.

Activities of Daily Living (ADL)

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

9.2.2 Coherence between AEs and the IMP / Background Medication

The Investigator must provide an assessment of causal relationship of each of the clinical trial IMPs as well as of endocrine therapy (background medication), if applicable, to each AE according to the following scale:

Y (Yes)	There is a reasonable possibility that the IMP or background medication caused the AE.
N (No)	There is no reasonable possibility that the IMP or background medication caused the AE and other causes are more probable.

9.2.3 Outcome of AEs

The outcome of an AE at the time of the last observation will be classified as:

Recovered/ resolved	All signs and symptoms of an AE disappeared without any sequelae at the time of the last interrogation.
Recovering/ resolving	The intensity of signs and symptoms has been diminishing and/ or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution.
Not recovered/ not resolved	Signs and symptoms of an AE are mostly unchanged at the time of the last interrogation.
Recovered/ resolved with sequel	Actual signs and symptoms of an AE disappeared but there are sequelae related to the AE.
Fatal	Resulting in death. If there are more than one AE only the adverse event leading to death (possibly related) will be characterized as 'fatal'.
Unknown	The outcome is unknown or implausible and the information cannot be supplemented or verified.

9.2.4 Action taken with the IMP / Background Medication

The action taken with IMP / background medication will be assigned to one of the following categories:

Dose not changed	No change in the dose of IMP / background medication.
Dose reduced	Reduction in the dose of IMP / background medication.
Temporary discontinuation	Temporary discontinuation / dose interruption of IMP / background medication.
Dose increased	Increase in the dose of IMP / background medication.
Drug withdrawn	Discontinuation of IMP / background medication.
Unknown	The information is unknown or implausible and it cannot be supplemented or verified.
Not applicable	The question is implausible (e.g. the patient is dead).

9.2.5 Countermeasures

The term 'Countermeasures' refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. The following categories will be used to categorize the countermeasures to adverse events:

None	No action taken
Drug treatment	Newly-prescribed medication or change in dose of a medication
Others	Other countermeasures, e.g. an operative procedure

9.3 *Reporting of Serious Adverse Events and Adverse Events of Special Interest by Investigator*

All SAEs and AESIs must be reported by the investigator to the pharmacovigilance department at the KKS Heidelberg immediately, but not later than 24 hours after the SAE/AESI becomes known using the "Serious Adverse Event" form.

The reporting is performed by faxing of a completed SAE form to the following fax number:

+49 (0)6221 / 56-33687

The initial report must be as complete as possible, including details of the current illness and (serious) adverse event as well as an assessment of the causal relationship between the event and the trial treatment.

Follow-up SAE/AESI information is proceeded in the same way. The 24 hour timeline also applies to follow-up information.

9.4 *Reporting of Pregnancies*

All pregnancies (including those occurring in the partner of a male study subject), where the fetus may have been exposed to the IMP, shall be transmitted to pharmacovigilance department of the KKS. Pregnancies are followed-up until the outcome of the pregnancy is known, whenever possible, based upon due diligence taken to obtain the follow-up information.

The reporting is performed by faxing of a completed pregnancy form to the following fax number:

+49 (0)6221 / 56-33687

9.5 *Second SAE Assessment*

All SAEs are subject to a second assessment by a designated person, who is independent from the reporting investigator and pharmacovigilance department at the KKS Heidelberg.

(...)

All SAEs are forwarded by E-Mail immediately (not later than 24 hours after receipt) by the responsible person at KKS Heidelberg to the designated persons for second assessment. The second assessor will fill out a 'Second Assessment Form' for each SAE and return it by E-Mail or send it back per fax to the responsible person at the KKS Heidelberg within 48 hours,

Fax number: ***+49 (0)6221 / 56-33687***

E-Mail: V-KKS.SAE@med.uni-heidelberg.de

The 'Second Assessment Form' will contain the following information:

I) Assessment of relationship between SAE and IMP / background medication
II) Assessment of expectedness of SAE (derived from IB or SPC)
III) Assessment of relationship between SAE and the underlying disease
IV) Statement if the benefit/ risk assessment for the trial did change as a result of SAE.

9.6 *Expedited Reporting*

SUSARs are to be reported to the ethics committee(s), regulatory authorities (in this trial: BfArM) and to all participating investigators within regulative defined timelines i.e. they are subject to an expedited reporting.

The expedited reporting is carried out by the pharmacovigilance department of KKS Heidelberg. Only SUSARs occurring after administration of IMP undergo expedited reporting.

9.7 *Emergency Treatment*

During and following a patient's participation in the trial, the investigator should ensure that adequate medical care is provided to a patient for any AE, including clinically significant laboratory values. The investigator should inform a patient when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

Details on procedures are given in the respective sub-protocol.

9.8 *Adverse events after the regular safety follow up period*

After the study treatment completion and performed safety follow up visit there is no obligation to actively report information on new AEs or SAEs occurring in former study patients. This includes new AEs/SAEs in patients still being followed up for endpoint or survival. After the end of the safety follow-up und during the primary endpoint and survival follow-up, investigators are asked to report all AESIs as well as serious adverse events that are believed to be related to prior exposure to study treatment (serious adverse drug reaction, SADR) directly to the pharmaceutical companies for Pharmacovigilance purposes and characterisation (and in copy to studienzentrale_dm@nct-heidelberg.de).

Additionally, at any time after a patient has completed the study, if an Investigator learns of any SAE including sudden death of unknown cause, and he/she considers there is a reasonable possibility that the event is causally related to the investigational product, the investigator should notify the applicable pharmaceutical company.

Roche Pharma AG (study arms 1-Atezolizumab, 2-Inavolisib, 3-Ipatasertib, 6-Trastuzumab/ Pertuzumab)

E-Mail: grenzach.clinical_safety@roche.com

AstraZeneca (study arm 4-Olaparib)

E-Mail: AEMailboxClinicalTrialTCS@astrazeneca.com

Gilead (study arm 5-Sacituzumab Govitecan)

E-Mail: Safety_FC@gilead.com or Fax: 1-650-522-5477

For additional reporting of SADRs of background therapy outside the period of observation and documentation of AEs refer to chapter 9.14.

9.9 *Pregnancy*

9.9.1 Maternal exposure

If a patient becomes pregnant during experimental study treatment, treatment has to be discontinued immediately. The outcome of any conception occurring from the date of the first dose until 1 months (30 days) after the last dose of IMP, if not otherwise specified in the sub-protocol, should be documented and followed up.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

If any pregnancy, suspected pregnancy, or positive pregnancy test occurs in the course of study treatment, it must immediately and no more than 24 hours after getting notice of the pregnancy be reported to the KKS Heidelberg (on behalf of sponsor) by fax using a 'Pregnancy Reporting Form'.

All pregnancies should be followed up and documented, even if the patient was withdrawn from the study, until its outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality). An additional informed consent will be obtained in such case.

The outcome must be notified immediately by the investigator to the KKS Heidelberg (on behalf of sponsor) within 24 hours of first knowledge as a follow-up to the initial report.

For any event during the pregnancy, which meets a seriousness criterion, the investigator will also follow the procedures for reporting SAEs (complete and send the SAE form to the KKS Heidelberg by fax within 24 hours of the investigator's knowledge of the event).
All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death at any time thereafter that the investigator suspects as related to the exposure to the IMP should also be reported to the KKS Heidelberg by fax within 24 hours of the investigators' knowledge of the event.

The KKS Heidelberg (on behalf of sponsor) informs the pharmaceutical company's representatives within one working day from the date the KKS, becomes aware of the pregnancy related SAE.

9.9.2 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during study treatment and for a certain time following the last dose respective to the different sub-protocols or, if not further specified, for 3 months.

Pregnancy of the patient's partners is not considered to be an adverse event. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should if possible be followed up and documented. An additional informed consent will be obtained in such case.

The outcome of any conception occurring from the date of the first dose until 3 months (if not further specified in the sub-protocol) after the last dose should be followed up and documented.

9.10 *New Cancers*

The development of a new primary cancer (including skin cancer) should be regarded as an SAE. New primary malignancies are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original cancer. Symptoms of BC metastasis or the BC metastasis itself should not be reported as an AE/SAE, as they are considered to be disease progression.

9.11 *Deaths*

All deaths that occur during the study, or before EOS, must be reported as follows:

- Death clearly the result of BC disease progression has to be documented in the eCRF but not reported as an SAE.
- During experimental study treatment and safety follow up (AE reporting period): Where death is not due (or not clearly due) to progression of the BC disease under study, the AE causing the death must be reported to the pharmacovigilance department at the KKS Heidelberg within 24 hours after the death becomes known using the "Serious Adverse Event" form. (9.1.2 Serious Adverse Event). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. Deaths with an unknown cause should always be reported as a SAE.
- After the end of the adverse event reporting period, all deaths should be reported through use of the end of study status-form in the eCRF.

9.12 *Adverse Events of Special Interest (AESIs)*

Table 4: AESIs applicable for all IMPs

General AESIs (applicable for all IMPs)
1. Potential drug-induced liver injury (DILI) as defined by Hy's Law (refer to 7.2.2.1) - Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x upper limit of normal (ULN) (of which ≥ 35% is direct bilirubin) - Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice 2. Suspected transmission of an infectious agent via a medicinal product (STIAMP), defined as follows: Any organism, virus, or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected

For IMP-specific AESIs refer to respective sub-protocol.

9.13 *Other Reportings*

Refer to sub-protocols.

9.14 *Safety Monitoring of Background Therapy*

During the following phases of the trial, when only endocrine therapy (if applicable) is administered

- from screening until baseline
- after the safety follow up visit (IMP-arms)
- during and after observation (observational arm)

serious adverse drug reactions (SADRs) related to these therapies have to be collected and documented in the eCRF for safety monitoring purposes.

The safety monitoring of background therapy includes SADR reviews by the CI/Co-CI on a regular basis.

Please note, that this documentation does not replace the legally binding reporting requirements of the investigator for respective events.

10 Statistical Considerations

10.1 *Study Design*

This is an open-label, multicenter phase-II umbrella study in patients with eBC with treatment allocation according to results from molecular genomic profiling and target prioritization by a multidisciplinary molecular tumor board.

Patients are allocated to one of the treatment arms. In case of Biomarker-negativity or failure to conduct molecular profiling patients are allocated to the observational arm. Thus, the observational arm is not a control-arm but rather provides information on patients although high risk not eligible for post-neoadjuvant investigational therapy to allow together with all patients receiving investigational post-neoadjuvant therapy the evaluation of the totality of all high-risk patients eligible for the study. The primary endpoint IDFS is assessed for the totality of all high-risk patients eligible for the study and compared to data from the literature and data from controls from the Südwestdeutsches Brustcentrum (SWBC) Heidelberg cohort (http://www.sw-brustcentrum.de/) treated during the recruitment period of COGNITION-GUIDE.

10.2 *Analysis Variables*

10.2.1 Primary analysis

Invasive Disease-free Survival (IDFS) is defined according to Hudis et al.[1] as the time from surgery to whatever comes first a) ipsilateral invasive breast tumor recurrence, b) local/regional invasive breast cancer recurrence, c) distant recurrence, d) death attributable to any cause incl. breast cancer, e) contralateral invasive breast cancer or f) Second primary non-breast invasive cancer. Patients without event are censored at the last date of follow-up with tumor assessment.

10.2.2 Secondary Analysis

Distant Disease Free Survival (DDFS) is defined according to Hudis et al.[1] as the time from surgery to whatever comes first a) distant recurrence, b) death attributable to any cause incl. breast cancer or c) second primary non-breast invasive cancer. Patients without event are censored at the last date of follow-up.

Overall survival is defined as the time from surgery to time of death from any cause. Patients without event are censored at the last date of follow-up.

10.2.3 Explorative Analysis

Patient-reported outcomes (PRO)

The following Patient-Reported Outcomes are assessed:

- **Health-related QoL** is calculated as the new EORTC QLQ-C30 Summary Score recommended by the EORTC Quality-of-Life Group. In addition, the EORTC QLQ Function and Symptom Scores are calculated according to the actual EORTC Scoring Manual.
- **QoL in breast cancer patients** is calculated from the EORTC QLQ-BR45 according to the EORTC Scoring Manual
- **Fatigue** is calculated from the EORTC QLQ-FA12 according to the EORTC Scoring Manual.
- **Sleep problems** are calculated from the PSQI according to the corresponding scoring guidelines.
- **Perceived cognitive impairment** and **impact of cognitive changes** are calculated from the FACT-cog according to the corresponding scoring manual.
- **Anxiety** is calculated from the PHQ-4 according to the corresponding scoring manual.
- **Depression** is calculated from the PHQ-4 according to the corresponding scoring manual.
- **Distress** is assessed on a numerical 0-10 rating scale.
- **Patient's satisfaction with the received treatment** is calculated according to the PSQ-18 scoring manual.

Mutational Level measured in Liquid Biopsies
Mutational levels are summarized by mean, standard deviation, median, minimum and maximum, and plotted by time. Changes are examined descriptively.

10.2.4 Safety Analysis

Endpoints include incidence of adverse events and their outcome, severity, including serious adverse events, adverse events of special interest and special situations; the relation of adverse events to the study treatment and to endocrine anti-cancer therapy (background medication), if applicable; dose modifications for toxicity; premature discontinuation of experimental study treatment; and number of laboratory values that fall outside of pre-determined ranges and/or show prominent worsening from baseline. Toxic effects are graded according to NCI CTCAE v5.0. Patient-reported outcomes are excluded from safety reporting.

10.3 *Sample Size Calculation*

Based on historical data the DFS in high risk patients with early breast cancers following neoadjuvant chemotherapy defined by no pathological complete response (for TNBC and HER2+ BC) and a high CPS-EG-score (for HR+HER2- BC) at 4 years after surgery is in the range of 60% to 70% [2-5]. Therefore, we test the one-sided null hypothesis H0: IDFS (4-year) ≤70%. Assuming exponential survival, uniform accrual over 3 year 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 the Kaplan–Meier estimator is used[30]. To show 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. The following patient allocation to the respective study-arms is expected:

- Arm 1 Atezolizumab (Immune Evasion) 18-26% (43-62 patients (pts))
- Arm 2 Inavolisb (PI3K) 4-9% (10-22 pts)
- Arm 3 Ipatasertib (AKT) 8-14% (19-34 pts)
- Arm 4 Olaparib (PARP, DNA-Repair) 15-21% (36-50 pts)
- Arm 5 Sacituzumab Govitecan (TROP-2) 18-24% (43-58 pts)
- Arm 6 Trastuzumab / Pertuzumab (ERBBB) 2-3% (5-7 pts)
- Arm 7 Observation* 8-14% (19-34 pts)
  (*Biomarker-negative or inability to conduct molecular profiling)

10.4 *Analysis Populations*

10.4.1 Full Analysis Population

The Full Analysis Population (FAP) includes all enrolled patients with assignment according to the recommendations of the molecular tumor board to one of the experimental treatment arms or the observational arm. Patients who were allocated to one of the experimental treatment arms but did not subsequently receive treatment are included in the FAP. The analysis of data using the FAP therefore follows the principles of intention to treat (ITT).

Patients' disposition and reasons for ending the study is presented in frequency distribution tables and individual data listing. Descriptive statistics of the baseline characteristics are generated across all patients. Frequency distributions are presented for the categorical variables. Summary statistics and number of assessed patients are calculated, as appropriate, for the quantitative variables. Individual data are presented in listings.

Efficacy analysis includes descriptive analyses of the primary and secondary endpoints overall as well as for each study arm separately and where required also joint analysis of different treatment arms.

The evaluation of efficacy to reject or keep the null hypothesis is based on the FAP.

10.4.2 Per Protocol Populations

All enrolled patients of the FAP who have received at least one dose of study treatment in one of the experimental treatment arms are subject to the per protocol analysis (per protocol population-1).

Furthermore, in a further sensitivity analyses patients with important protocol deviations are excluded (per protocol population-2). Definitions of important protocol deviations are given in the statistical analysis plan (SAP).

Additionally, all patients, who were assigned to the observational arm and those who did not receive any experimental treatment (actually) although assigned to one of the experimental treatment arms are analysed together (per protocol population-3).

Details of the per protocol analysis are specified in the SAP.

10.4.3 Safety Population

All enrolled patients who have received at least one dose of experimental treatment are subject to the safety analysis. The safety analysis is performed for the entire study population as well as for each treatment arm separately. Details of the safety analysis are specified in the SAP.

10.5 *Statistical Methods*

Details of the analysis are specified in the SAP.

Statistical analysis is performed using SAS Software.

In cases surgery is performed more than once, time of the first surgery is considered (referring to all analyses with regard to surgery).

10.5.1 Demographic and other Baseline Characteristics

Categorical baseline characteristics, like sex, history of cancer, performance status (ECOG), initial and post-neoadjuvant tumor staging, previous anticancer treatment, concomitant illness at trial initiation, and concomitant treatment maintained, are summarized by frequency tables overall and for each study-arm. Summary statistics are provided for quantitative variables like age, weight and, laboratory values overall and for each study-arm.

10.5.2 Study Therapy, Treatment Compliance, and Follow-up

Summary statistics are presented for the dosage of all IMPs in each study-arm received at each cycle, dose modifications for toxicity, discontinuation and withdrawal from study treatment, as well as if applicable standard endocrine therapy and standard PNACT received including discontinuation or withdrawals, and drop-out from the follow-up during the post-study phase. The number of cycles administered, actual and total doses administered, dose modifications, delays and omissions, as well as reasons for deviation from planned therapy and overall duration of treatment, are summarized overall and for each study-arm.

10.5.3 Analysis of the Primary Endpoint

The primary endpoint IDFS is analyzed according to the Kaplan-Meier method and confidence interval (CI) estimation for IDFS is based on the cumulative hazard function using Greenwood's formula for variance estimation.

10.5.4 Analysis of Secondary Endpoints

IDFS, DDFS and OS

IDFS for each study arm and DDFS as well as OS overall and for each study-arm are analysed as described for IDFS above (10.5.3).

The method of Kaplan and Meier is used to estimate the distributions with respect to IDFS, DDFS and OS. Cox proportional hazards regression are used to examine the influence of covariates on IDFS, DDFS and OS overall and for each study-arm.

10.5.5 Analysis of Explorative Endpoints

Analysis of Patient-Reported Outcomes (PROs)

The scales are scored and analyzed according to the applicable scoring manual (refer to 10.2.3).

The PRO subscales and single item sub-scores are summarized by the mean, standard deviation, median, minimum and maximum, and plotted by time overall and for each study-arm. Changes from baseline for all domains are examined descriptively overall and for each study-arm.[31,32]

Mutational Level measured in Liquid Biopsies

Mutational levels are summarized by mean, standard deviation, median, minimum and maximum, and plotted by time. Changes are examined descriptively.

10.5.6 Other Analyses

Patients Disposition are tabulated overall and for each study-arm. In addition, the number of patients who withdrew from the study and reasons for discontinuation will be summarized overall and for each study-arm. The number and percentage of patients with normal and abnormal ECG results are summarized overall and for each study-arm. Summary statistics for baseline values and follow-up will be displayed for QT and QTc correction methods overall and for each study-arm.

10.5.7 Analysis of Safety Endpoints

Safety Analysis

The assessment of safety is based on the frequency of adverse events (see Section 9) and on the number of laboratory values that fall outside of pre-determined ranges and/or show prominent worsening from baseline during the study phase.

Adverse events (AE) are summarized by presenting the number and percentage of patients having

any AEs or

serious adverse events (SAEs) as well as

adverse events of special interests (AESIs)

special situations

and SADRs of background medication.

Adverse events are additionally summarized by determining and summarizing the highest toxicity grade per toxicity for each treatment cycle during the study phase overall and for each study arm. Furthermore, the most common AEs (those occurring in at least 10% of the treatment group) will be determined. Any other information collected (e.g. severity or relatedness to study drug) are summarized as appropriate. Laboratory data are summarized by presenting summary statistics of raw data and change from baseline values overall and for each study arm. Incidence rates are summarized along with two-sided Pearson-Clopper 95% confidence intervals.

10.5.8 Handling of Missing Data

Missing values are not replaced or imputed. For patients with incomplete follow-up, time to last follow-up date is used as the censoring time in the analysis of time-to-event data.

10.6 *Safety Monitoring Analyses*

Interim safety analyses are performed in the entire study after 24 and 36 months. Safety monitoring is additionally performed in each treatment arm separately after 6 and 12 patients have finished at least one cycle of the study treatment. Safety assessments consist of evaluating AEs, SAEs, AESIs, laboratory parameters including hematology and chemistry, vital signs, and physical examinations. Results of the safety monitoring analyses are provided to the CI, Co-CI, scientific coordinator and the clinical counselors as well as after their assessment and rating to

the IDMC. The IDMC provides the sponsor with recommendations regarding trial modifications after each safety monitoring report.

11 Data Management

11.1 Data Collection

As used in this protocol, the term Case Report Form (CRF) should be understood to refer to an electronic data record (eCRF). The data collection is performed using an electronic data capture (EDC)-system.

Data collection into an eCRF can only be done by authorized persons. Access to all study data is protected by password. Each entry or change of data is tracked by name and exact date (audit trail). Any change of data has to be explained. The investigator signs the CRF electronically as per agreed project process.

A copy of the eCRF is provided by data management and archived at the study site at the end of the trial.

PRO questionnaires are completed online via LimeSurvey by the patient. Access to the online questionnaires is provided by a link and via an individual access code. The software is supported and hosted by the Information Technology Core Facility (ITCF) at the DKFZ. The collected data is stored under the usual data protection agreement with the ITCF at the DKFZ Heidelberg. No personal data is stored on the LimeSurvey application.

11.2 Data Handling

Data entries on eCRF undergo an automatic online check for plausibility and consistency. Additional queries are generated on the basis of further checks combined with a visual control by a responsible monitor or data manager.

The site team has to address and resolve or clarify all queries.

After all queries have been resolved the trial database is closed and the ability to edit the database will be removed.

Derived data sets, combining eCRF and PROs data are produced. The link between the questionnaires and the CRF is maintained by the Patient-ID which is recorded in the eCRF.

All data management activities are done according to the current Standard Operating Procedures (SOPs) of the NCT Trial Center.

11.3 Storage and Archiving of Data

All essential trial documents will be archived in accordance with the current legislation, however, for at least 25 years after the trial termination. The sponsor is responsible for archiving of the TMF.

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including Patient Identification List and all relevant correspondence) according to section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations. The Patient Identification List will be archived for at least 25 years after trial termination.

If the investigator relocates, retires, or for any reason withdraws from the study, the sponsor / NCT trial center should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution or to the sponsor. The investigator must obtain sponsor´s written permission before disposing of any records, even if archiving requirements have been met.

12 Ethical and Legal Aspects

12.1 *Good Clinical Practice*

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by Good Clinical Practice (GCP) and the ethical principles described in the current version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

Compliance / GCP Statement: The trial will be conducted in accordance with German Drug Law (Arzneimittelgesetz, AMG), the German GCP Ordinance (GCP-Verordnung) and the International Council on Harmonisation Good Clinical Practice (ICH-GCP E6 (R2)).

12.2 *Patient Information and Informed Consent*

Before being admitted to the clinical trial, the patient must consent in written form to participate after the nature, scope, and possible consequences of the clinical trial have been explained in a form understandable to him or her. Before start of experimental study treatment, patients of study arms 1-6 must consent to an additional informed consent form containing information about the applicable arm-specific IMP treatment.

The original personally signed and dated Informed Consent Form must be kept on file by the investigator(s), and documented in the case report form.

A copy of the signed informed consent document must be given to the patient. The documents must be in a language easily understandable to the patient and must clearly state who informed the patient, which is confirmed by the dated signature of the responsible investigator.

If new safety information results in significant changes in the risk/benefit assessment, or if significant changes are made in the protocol, the consent form has to be reviewed and updated if necessary. All patients (including those already being treated) should be informed of the new information and must give their written informed consent to continue the study.

12.3 *Confidentiality*

The data obtained in the course of the trial will be treated pursuant to the General Data Protection Regulation (EU-DSGVO, EU 2016/679), the Data Protection Law of the Federal State (Landesdatenschutzgesetz), and the § 40 (2a) AMG.

During the clinical trial, patients will be identified solely by means of an individual identification code (Patient ID). Storage of trial findings on a computer will be done in accordance with local data protection law and will be handled in strictest confidence. For protection of these data, organizational procedures are implemented to prevent distribution of data to unauthorized persons. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The patient consents in writing to relieve the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorized persons (inspectors, monitors, auditors). Authorized persons (clinical monitors, auditors, inspectors) may inspect the patient-related data collected during the trial, ensuring the data protection law.

The investigator will maintain a patient identification list (Patient IDs with the corresponding patient names) to enable records to be identified.

Patients who did not consent to circulate their pseudonymized data will not be included into the trial.

12.4 *Responsibilities of Investigator*

The Principal Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol and any amendments, the trial treatments, and their trial-related duties and functions.

The Principal Investigator should maintain a list of investigators and other appropriately qualified persons to whom he or she has delegated significant trial-related duties (Log of Staff).

The investigator(s) should support monitoring, auditing and inspections as described in sections 13.1 and 13.2.

12.5 *Approval of Trial Protocol and Amendments*

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) as well as to the competent federal authority (BfArM or PEI). A written favourable vote of the EC and an (implicit) approval by the competent higher federal authority are a prerequisite for initiation of the clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member.

Before the first patient is enrolled in the trial, all ethical and legal requirements must be met. All planned substantial changes will be submitted to EC and the competent higher federal authority in writing as amendments. They have to be approved by the EC and the competent higher federal authority.

The coordinating investigator or the NCT Trial Center, and if applicable the investigator(s) will keep a record of all communication with the EC and the regulatory authorities.

12.6 *Continuous Information to Independent Ethics Committee*

Pursuant to the German Drug Law (AMG) and the GCP Regulation, the EC and the competent higher federal authority will be informed of all suspected serious unexpected adverse reactions (SUSARs) which occur during the trial. Both institutions will be informed in case the benefit-risk assessment did change or any others new and significant hazards for patients' safety or welfare did occur. Furthermore, a report on all observed serious adverse events (SAEs) will be submitted once a year (Development Safety Update Report (DSUR).

The EC and the regulatory authorities must be informed of the end of the trial. They will be provided with a summary of trial results within one year after the end of clinical phase (LPLV).

12.7 *Notification of Regulatory Authorities*

The local regulatory authorities as responsible for each particular investigator and the competent higher federal authority will be informed before the beginning, during and at the end of the trial according to §67 AMG and §13 GCP-V. The NCT Trial Center takes over notification of his/ her local regulatory authority and the competent higher federal authority according §67 AMG and §12 (1, 2, 6) GCP-V.

12.8 *Registration of the Trial*

Prior to the beginning of the clinical phase (FPI) the coordinating investigator will register the trial at the public accessible clinical trial register *ClinicalTrials.gov* possessing the status of a primary register according to the International Clinical Trials Registry Platform (ICTRP) and correspondingly is listed at the International Clinical Trials Registry Platform of the World Health Organization (WHO, http://www.who.int/ictrp/en/). The requirements are fulfilled by the European Clinical Trials Register and submission of EMA Module 1 (Clinical Trial Application Form).

The registration is a prerequisite for a publication in many peer-reviewed journals (see Uniform Requirements for Manuscripts Submitted to Biomedical Journals by the International Committee of Medical Journal Editors; (http://www.icmje.org/ publishing_10register.html).

12.9 *Insurance*

According to § 40 AMG, the sponsor has to subscribe to an insurance policy which covers in its terms and provisions its legal liability for injuries caused to participating persons. The insurance policy also covers any damage done to the patient, even if the harm done arises out of strictly following the procedures described in this protocol and abiding as applicable law and professional standards. The insurance was taken out at HDI Global SE (insurance policy number: 5701032703012, registration number: 14042022103, maximum limit: € 500.000 per participating person).

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The patient is responsible for notification. The insured person must agree to help clarify the cause and the extent of damage with all appropriate measures. He is also obliged to take measures himself to reduce damage as much as possible. During the conduct of the experimental treatment phase of the trial, the patient must not undergo other clinical treatment except for cases of emergency. Within this trial phase, the patient is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance must be delivered to the patient.

The insurance company has to be informed about all amendments that could affect patients' safety, and must also receive the actual version of the informed consent.

12.10 *Risk assessment in a pandemic situation*

In case of a pandemic (e.g. Covid-19), the sponsor determines measures to maintain the process of the trial as far as possible, such as off-site monitoring, regular contact with the IMP supplier to ensure deliveries, regular assessment of the situation at the trial sites, adjustment of trial schedule (performance of physical visits only if strictly necessary), adjustment of recruitment if necessary. However, patients cannot be left without any cancer therapy due to the high treatment demand.

13 Quality Assurance

13.1 *Monitoring*

Monitoring will be done by personal visits from a clinical monitor according to SOPs of KKS Heidelberg and a specific monitoring manual. The monitor will review the entries into the CRFs on the basis of source documents. The investigator must allow the monitor to verify all essential documents and must provide support at all times to the monitor.

By frequent communications (letters, telephone, fax), the site monitor will ensure that the trial is conducted according to the protocol and to regulatory requirements.

A detailed description of the monitoring process will be provided in a separate clinical monitoring plan.

13.2 *Inspections/ Audits*

Regulatory authorities and an auditor authorized by the sponsor may request access to all source documents, CRF, and other trial documentation. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14 Agreements

14.1 *Financing of the Trial*

This is a non-commercial trial that is financed using funds of the National Center of Tumor Diseases (NCT) and by the Federal Ministry of Education and Research (BMBF). Study drugs are provided free-of charge by Roche Pharma AG, AstraZeneca and Gilead.

14.2 *Declaration of Interests*

Before the start of the trial, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsors / a funding company, in the investigational product(s), or any commercial organisation being involved in the clinical trial. The investigator has also to confirm that he has not entered into any financial arrangement whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

14.3 *Dissemination Policy*

The research efforts and results of COGNITION-GUIDE shall be presented to the scientific community as well as the general public. The dissemination policy aims to address the project progress and outcome to target audiences on all stages of the project appropriately and to achieve a sustainable impact in the corresponding research field and the general public.

14.3.1 Reports

The final trial report is prepared within 6 months after LPLV. The study results will be released to the participating physicians, referring physicians and the general medical community; they will be made publicly available according to legal requirements.

14.3.2 Publication

All information concerning the trial is confidential before publication. The results of COGNITION-GUIDE will be made available to the scientific community via publications in peer-reviewed scientific journals, and talks or presentations at scientific meetings. Collaborative results will be jointly analyzed and published. All partners are committed to the principles of good scientific practice. Manuscripts on behalf of COGNITION-GUIDE will be pre-circulated to all participants and co-authors in advance of submission; everyone will be invited to comment or contribute additional information or data. Notwithstanding this, absolute confidentiality will be enforced.

Results will be published preferably in “Open Access” journals. Publications that are not a priori in an Open Access format will be deposited in PubMed Central, an Open Access repository.

15 Signatures

The present trial protocol including sub-protocols for study arms 1-6 was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- The current benefit-risk assessment of the investigational medicinal product
- Moral, ethical, and scientific principles governing clinical research as set out the principles of GCP and in the applicable version of Declaration of Helsinki.

The investigator will be supplied with details of any significant or new finding, including relevant safety information relating to treatment with the investigational medicinal product.

Date: _____	Signature:	
	Name (block letters):	Prof. Dr. Andreas Schneeweiss
	Function: Coordinating Investigator / LKP, on behalf of the sponsor	
Date: _____	Signature:	
	Name (block letters):	Prof. Dr. Richard F. Schlenk
	Function: Biostatistician / Co-CI	

16 Declaration of Investigator

I have read the above trial protocol including sub-protocols for study arms 1-6 and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enroll the first patient only after all ethical and regulatory requirements are fulfilled. I pledge to obtain written consent for trial participation from all patients before enrollment.

I know the requirements for accurate reporting of serious adverse events, and I pledge to document and notify such events as described in the protocol.

I pledge to retain all trial-related documents and source data as described.

Date: _____ Signature: _____

Name (block letters): _____

Trial Center (address): _____

_____

_____

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18 Appendix

18.1 *Sub-Protocols*

- Arm 1 Atezolizumab (anti-PD-L1 antibody)
- Arm 2 Inavolisib (PI3K inhibitor)
- Arm 3 Ipatasertib (AKT inhibitor)
- Arm 4 Olaparib (PARP inhibitor)
- Arm 5 Sacituzumab Govitecan (TROP-2)
- Arm 6 Trastuzumab/Pertuzumab (anti-HER2 antibody)