Adjuvant **D**ynamic marker-**A**djusted **P**ersonalized **T**herapy trial optimizing risk assessment and therapy response prediction in early breast cancer

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Table of Contents

List of Abbreviations

Abbreviation	Term
(S)AE	(Serious) Adverse Event
ADAPT	Adjuvant Dynamic marker-Adjusted Personalized Therapy
AGO	Arbeitsgemeinschaft Gynäkologische Onkologie
AHSR	Acute Hypersensitivity Reaction
AI	Aromatase Inhibitors
AKT	Protein Kinase B
ALAT/SGPT	Alanine Transaminase/Serum Glutamic Pyruvic Transaminase
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
ASAT/SGOT	Aspartate Transaminase/Serum Glutamic Oxaloacetic Transaminase
AUC	Area Under the Curve
BC	Breast Cancer
Bcl-2	B-cell lymphoma 2 (Protein)
BRCA1/2	BReast CAncer 1/2
BSA	Body Surface Area
C	Cyclopphosphamide
Cb	Carboplatin
CCNB1	G2/Mitotic-specific Cyclin-B1 (Protein)
CHF	Congestive Heart Failure
CISH	Chromogenic In-Situ Hybridization
CR	Complete Response
CRA	Clinical Research Associate
CTC(AE)	Common Toxicity Criteria (for Adverse Events)
d	Day
DCIS	Ductal Carcinoma *in situ*
DDFS	Distant Disease Free Survival
DFS	Disease Free Survival
Doc	Docetaxel
DSMB	Data Safety Monitoring Board
E	Epirubicin
eBC	Early Breast Cancer
ECG	Electro Cardiogram
ECOG	Eastern Cooperative Oncology Group (Performance Status)
e-CRF	Electronic Case Report Form
EFS	Event-free Survival
EOT	End Of Treatment
ER	Estrogen Receptor
ERK	Extracellular-Signal-regulated Kinase
FISH	Fluorescent In-Situ Hybridization
FN	Febrile Neutropenia
GCP	Good Clinical Practice
G-CSF	Granulocyte-Colony Stimulating Factor
GGI	Genomic Grade Index
GnRH	Gonadotropin-releasing Hormone
HER2+	Human Epidermal Growth Factor Receptor 2 positive
HR+	Hormone Receptor positive
i.v.	Intravenous
IGF	Insulin-like Growth Factor
IHC	Immunohistochemistry
ITT	Intention To Treat
KI	Karnofsky Index
LN	Lymph Nodes
LVEF	Left Ventricular Ejection Fraction

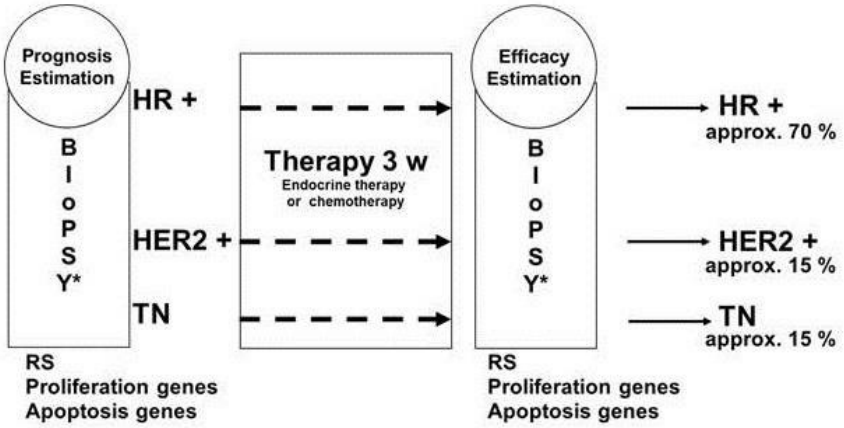
Abbreviation	Term
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleid Acid
MYBL2	Myb-related protein B
nab-Paclitaxel	Nanoparticle Albumin-Bound-Paclitaxel
OS	Overall Survival
p.o.	Per os
Pac	Paclitaxel
PAI-1	Plasminogen Activator Inhibitor-1
pCR	Pathological Complete Response
PD	Progressive Disease
PFS	Progression-Free Survival
PI3K	Phosphatidylinositol 3-kinases
PR	Progesterone Receptor
PR	Partial Response
pS6K	Ribosomal Protein S6 Kinase, 70kDa, Polypeptide 1
PTEN	Phosphatase and Tensin Homolog
pts	Patients
RCB	Residual Cancer Burden
RD	Residual Disease
RPPA	Reverse Phase Protein Arrays
RS	Recurrence Score
SCUBE2	Signal Peptide, CUB Domain, EGF-like 2
SD	Stable Disease
SISH	Silver In-Situ Hybridization
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
STAT5	Signal Transducer and Activator of Transcription 5A (Protein)
STK15	Aurora A Kinase
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Trastuzumab
Tam	Tamoxifen
TMA	Tissue Microarray
TN	Triple Negative (HER2-/HR-)
UNL/LNL	Upper Normal Limit/Lower Normal Limit
uPA	Urokinase-type Plasminogen Activator
WHO	World Health Organization

1 Study Summary – ADAPT

Title of the study	**A**djuvant **D**ynamic marker-**A**djusted **P**ersonalized **T**herapy trial optimizing risk assessment and therapy response prediction in early breast cancer
Preface	ADAPT is one of the first new generation adjuvant trials dealing with individualization of adjuvant decision making in early breast cancer. Besides conventional prognostic factors, prognosis is evaluated by molecular markers/signatures. Furthermore, ADAPT tries to establish early predictive molecular surrogate markers for response under a short induction treatment. ADAPT consists of an umbrella protocol and four different sub-trials with the following endpoints: **ADAPT umbrella** Population: all early breast cancer patients who are candidates for chemotherapy by conventional prognostic criteria Clinical objective: identification of a population with excellent outcome in HR+, HER2+, TN breast cancer (comparator HR+/HER2-/RS≤11, pN0-1) Biomarker evaluation: comparison of response markers in HR+, HER2+ and TNBC. **ADAPT HR+/HER2-** Population: early breast cancer with hormone receptor positive, HER2 negative disease, who are candidates for adjuvant chemotherapy by conventional prognostic criteria **ADAPT HR+/HER2- part I** Low risk (≤11) and intermediate risk (12-25) by RS with response: Clinical objective: comparison of outcome of low risk patients with intermediate risk patients/responders receiving endocrine therapy only Biomarker evaluation: allocation to endocrine therapy only on the basis of early response (Ki-67 drop) under endocrine induction therapy **ADAPT HR+/HER2- part II** In intermediate risk (12-25) with low response and high risk (N0-1/RS ≥26 or G3 and Ki-67 ≥40% in Tumors >1cm or all N2/3) patients – chemotherapy trial Clinical objective: comparison of nab- paclitaxel weekly for eight weeks versus paclitaxel at two week intervals for eight weeks followed by dose dense EC (q2w) for eight weeks Biomarker evaluation: allocation with subsequent randomization to chemotherapy on the basis of low/missing early response (Ki-67 drop) under endocrine induction therapy **ADAPT HER2+** Population: early breast cancer with HER2 over-expressing disease **ADAPT HER2+/HR+** Clinical objective: efficacy comparison of T-DM1 or T-DM1 + endocrine therapy or Trastuzumab + endocrine therapy for 12 weeks Biomarker evaluation: predictive value of dynamic testing for pCR and EFS **ADAPT HER2+/HR-** Clinical objective: efficacy comparison of trastuzumab + pertuzumab versus trastuzumab + pertuzumab + paclitaxel Biomarker evaluation: predictive value of dynamic testing for pCR and EFS

	ADAPT HER2-/HR- (triple negative, TN) Population: early breast cancer with triple negative disease Clinical objective: efficacy comparison of nab-paclitaxel + gemcitabine versus nab-paclitaxel + carboplatinum Biomarker evaluation: predictive value of dynamic testing for pCR and EFS **General trial recommendations are subsumed in the umbrella protocol; specific considerations are found in the corresponding sub-protocols**
ADAPT UMBRELLA	
Study Overview	The most important questions in adjuvant therapy of breast cancer to be resolved in the next decade are: *Who can safely be spared chemotherapy* and *who has the maximum benefit from chemo-, endocrine and anti-HER2 -therapy?* The first question has been explored scientifically far more than the latter one and represents the major basis of decision making regarding adjuvant systemic therapy today. A number of well evaluated prognostic tests identify patients with a low-risk profile resulting in a potentially low enough benefit from chemotherapy to justify omission of chemotherapy. A number of clinical trials are currently addressing this question such as TAILORx, MINDACT, NNBC-3, WSG-planB[1]. The second question is much more difficult to resolve. The clinically most relevant predictor for adjuvant endocrine therapy is steroid hormone receptor protein expression. Similarly, benefit from anti-HER2 therapy seems to be restricted largely to patients demonstrating over-expression and/or amplification of the HER2/neu oncogene, accounting for 10-20% of patients with breast cancer. The strongest clinical parameter for prediction of outcome after chemotherapy is the rate of pathological complete remissions in the neoadjuvant chemotherapy setting. In the adjuvant setting, the Recurrence Score (RS) has been demonstrated to predict outcome after chemotherapy in hormone sensitive disease. Furthermore, HER2 over-expression correlates with anthracycline sensitivity, and luminal subtypes benefit differently from taxanes. Recent data derived mainly from primary endocrine therapy and less from primary chemotherapy indicate that early sequential evaluation of proliferation markers such as Ki-67 correlates strongly with pCR and overall outcome. **Within the ADAPT-trial, prognostic evaluation (*static*) and early prediction (*dynamic*) will be combined**. The prognostic profile is evaluated at the time of diagnosis in core biopsy material and a second evaluation of proliferative markers (HR+/HER2- setting) as well as proliferative/apoptotic markers and/or imaging (HER2+ and triple negative (TN) setting) is done after a short period (3 weeks) of specific therapy in sequential tissue samples. Since the evidence is strongest for hormone sensitive disease, Ki-67 is used to early identify responders in the intermediate risk group, who are then considered to be sufficiently treated by endocrine therapy alone. Low responders and patients initially identified as high-risk for recurrence are randomized to a chemotherapy protocol optimizing dose-dense taxane based chemotherapy. The **ADAPT HR+/HER2- sub-trial** is therefore a modern biomarker-based adjuvant trial moving the ideas of earlier trials such as TAILORx, NNBC-3, WSG-planB or MINDACT forward. Besides better definition of prognosis it will improve early prediction with the aim to reduce overtreatment with chemotherapy. The **ADAPT parts for HER2+/HR- and TN** breast cancer will establish and utilize the dynamic test in a twelve week neoadjuvant concept and correlate these early 3 week results with pCR rates. **The ADAPT project aims at early therapy individualization by integration of early dynamic response data into clinical management.** In terms of an **early enrichment strategy** which aims at sparing unnecessary toxic therapies

	and costs without compromising outcome. ADAPT thus may help not only to reduce over-treatment, but may also separate patients, who are correctly treated from those, who are mistreated.
Rationale	Adjuvant (chemo)therapy decisions in early breast cancer (eBC) today are mainly based on the individual prognostic disease profile as determined by clinical-pathological factors, prognostic genomic signatures or single molecular markers such as uPA/PAI-1. Predictive information in this setting can be only derived from RS for FAC and CMF-chemotherapy and from uPA/PAI-1 for CMF -chemotherapy. Therefore actual response to therapy will mostly **not** be considered in the decision-making procedure today. However, for endocrine therapy, response to a short course of endocrine treatment as defined by a decrease in tumor cell proliferation correlates strongly with outcome. For chemotherapy, pathologic complete remission in a neoadjuvant setting is an excellent predictor of therapy outcome, particularly in HER2+/HR-, HER2+/HR+ and TN disease. ADAPT aims to establish early molecular surrogate markers (*dynamic* test) and molecular imaging markers (breast MRI) for endocrine response (HR+/HER2-) or pCR (HER2+/HR-, HER2+/HR+ and TN). Such a *dynamic* response evaluation after 3-week induction therapy aims at early identification of “good responders” vs. “low responders”. This information is used as a modern personalized enrichment strategy in HR+ disease at a very early stage of treatment and will be evaluated for HER2 over-expressing and TN breast cancer. Within the ADAPT HR+/HER2- sub-trial, adjuvant chemotherapy will be spared in patients with low risk as identified by Recurrence Scores ≤11 and intermediate risk patients (RS 12-25) with early therapy response. In HER2+/HR-, HER2+/HR+ and TN disease, exploratory biomarker analysis will be performed for future optimization of patient selection regarding targeted therapies. Furthermore, different new anti-HER2 compounds (HER2+) and experimental chemotherapy combinations (TN) will be explored.
Objectives	<u>Primary objective</u> • Identification of a responder sub-population with intermediate and high risk, which due to therapy has an EFS comparable to HR+/RS≤11 <u>Secondary objectives</u> • Relapse free and overall survival in corresponding groups • Overall survival • Toxicity • Cost- effectiveness • distant disease-free survival (DDFS) • local and regional relapse-free survival (LRFS and RRFS) <u>Tertiary objectives</u> • Assessment of impact of lifestyle factors (body mass index/change of weight), sport activity, alcohol and smoking on prognosis in a subset of patients • Evaluation of all molecular, pathological and clinical markers and their combinations in terms of predictive and prognostic value • Additional translational research questions occurring during the trial will be defined in sub-protocols. Further specific objectives are defined within the sub-protocols. Toxicity and cost-effectiveness are common endpoints of all sub-protocols. Toxicity and

	general health economic issues within the whole protocol will be analyzed, when results from the sub-protocols are available. Additional "translational research" questions occurring during the trial will be defined in sub-protocols.
Trial design	 Prospective, multi-center, controlled, non-blinded, randomized phase III
"Test" Treatment	3 weeks of pre-surgical endocrine treatment for HR+/HER2- patients **or** 3 weeks of neoadjuvant targeted therapy ± chemotherapy for HER2+/HR- patients **or** 3 weeks of T-DM1 or T-DM1 + antihormonal therapy or trastuzumab + antihormonal therapy for HER2+/HR+ patients **or** 3 weeks of neoadjuvant chemotherapy for TN patients In patients with HER2 positive or triple negative tumors as well within Elderly study and significant tumor burden after 12 weeks of neoadjuvant therapy, the neoadjuvant therapy may be prolonged as **post-study treatment**. The remaining tumor burden must be proven histologically, i.e. the tumor sample will be sent to the central pathology. **Ultrasound assessment**: In accordance with the schedule of the respective sub-protocols the tumor (marker lesion) is measured in all three dimensions. The two longest diameters must be documented. Progressive Disease (PD) is defined as ≥20 percent increase of at least 5 mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameters recorded. In case of PD the therapy should be changed (or surgerry performed) at discretion of the investigator. Response will be evaluated on an exploratory basis. The tumor needs to be marked with a clip before the first cycle of chemotherapy to be able to reliably identify the region of the former tumor at the time of surgery. For exploratory response assessment all 3 criteria (WHO 1-D (≥50% reduction of the longest diameter of tumor) and 2-D (reduction ≥50% of the product of two longest diameters) as well RECIST 1.1 (>30% reduction of the longest diameter) will be applied (RECIST 1.1 does not recommend use of ultrasound as response tool). For clinical response reduction of the tumor in breast more than 50% of the product of two longest diameters will be defined as a partial response, increase of tumor size >25% as a tumor progress, changes between these both definitions as stable disease, complete disappearance of tumor in the breast as complete response[2,3].

Supportive treatment	G-CSF prophylaxis according to AGO guidelines for patients receiving chemotherapy. Primary G-CSF prophylaxis with Pegfilgrastim according to current AGO guidelines (e.g. FN-risk >20%, dose-dense therapies, TAC q2w, etc.) Secondary G-CSF prophylaxis according to current AGO guidelines (e.g. weekly with nab-Paclitaxel). Treatment with ESF according to SmPC
Selection of patients	General Inclusion Criteria: • Female patients, age at diagnosis 18 years and above (consider *ADAPT Elderly* for patients at 70 years and above) • Histologically confirmed unilateral primary invasive carcinoma of the breast • T1 - T4 (except inflammatory breast cancer) • All N • Patients should be candidates for (neo)-adjuvant chemotherapy by conventional prognostic criteria • No clinical evidence for distant metastasis (M0) • Known HR status and HER2 status (local pathology) • Tumor block available for central pathology review • Performance Status ECOG ≤ 1 or KI ≥ 80% • Negative pregnancy test (urine or serum) within 7 days prior to registration in premenopausal patients • Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements • The patient must be accessible for treatment and follow-up Additional Inclusion criteria for patients receiving chemotherapy: • Laboratory requirements for patients receiving chemotherapy (within 14 days prior to randomization): o Leucocytes ≥ 3.5 x 10^9/ L o Neutrophils ≥1,5 x 10^9/ L o Platelets ≥ 100 x 10^9/L o Hemoglobin ≥ 10 g/dL o Total bilirubin ≤ 1 x ULN o AP <5.0 UNL o ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 x UNL o Creatinine ≤ 175 µmol/L (2 mg/dl) • LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization) General Exclusion Criteria: • Known hypersensitivity reaction to the compounds or incorporated substances • Prior malignancy with a disease-free survival of < 10 years, except curatively treated basalioma of the skin or pTis of the cervix uteri • Non-operable breast cancer including inflammatory breast cancer • Previous or concurrent treatment with cytotoxic agents for any reason after consultation with the sponsor

	• Concurrent treatment with other experimental drugs. Participation in another interventional clinical trial with or without any investigational not marketed drug within 30 days prior to study entry (concurrent participation in non-interventional post authorization safety studies not influencing the primary study endpoints is allowed) • Male breast cancer • Concurrent pregnancy; patients of childbearing potential must implement a highly effective (less than 1% failure rate) non-hormonal contraceptive measures during the study treatment • Breast feeding woman • Sequential breast cancer • Reasons indicating risk of poor compliance • Patients not able to consent Additional Exclusion Criteria for patients receiving chemotherapy: • Known polyneuropathy ≥ grade 2 • Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study • Uncompensated cardiac function • Inadequate organ function including: o Leucocytes < 3.5 x 10^9/l o Neutrophils <1,5x10^9/l o Platelets < 100 x 10^9/l o Bilirubin above normal limits o Alkaline phosphatase ≥ 5 x UNL o ASAT and/or ALAT > 2.5 x UNL
Efficacy evaluation	An intention to treat (ITT) analysis will be conducted for all randomized comparisons. Analyses that are not randomized comparisons will be conducted among the eligible patients (per protocol).
Statistical considerations	<u>Primary endpoints</u> As stated in the sub-protocols, primary endpoints for the individual sub-studies are specific to the patient groups considered: • HR+/HER2-: Five-year EFS. • HR+/HER2+: pCR • TN: pCR • HR+/ HER2-: pCR • Elderly: pCR (Precise event definitions are specified below.) In addition, for ADAPT umbrella, 5-year EFS will be a primary endpoint for comparisons involving <u>all five sub-studies:</u> Five-year EFS will be prospectively compared between two groups defined as follows: • <u>ADAPT Umbrella Test Group</u> comprising • Patients with intermediate risk (RS 12-25) with early good response (and no chemotherapy); • Patients with pCR in HR+/HER2+ disease; • Patients with pCR in HR+/HER2- disease; • Patients with pCR in TN disease • Patients with pCR within ELDERLY substudy

	• ADAPT Umbrella Control Group comprising • Low-risk HR+/HER2- (RS < 12, N0-1) patients Under the trial assumptions, the ADAPT Umbrella Test Group would comprise 1120 HR+/HER2- patients for whom chemotherapy can be spared and 170 or more patients with pCR from the other substudies, i.e., expected 1365 patients. The outcome of the ADAPT Umbrella Test Group will be compared to that of the ADAPT Umbrella Control Group, containing an expected 640 HR+/HER2- patients defined as low risk (by RS), and with no chemotherapy. Again, assuming 94% 5-year EFS in this control group, a one-sided test of non-inferiority at the 95% confidence level will have 80% power for a survival non-inferiority margin corresponding to 3.2% (i.e., 90.8% EFS). Under the stated 5-year EFS assumptions (i.e., 94% "true" 5-y), the power of this test with the stated non-inferiority margin will remain at least 80% if the total number of patients in the control group is at least 640 and the total number in the ADAPT Umbrella Test Group is at least 1290; e.g., a smaller number of pCR (e.g. due to smaller number of recruited patients) in one of the subgroups of the ADAPT Umbrella Test Group will not reduce power as long as the total is at least 1290. Secondary endpoints In all sub-studies and for groups within the studies, the following secondary endpoints (defined below) will be prospectively evaluated: • Overall survival • Relapse free survival • Distant disease-free survival • Local and regional relapse-free survival (LRFS and RRFS) • Quality of life • Toxicity In the ADAPT Umbrella project, these endpoints will be utilized in analyses including • Translational research/prognostic factor analysis • Cost-effectiveness analysis • Comparisons with historical, evidence based outcome estimates (e.g., using Adjuvant Online) Toxicity and health economic issues in the main protocol will be evaluated when the results from the sub-protocols are available. Additional ("Tertiary") endpoints and related research questions Additional endpoints will be defined from the study data to assess and evaluate the following important questions. • Impact of lifestyle factors (body mass index/change of weight), sport activity, alcohol and smoking on prognosis in a subset of patients • Predictive and prognostic value of all molecular, pathological and clinical markers and their combinations Additional translational research questions occurring during the trial will be defined in sub-protocols.

Number of patients / enrolment period	Expected 5236 patients Number of sites: 60-80 Maximum patients per site: 15% of randomized patients per sub-study Enrolment start: Q1 2012 Interim enrolment stop: 2016 (due to regulatory reasons) Enrolment restart: 2018 Enrolment stop: Q4 2019 Follow-up period: 60 months per patient, may be prolonged half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study. Last patient until September 2024.
Study status	Recruitment status as of October2021: • HR+/HER2-: Total number of patients reached; recruitment for the substudy stopped • HR+/HER2+: Total number of patients reached, recruitment for the substudy stopped • TN: Total number of patients reached, recruitment for the substudy stopped • HER2+/ HR-: Recruitment for the substudy was prematurely stopped after enrolment of 120 Patients due to low propability of reaching primary objective. • Elderly: Recruitment was prematurely stopped due to very low enrolment numbers.

2 Introduction and Background

During the last decades, impressive progress in breast cancer treatment has been made due to improved detection and therapy. Large metaanalyses have documented impressive cure rates by modern chemo, immuno and –endocrine therapy in early breast cancer. According to national and international guidelines adjuvant therapy is considered if the risk of recurrence exceeds a 10% ten year risk. This implies a large field of over-treatment, which is especially alarming in patients receiving cytotoxic drugs. Adjuvant chemotherapy is today given to the majority of women who are diagnosed with breast cancer. In patients with HER2 positive and triple negative disease the treatment benefit of chemotherapy is significant, but in HR positive disease especially in patients with 0-3 positive lymph nodes single trials as well as meta-analyses have shown that only a small proportion of women will benefit from this treatment[4,5]. Consequently, the most important questions in adjuvant therapy of breast cancer to be resolved in the next decade are: Who can be spared chemotherapy and who has the maximum benefit from chemo-, endocrine and anti-HER2 -therapy?

Who can be spared chemotherapy - on the basis of a low-risk profile?
For adjuvant chemotherapy the majority of over-treated patients must be suspected in the HR+ subgroup. Molecular classification of breast cancer identifies at least four classes (luminal A: HR+ and low proliferation, luminal B: HR+ and high proliferation, HER2 and basal-like/triple negative (ER/PR/HER2-) subtypes) with very distinctive clinical course and outcome. The disease heterogeneity model revolutionized substantially our understanding of breast cancer[6,7] and re-qualified prognostic impact of clinical-pathological prognostic factors. Novel risk assessment tools (e.g. 21-gene Recurrence Score (RS) (Oncotype Dx®)[8,9], 70-gene signature (Mammaprint®)[10] in addition to validated protein markers like uPA/PAI-1[11] are available for clinical use.
The most recent St. Gallen Consensus 2011 recommends the use of adjuvant chemotherapy in patients with luminal B tumors along with the use of the 21-gene Recurrence Score for selection of patients not benefiting from chemotherapy. The German AGO guidelines recommend the use of either Recurrence Score (preferrably within clinical trials) or invasion markers uPA/PAI-1 (as the only test with level I evidence) for indication of chemotherapy.

The Recurrence Score includes 16 cancer-related and five reference genes whose level of expression (mRNA level) are used to calculate a continuous Recurrence Score from 0 to 100. Although the score is continuous patients are categorized as having low (0-18), intermediate 18-30 and high RS (above 30). Within further trials (TAILORx, PlanB etc) lower cut-offs (0-11/12-25) were used. The RS was developed and validated as a prognostic factor in tamoxifen-treated patients with node-negative HR+ breast cancer from the NSABP-B14 trial[8]. Later analyses of the NSABP-B20 trial demonstrated a strong benefit from adjuvant CMF/MF chemotherapy only among patients with high Recurrence Scores, minimal if any benefit in patients with low Recurrence Scores and uncertain benefit in patients with intermediate RS[9]. Several trials have since confirmed these results, showing very low risk in low RS patients with node-negative or positive (1-3 LN) BC treated with either endocrine therapy alone[12] or by additional chemotherapy[13,14]. Moreover, in the node positive setting a significant chemotherapy benefit was shown only in patients with high RS tumors[14]. RS identifies approximately 50-60% of patients as having intermediate risk and uncertain benefit from adjuvant chemotherapy. Prediction of chemotherapy efficacy is so far confined to data from CMF/CAF chemotherapy.

Molecular classification also provides evidence for an excellent prognostic stratification of patients. Molecular classification can be done by DNA array analysis (as first shown by Perou et al.[6]), immunhistochemistry (expression analysis of proliferation marker Ki-67 or HER2[15]) as well as by supervised analysis of 50 selected genes (PAM-50 signature[7]).
Until such molecular classification is available for clinical routine, the St. Gallen Consensus recommends the use of proliferation markers as the best available surrogate marker for discriminating between luminal A and B disease.
Ki-67 is a validated proliferation marker, which is expressed in all phases of cell cycle except G0[16]. However, despite a large body of evidence demonstrating Ki-67 expression as a strong

prognostic marker in early BC, there is still no consensus regarding either the optimal cut-off for defining high proliferation cancers (e.g. 14%[15] or 19[17]/20%[18]) or the optimal number of proliferation groups (low vs. high with or without intermediate). Correlation analysis with a genomic assay (PAM-50) resulted in an optimal cut-off of 13.25% with only modest sensitivity of 78%[15]. A recently published study showed a higher prognostic value of the PAM-50 signature compared to that of mere immunohistochemical assessment in tamoxifen treated patients, supporting the hypothesis that Ki-67 alone is not sufficient for discriminating the two prognostic subgroups of luminal tumors[19].
Currently available data indicate that Ki-67 is not predictive of overall benefit from adjuvant chemotherapy[17]. Data from the neoadjuvant setting indicate however that Ki-67 may be predictive for benefit from neoadjuvant therapy[20] or taxane incorporation into adjuvant chemotherapy[18,21,22].
There are also data indicating that Ki-67 may predict clinical benefit from aromatase inhibitors (vs. tamoxifen)[23]. In addition, there are published data that indicate that a set of immunhistochemical markers, IHC4 (i.e. ER, PR, HER2, Ki-67) may be comparable to the Recurrence Score as a prognostic tool if determined by an experienced central laboratory. The pairwise correlation with the RS was however only moderate (0.7) and importantly the algorithm for IHC4 has not been validated in an independent trial.

uPA/PAI-1 are invasion factors, associated with poor prognosis and enhanced benefit from CMF chemotherapy in node-negative disease. These markers have achieved the highest level of evidence (LOE I) by the randomized Chemo N0 trial with long-term results[24]. Their use is also supported by a published meta-analysis as well as standardized quality assurance and low costs. Together with Recurrence Score, uPA/PAI-1 is mentioned by the ASCO tumor marker guideline.
Recent as well as ongoing trials like TAILORx (RS), MINDACT (Mammaprint), NNBC-3 (uPA/PAI-1), and WSG-planB (RS) will provide further evidence regarding the use of prognostic markers still within this decade[1]. They will identify a growing population of patients with a low enough risk of recurrence to spare them from unnecessary adjuvant chemotherapy. Interim data from the WSG-planB trial show that high RS is predictive of high uPA/PAI-1 and luminal B subtype but not the converse. There is substantial discordance in the low and intermediate risk groups. These results underline the significant heterogeneity of tumors, particularly within low and intermediate risk disease. Therefore, the above mentioned trials, despite potentially decreasing the number of patients treated by (neo-)adjuvant chemotherapy, may still result in a substantial number of early BC patients at intermediate risk of recurrence who will be left with an uncertain benefit from chemotherapy.

Which patients have the most significant benefit from chemo-, endocrine and anti-HER2-therapy?

HR+: In hormone receptor positive disease, next to the "*static*" approach of analyzing baseline prognostic and predictive markers, there are data from several trials indicating that a response in proliferation markers after a short course (i.e. 2 weeks to 4 months) of primary endocrine therapy (e.g. measured by proliferation marker Ki-67) is associated with a good prognosis even with endocrine therapy alone[25-27]. The proliferation response yet seems to be similar in luminal A and B disease[28]. All these studies agree that the *dynamic* proliferation response after a short endocrine treatment interval was prognostically more important than baseline proliferation values. ADAPT aims to combine optimized baseline prognostic assessment with a potentially predictive dynamic proliferation response to pre-surgical endocrine therapy. Such an approach also allows addressing the biological heterogeneity of intermediate risk disease with its unclear benefit from chemotherapy. Extrapolating these data to HR+ patients with 0-3 positive lymph nodes – assuming (based on available data) an endocrine response in at least 70% of patients[27], this could result in a substantial proportion of patients having such excellent prognosis that they could safely be spared chemotherapy.
All other patients with initially high-risk disease, i.e. with 4 or more involved lymph nodes or with high RS risk or with intermediate RS risk and low response to endocrine therapy will be randomized as part of the chemotherapy optimization.

In general, data from unicenter trials provide evidence for better toxicity profiles and efficacy for reverse sequence taxane-anthracycline based chemotherapy regimens, if compared to classical anthracycline-taxane schedules[29]. The first prospective comparison will be addressed within the ADAPT protocol.

HER2+ and TN:
Both subtypes account for 10-15% of primary BC cases, respectively and correlate with poor prognosis, but high chemosensitivity[30-32]. Unselected use of adjuvant polychemotherapy over 18-24 weeks, containing anthracyclines and taxanes (e.g. 4xEC→4xDoc, 6xTAC, 4xEC-12xpaclitaxel weekly) is standard treatment for all patients with these subtypes. In HER2 positive disease, simultaneous use of trastuzumab with the taxane-containing polychemotherapy and then completion for one year total is recommended for all patients.

HER2+:
Anti-HER2 therapy is currently restricted to the population of patients with HER2 over-expressing tumors, accounting for 10-15% of patients[33]. Integration of one year of targeted therapy with trastuzumab in combination with adjuvant polychemotherapy[34,35] as well as in the neoadjuvant regimen[36] has significantly changed the prognosis of HER2 positive BC and resulted in an increase of pCR rates[37]. In the neoadjuvant setting at least 25-40% of patients achieve a pCR even after a short course of paclitaxel weekly pre-surgical chemotherapy combined with trastuzumab[38,39]. In patients who suffer from recurrence there is some evidence for reduced benefit from T due to a truncated HER2 receptor p95[40,41], but the data are highly controversial. Loss of oncogene PTEN or stem cell factors[42] etc. are discussed as further possible resistance mechanisms.
Recently published data for double blockade in combination with monochemotherapy show nearly doubling of pCR (lapatinib[38] or pertuzumab[43] with standard trastuzumab).

Cross comparison between the GeparQuinto[44] (24 wks of EC→Doc + T) and the Neo-ALLTO (12 wks of Pac+ T) trial revealed comparable pCR rates, so that optimal chemotherapy in HER2+ disease remains to be defined. Furtherly, up to now HER2+/HR+ BC and HER2+/HR- disease have not been regarded upon separately, although the prognosis of HER2+/HR+ BC is essentially better[45,46]. Chemotherapy is accepted as an unquestioned standard, although there is the option of endocrine treatment in this population.

In summary these data suggest that under standard “one size fits all” chemo and anti-HER2 therapy a potential proportion of patients remain under, mis- and over-treated[47].
There is an urgent need for predictive markers for the selection of patients benefitting from targeted monotherapy, dual targeted therapy with or without mono and polychemotherapies.

TN:
Standard therapy of TN breast is even less well defined. There are data for chemotherapy, chemotherapy plus PARP inhibitors and chemotherapy plus bevacizumab.
For chemotherapy the triple negative paradox (chemoresistance with oftenly fatal outcome versus chemosensitivity associated with good prognosis) presents an important clinical challenge[48,49]. Previous studies revealed excellent pCR rates even after a short course of chemotherapy (paclitaxel/carboplatin) in subgroups of TNBC patients.[39] High proliferation and similar phenotype (BRCA-ness, in about 40% of cases) or strong association with BRCA1 mutation are under discussion as a reason for higher efficacy of dose-intense or dose-dense schedules as well as for response to alkylating agents (cyclophosphamide, platinum salts)[50,51].Today, the strongest clinical parameter for chemotherapy outcome prediction is pathological complete remission (pCR)[30,32]. The I-SPY trial revealed excellent outcome for both basal-like and HER2+ or overall high-risk tumors according to gene signature, if pCR was achieved. Poor prognosis in this same trial is mostly attributable to therapy-resistances and/or extensive post-chemotherapy tumor burden. I-SPY and other trials reported that sequential core biopsy assessment or tumor changes in breast MRI[52] allow early prediction of pCR or high residual tumor burden, particularly in TNBC and HER2 disease[53].
MMP9 and FRZB were downregulated at the second biopsy as compared to baseline levels in patients, who did not experience pCR. CD40 and Toll-like receptor signaling were significantly

modulated in these tumors[54]. Moreover, several trials have shown that levels of remaining proliferation in residual tumor tissue (as measured by Ki-67) are highly prognostic in the non-pCR population[55].

BRCA1 mutation or inactivation (e.g. by promoter hypermethylation) results in genetic instability and altered DNA repair (for review[56]).

This provides the basis for combination strategies of chemotherapy (e.g. platinum agents)[50,57] with PARP inhibitors[58], which showed promising efficacy in extensively pre-treated BRCA1/2[59] mutated breast and ovarian carcinoma as monotherapy and in combination with chemotherapy in unselected TNBC[60]. However, after first encouraging results in unselected TNBC, later data are controversial. This demonstrates the necessity for selection of patients, who are candidates for such combination strategies e.g. with platinum salts (e.g. by BRCA1 or DNA repair inactivation[61] (e.g. by RAD 51[62] status) and early definition of patients with low/high likelihood of pCR.

GeparQuinto trial revealed a higher pCR rate of neoadjuvant chemotherapy (EC-Doc) if combined with bevacizumab in the subgroup of TNBC patients[63]. In contrast, the recently presented NSABP B40 study revealed overall significantly better pCR rate in the bevacizumab-containing arms, but attributed the benefit to the subgroup of HR+/HER2- patients[64].

Due to the above mentioned trials and the high therapeutic efficacy in first line[65] or second-line metastatic breast cancer[66] combination of paclitaxel weekly with bevacizumab or combination chemotherapy alone can be considered as standard in TNBC. However there is still no consensus about optimal combination chemotherapy in the TNBC (e.g. (nab)-taxane + carboplatinium vs. other partner (e.g. gemcitabine).

Unfortunately, no predictive markers for use of carboplatin or PARP inhibitors in TNBC are known so far.

Due to the high proportion of primarily resistant disease and the high heterogeneity of treatment options an early predictive marker is urgently needed in this subgroup.

Breast Ultrasound for Early Prediction of pCR after NACT of Breast Cancer

Breast ultrasound is one of best evaluated methods for response evaluation of NACT of breast cancer. The rate of prediction of pCR is up to 80%. The PPV in literature is greater than 75% for identifying the presence of residual disease. The NPV is less than 50%[67]. GEPARTRIO trial enrolled 2090 patients to a neoadjuvant chemotherapy protocol comparing TAC x 6 versus TAC x 8. Early response in this trial was assessed by ultrasound after two courses of TAC. A complete response was defined as no sonographic signs of disease, a partial response if the product of the two largest perpendicular diameters of the primary tumor was reduced by 50 % or more. If the reduction in tumor size was less than 50% or the tumor did not increase by 25 % or more the response was documented as no change. More growth or the occurrence of a new lesion was classified as progressive disease. Patients with no change at the first control (after 2 x TAC) were randomized to further TAC versus navelbine/capecitabine. Patients receiving non cross resistant chemotherapy in the case of no change had an significant survival benefit from changing the regimen[68].

Breast MRI: Data from several trials also indicate a high predictive potential of **functional oncological imaging** for selection of patients with highly chemosensitive tumors[52 53]. Already after a short induction therapy, changes in contrast medium kinetics in contrast-enhanced MRI (DCE-MRI) or ADC (apparent diffusion coefficient) changes in diffusion-weighted MRI or drop of the cholin peak in ^{1}H-MR-Spectroscopy are possible measurement instruments for an imaging approach as an alternative non-invasive and complimentary method for dynamic patient stratification within the ADAPT trial. A further advantage of breast MRI is the analysis of whole tumor (and not just a small single biopsy area) which better accounts for individual tumor heterogeneity.

Along with the ongoing I-SPY-2 trial, which is assessing several targeted agents as partners for neoadjuvant polychemotherapy in the US, the ADAPT trial previews a prognostic profile at time of diagnosis in core biopsy material and a second evaluation of proliferative and apoptotic markers in a sequential tissue sample combined with breast MRI follow-up after a short period (again 3 weeks) of pre-surgical specific therapy.

The aim of ADAPT TN is to identify an early surrogate marker for response in this potentially very heterogeneous sub-group, which may help to identify subsets with maximum benefit.

ADAPT trial in the context of the German and International Trials

Up to the late nineties adjuvant treatment of breast cancer has been improved by large scale classical phase III trials generally testing the adjuvant standard versus standard + a new promising compound in an unselected patient population comprising all early breast cancer patients. Since the beginning of this century the molecular classification of breast cancer has revolutionized our understanding of the disease. Retrospective analyses of the earlier large scale prospective phase three trials explain why chemotherapy is unnecessary in certain subgroups or does not work in certain subgroups. Furthermore the conventional decisional basis of adjuvant treatment has been questioned. Recent trials reported for grading, hormone receptor and HER2 expression discrepancies between central and local pathology in 40% (n=750, prospective phase III EC-Doc trial, 32% (n=3100, PlanB trial for grading and in 12% for hormone receptor status (EC-Doc trial). Her 2 overexpression discrepancies are reported to 20 % in currently conducted trials (GeparQuattro, EC-Doc, ALLTO).

The evidence level (US 1b, Germany 2) of these analyses and the clinical consequences to be drawn are subject of an international controversy. Anyway the different strategies of currently conducted trials reflect the beginning of a new era of adjuvant therapy:

- The number of neoadjuvant trials generating hypotheses for large scale adjuvant trials has increased dramatically
- Trials are conducted in subgroups (e.g. BCIRG 006 in HER2+ disease)
- Trials exploring the classical decisional basis for adjuvant therapy
    - MINDACT with a classical phase III design comparing in N0-1 classical pathology/IHC versus a genomic signature.
    - TailorX in hormone sensitive disease substituting a large part of conventional pathology and IHC by the new decision-making tool Oncotype DX
    - Plan B using Oncotype DX as an adjunct to conventional prognostic factors, thus leaving the classical phase III design. ADAPT trial in this situation of “revolution of adjuvant therapy of breast cancer” is a new generation of personalized medicine trial trying to integrate available biological knowledge beyond conventional pathology to a new form of design.

ADAPT BACKGROUND

ADAPT is conducted over all subtypes of early breast cancer. It combines neoadjuvant and adjuvant strategies. The main aim is to identify patients who are overtreated and those who are adequately treated.

HR+/HER2- Background

ADAPT only addresses to HR+ patients who are candidates for chemotherapy on the basis of conventional prognostic factors. The modern genomic test Oncotype DX in this situation is used as an add-on to conventional pathology. In the HR+ sub-population ADAPT‘s primary clinical efficacy endpoint is to spare chemotherapy to those patients who are already cured (low risk by Oncotype DX) and to those who do not need it (intermediate risk by Oncotype DX/good responders). Due to the absence of a classical phase III design for safety reasons a cut-off of 94% five year event-free survival has been chosen as a level where chemotherapy toxicity/mortality does no longer outweigh benefit. This cut-off is higher than the one proposed by St. Gallen Consensus or the one chosen in MINDACT. It has been confirmed by BIG and AGO trialists. The evidence level for identification of this subgroup by Oncotype DX testing is defined as level 1b by American specialists and by 2 by German specialists.

ADAPT trialist’s have been following this strategy since one generation of trials, so that they already can recur to a unique control from the first generation Plan B trial with an evenly identified population , which is homogeneously treated within a phase 3 trial. The analysis of the “low risk population” allows to reinsure about safety aspects, the analysis of the intermediate risk population allows comparison of the ”all chemotherapy strategy” versus

chemotherapy in “low responders” and the analysis of the high risk group will give an idea of the this group an proportion of patients whose risk might be underestimated by conventional pathology/IHC.

HER2+
Though, trastuzumab has substantially improved cure rates in HER2 positive breast cancer, there remains a substantial number of patients, who are primarily or secondarily resistant to trastuzumab. In the last years several promising anti-HER2 compounds have been developed and especially combinations of HER2 compounds have been very successful. Up to now, all HER2 over-expressing tumors are treated in the same way and growing knowledge is available about resistance and sequencing and scheduling of anti-HER2 therapy. The ongoing trials (ALTTO, Aphinity) will not take into consideration biological heterogeneity of HER2 over-expressing breast cancer. ADAPT tries to develop a molecular tool for early identification of “responders” and “low responders”, which may help to identify patients, who are sufficiently treated by one anti-HER2 agent and those, who might benefit from different combinations.

TN
TN breast cancer remains the most problematic entity. A large part of triple negative breast cancers are primarily resistant to chemotherapy and alternative strategies are urgently needed. A smaller part of the patients have highly chemosensitive disease and good cure rates. Current trials (Geparquinto) have been combining chemotherapy + targeted therapy. ADAPT tries to develop a molecular tool for early identification of “responders” and “low responders”, which may help to optimize chemotherapy and to identify patients who might benefit from non cross resistant/different approaches.

3 Rationale ADAPT Umbrella

The adjuvant therapy indication in early BC today is mainly based on the individual prognostic profile as determined by clinical-pathological factors, prognostic genomic signatures or single protein markers such as uPA/PAI-1. Response to therapy has not been included systematically into the decision-making procedure so far.
Early prediction of response might be a powerful second instrument to identify undertreatment, over-treatment and a unique tool to identify mistreatment. It will spare undue toxicity and undue costs if modern enrichment strategies could be integrated to adjuvant management.
Early molecular response assessment in all subgroups of breast cancer as clinically defined by hormone receptor status and HER2 over-expression is the primary goal of ADAPT.

In hormone sensitive disease data are already available identifying early Ki-67 drop under endocrine treatment as one potent early surrogate for event-free survival (EFS). The ADAPT-trialists suppose that these data are mature enough to spare chemotherapy to those patients with hormone sensitive disease, who are at intermediate risk, but are highly responsive to endocrine therapy.

In HER2 over-expressing and TN disease the data are less mature, so that the evaluation of the dynamic testing is the main goal defined within these sub-protocols.
Without interfering with this primary endpoint innovative new compounds such as T-DM1, Pertuzumab (HER2+) and bevacizumab (TN) can be evaluated in the sub-protocols. Together with the dynamic testing this will give important and early/quick information for the planning of large scale phase 3 trials.
The umbrella protocol of ADAPT will bring together the results of dynamic testing acquired in the different subgroups. It will allow over all subgroups the identification of patients who have intermediate to poor prognosis, but excellent outcome due to high therapy efficacy. This population is “diagnosed” early, so that one hypothesis might be to spare further therapy to these patients. The population not responding (i.e. mistreated) might become another major future focus of ADAPT and adaptive strategies and valuable information about this subgroup will be generated.

4 Study Objectives ADAPT Umbrella

Primary objective

- Identification of a responder sub-population with intermediate or high risk, which due to therapy has outcome (EFS) comparable to HR+/RS≤11

Secondary objectives

- Relapse free and overall survival in corresponding groups
- Overall survival
- Toxicity
- Cost-effectiveness
- distant disease-free survival (DDFS)
- local and regional relapse-free survival (LRFS and RRFS)

Tertiary objectives

- Assessment of impact of lifestyle factors (body mass index/change of weight), sport activity, alcohol and smoking on prognosis in a subset of patients
- Evaluation of all molecular, pathological and clinical markers and their combinations in terms of predictive and prognostic value
- Additional translational research questions occurring during the trial will be defined in sub-protocols.

Further specific objectives are defined within the sub-protocols. Toxicity and cost-effectiveness are common endpoints of all sub-protocols. Toxicity and general health economic issues within the whole protocol will be analyzed, when results from the sub-protocols are available.
Additional “translational research” questions occurring during the trial will be defined in sub-protocols.

5 Study Design

The ADAPT trial is a prospective, multi-center, non-blinded phase II/III trial with modular design. The ADAPT trial will evaluate a *dynamic* biology-guided test in breast cancer patients, independent of their tumor entity. Following the dynamic test the patients will be additionally treated according to their tumor entity in the scope of sub-protocols.
The patients qualifying for the participation in the ADAPT trial will obtain two sequential core biopsies within 3 weeks for prognostic evaluation and early prediction (see figure 1). The first core biopsy is the standard of care diagnostic biopsy and thus not part of the study protocol.
In between the core biopsies, patients will receive tumor-specific treatment, which either consists of pre-surgical endocrine therapy (HR+- HER2- and HER2+ patients) or neoadjuvant chemotherapy (TN, HER2+) and/or targeted therapy (HER2+/HR-, HER2+/HR+). The prognostic profile of the patients will be evaluated at the time of diagnosis from the first (diagnostic) core biopsy and pathological review. The response assessment is performed after three weeks of induction therapy in a second core biopsy or surgery (HR+/HER2- patients), which will allow evaluation of proliferation markers (HR+/HER2- setting) or proliferation and apoptotic markers (HER2+/HR-, HER2+ and TN setting).

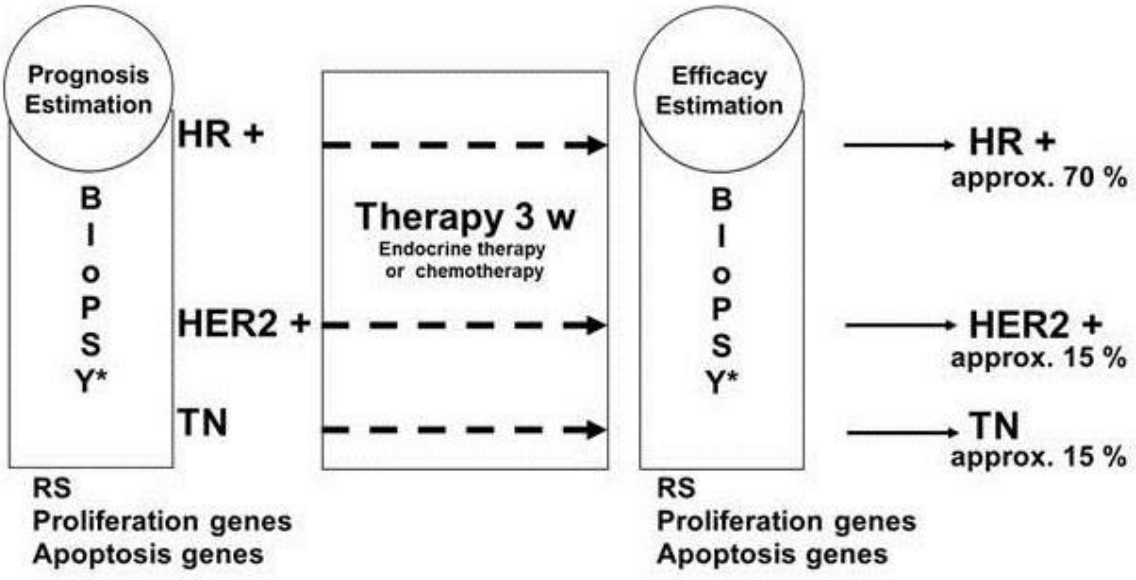


Figure 1: *ADAPT Trial Design*

5.1 Run-in Phase and Main Phase within the sub-protocols

All subprotocols of the ADAPT trial comprise two distinct phases, firstly a run-in phase and secondly a main phase. As soon as the run-in phase is over, an interim analysis will be performed. The interim analysis will have the following objectives:

- Evaluate the reproducibility of biomarker assessment
- Detect treatment related biomarker (proliferation/apoptosis) changes
- Detect treatment related imaging changes
- Assessment of logistics and clinical and laboratory feasibility of the trial
- Confirmation/readjustment of statistical assumptions made for run-in/main phase

In case of a conclusive interim analysis, recruitment will be continued. In uncertain cases results of the interim analysis will be presented to the DSMB. On the opposite, the trial will be aborted, if the analysis of the run-in phase will either show inefficient or unmanageable logistics or no or no significant effect for the repeated biomarker determination.
There are differences in patient numbers for HR+/HER2- and HER2+/HR-, HER2+/HR+ and TN sub-trials. The sample size for the run-in phase and the main phase will be:

	Run-in	Main
HR+/HER2-:	400	3600
HER2+/HR+:	130	250
HER2+/HR-:	75	145
TN:	130	206
Elderly:	130	170

6 Patient Enrollment

6.1 Screening ADAPT

All early BC patients will be screened for participation in the ADAPT trial.

Table 1: *Study Evaluations during Screening*

	INVESTIGATIONS	**TIMING**
Patient informed consent	Obtained	Prior to study entry[1]
Diagnostic core biopsy	Obtained	Prior to registration
ER/PR status	✔	Prior to registration
HER2 status	✔	Prior to registration
Ultrasound	✔	Prior to registration
History and physical exam	History including: • Diagnosis of unilateral primary invasive breast cancer from core biopsy • Assessment of cN and cT status • Receptor status (ER/PR/HER2) at diagnosis • Menopausal status • General medical history including cardiac history and allergy • Concurrent illness and existing signs and symptoms • Concomitant medications and their indication used within one month prior to study entry Physical examination including: • Height • Weight • Karnofsky index for performance status/vital signs Lifestyle parameter (optional in a subset of patients): • Smoking • Alcohol • Physical activity • Nutrition	≤ 3 weeks prior to registration
Imaging	Mandatory for all chemotherapy treated patients. In other patients, if indicated according to current AGO guidelines in suspected M1 disease: • Contralateral mammography and/or ultrasound (mammogram is preferred), where applicable • Chest-X-Ray (PA and lateral), CT or MRI • Abdominal ultrasound and/or CT scan and/or MRI • Bone scan; additional bone X-ray in case of hot spots in bone scan Other instrumental examinations as indicated by radiologist	≤ 3 months prior to registration[2]

[1]Informed Consent should be obtained prior to any tests specified in this clinical protocol that are not part of the patient's routine care

[2]Imaging can be done while induction treatment is given

Patients receiving chemotherapy will additionally be screened for the following parameters.

Table 2: *Study Evaluations during Screening for Patients Receiving Chemotherapy*

	INVESTIGATIONS	**TIMING**
	Hematology • Leucocytes • Platelet count • Hemoglobin	≤ 14 days prior to randomization
Laboratory	**Biochemistry** Liver function: • ASAT (SGOT) • ALAT (SGPT) • Total bilirubin Renal function: • Serum creatinine Electrolytes: • Na^+, K^+ • Cl^-	≤ 14 days prior to randomization Liver function tests are to be repeated within 3 days, if abnormal results
	Pregnancy test Urine or serum (if applicable)	≤ 7 days prior to registration
Evaluation during therapy	• Evaluation of risk factors of febrile neutropenia (HR+/HER2- patients only) • Ultrasound (only in neoadjuvant treated patients)	• Every chemotherapy cycle • HR+/HER2-: every 4 weeks during therapy • Elderly, TN, HER2+: After 3 weeks of induction therapy, 6 weeks and prior to surgery
ECG	ECG	≤ 6 weeks prior to randomization
LVEF	Echocardiography	≤ 6 weeks prior to randomization

6.2 General Inclusion Criteria ADAPT

Patients may be considered to participate in the ADAPT trial, if all of the following inclusion criteria are met:

- Female patients, age at diagnosis 18 years and above (consider *ADAPT Elderly* for patients at 70 years and above)
- Histologically confirmed unilateral primary invasive carcinoma of the breast
- T1 - T4 (except inflammatory breast cancer)
- All N
- Patients should be candidates for (neo) adjuvant chemotherapy according to conventional prognostic factors
- No clinical evidence for distant metastasis (M0)
- Known HR status and HER2 status (local pathology)
- Tumor block available for central pathology review
- Performance Status ECOG ≤ 1 or KI $\geq 80\%$
- Negative pregnancy test (urine or serum) within 7 days prior to registration in premenopausal patients
- Written info
- rmed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements
- The patient must be accessible for treatment and follow-up

Additional inclusion criteria for patients receiving chemotherapy:

- Laboratory requirements for patients receiving chemotherapy (within 14 days prior to randomization):
  - Leucocytes ≥ 3.5 x 10^9/L
  - Neutrophils >1,5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Hemoglobin ≥ 10 g/dL
  - Total bilirubin ≤ 1 x ULN
  - AP ≤5.0 ULN
  - ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 x UNL
  - Creatinine ≤ 175 µmol/L (2 mg/dl)
- LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization)

6.3 General Exclusion Criteria ADAPT

Patients who meet one of the following exclusion criteria will not be eligible for the ADAPT trial:

- Known hypersensitivity reaction to the compounds or incorporated substances
- Prior malignancy with a disease-free survival of < 10 years, except curatively treated basalioma of the skin, pTis of the cervix uteri
- Non-operable breast cancer including inflammatory breast cancer
- Previous or concurrent treatment with cytotoxic agents for any reason after consultation with the sponsor
- Concurrent treatment with other experimental drugs. Participation in another interventional clinical trial with or without any investigational non-marketed drug within 30 days prior to study entry (concurrent participation in non-interventional post authorization safety studies not influencing the primary study endpoints is allowed)
- Male breast cancer
- Concurrent pregnancy; patients of childbearing potential must implement a highly effective (less than 1% failure rate) non-hormonal contraceptive measure during the study treatment
- Breast feeding woman
- Sequential breast cancer
- Reasons indicating risk of poor compliance
- Patients not able to consent

Additional exclusion criteria for patients receiving chemotherapy:

- Known polyneuropathy ≥ grade 2
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study Uncompensated cardiac function
- Inadequate organ function including:
  - Leucocytes < 3.5 x 10^9/l
  - Neutrophils <1,5 x 10^9/l
  - Platelets < 100 x 10^9/l
  - Bilirubin above normal limits
  - Alkaline phosphatase ≥ 5 x UNL
  - ASAT and/or ALAT > 2.5 x UNL

6.4 Registration

Registration to the ADAPT trial can be made once eligibility of the patient is checked (including local pathology, availability of tumor block for central pathology, radiological results, eligibility for Oncotype DX® (HR+/HER2- patients only) as well as laboratory and ECG/LVEF for patients

receiving neoadjuvant chemotherapy without endocrine induction treatment). The registration forms have to be filled in online in the e-CRF. After completion it has to be printed, signed by an investigator and faxed to the coordinator of the study. A registration package outlining the exact process for registering a patient will be forwarded to all sites at the site initiation visit by the site Clinical Research Associate (CRA).

Fax: +49 (0)611 160248 - 29

The following information will be requested:

- Institution name
- Investigator's name
- Patient's identifiers (site number, patient code)
- Patient's birth date (month/year)
- Type of tumor (HR+/HER2-, HER2+/HR-, HER2+/HR+ or TN)
- Date start of treatment planned

6.5 Randomization

Randomization is only applicable within the respective ADAPT sub-trials.
According to local pathology results from the first diagnostic core biopsy regarding tumor entity, patients will be allocated to one of the four ADAPT sub-trials for either HR+/HER2-, HER2+/HR-, HER2+/HR+ or triple negative breast cancer.

For **HR+/HER2- patients** the results of the efficacy estimation of induction treatment and/or risk assessment by standard factors (nodal status, grade, Ki-67) will support the subsequent treatment decisions. After evaluation of proliferation changes and Recurrence Score from the surgical tissue sample by the central pathology, all *eligible* patients have to be allocated by the WSG study coordinator to the corresponding treatment arms. High risk (N2 or RS ≥26 or G3 with Ki-67≥40% and >1 cm) HR+/HER2- patients or HR+/HER2- patients with intermediate risk according to RS (12-25) and low response to endocrine therapy will be randomized for one of two chemotherapy arms.HR+/HER2-/N0-1 with RS ≥26 and all N2 or 3 patients or withG3/Ki-67 >40% and tumor size>1 cm can be randomized directly to the chemotherapy trial without prior 3 week endocrine ("test" treatment). There will be no randomization for low risk patients (RS<12, N0-1) or patients with intermediate risk and good response.

HER2+ and **TN patients** are randomized right after registration to the respective treatment arms.

The randomization forms have to be filled in *online* (e-CRF). After completion, it needs to be printed, signed by an investigator and faxed to the study coordinator. A randomization package outlining the exact process for randomizing a patient will be forwarded to all sites at the site initiation visit by the site CRA. For further information, please refer to the respective sub-protocol.

6.6 Reasons for Premature Discontinuation or Withdrawal from Treatment

Reasons for premature withdrawal or discontinuation include:

- Unacceptable Toxicity
- Withdrawn Consent
- Relapse
- Second primary malignancy (with the exception of curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix)

- Administration of other systemic cancer treatment other than study drug or endocrine therapy as per protocol
- Pregnancy
- Death

The reason and date of therapy discontinuation for all patients will be documented in both the patient's file and the case report form (e.g. completed treatment, adverse event, lost to follow-up, etc.).
The investigator will attempt to complete all discharge procedures at the time a patient is withdrawn from the study.
Patients, who stop chemotherapy for any reason other than having been treated with systemic anticancer therapy for disease relapse or 2nd primary malignancy **must** be followed in a regular follow-up.

7 Study Plan

Tumor evaluation is done by a core biopsy as standard of care in breast cancer. Evaluation of the tumor entity from the first (diagnostic) core biopsy will be done by the study site's **local pathologist**. For comparison of local and central pathological results, a sample of the diagnostic core biopsy has to be shipped to the central pathology laboratory (for contact data please refer to chapter 7.4). The hormone receptor and HER2 status as determined by the local pathologist will define the type of induction treatment.

7.1 Induction Treatment

The treatment for each patient within the ADAPT trial is dependent on the type of the primary tumor (HR+/HER2-, HER2+/HR-, HER2+/HR+ or triple negative). The respective induction treatment is defined in the sub-protocols (chapter 7).
Patients will be treated by induction therapy for three –six (in Elderly protocol) weeks (except patients randomized directly to chemotherapy within HR+/HER2- protocol), after which a second tumor sample will be collected either at surgery or by a second core biopsy for efficacy estimation and response assessment (or clinical response assessment within ELDERLY).

7.2 Efficacy Estimation (Second Core Biopsy/Surgery)

Following 3-weeks of induction therapy, patients are subjected to efficacy estimation, which will be done by a second core biopsy or by a tumor sample obtained from surgery for HR+/HER2- patients. In any case, the tumor sample for efficacy estimation will be analysed by **central pathology review**. The second core biopsy **must not** be derived from radiologically-guided vacuum biopsy.

7.3 Recurrence Score (HR+/HER2- Patients only)

All HR+/HER2- patients without high clinical risk characteristics described above (c/pN2/3, G3/Ki-67$\geq$40% and 1 cm) must have agreed in writing to RS evaluation as well as future participation in the ADAPT HR+/HER2-. Determination of the first RS is not part of the ADAPT trial and will be performed as standard of care (in HR+/HER2-). For RS determination by Oncotype DX(R) in the Institute of Pathology, University Hannover (including delegation of analytical services to Genomic Health Inc., 301 Penobscot Dr, Redwood City, CA 94063, USA) a paraffin-embedded primary tumor block from the diagnostic core biopsy has to be shipped, to the attention of Prof. Kreipe:

Prof. Dr. H. H. Kreipe
Institut für Pathologie an der

Medizinischen Hochschule Hannover
Postfach 610140
30601 Hannover

Tel. +49 511 532 4580
Fax +49 511 532 5799
E-Mail: Kreipe.Hans@mh-hannover.de

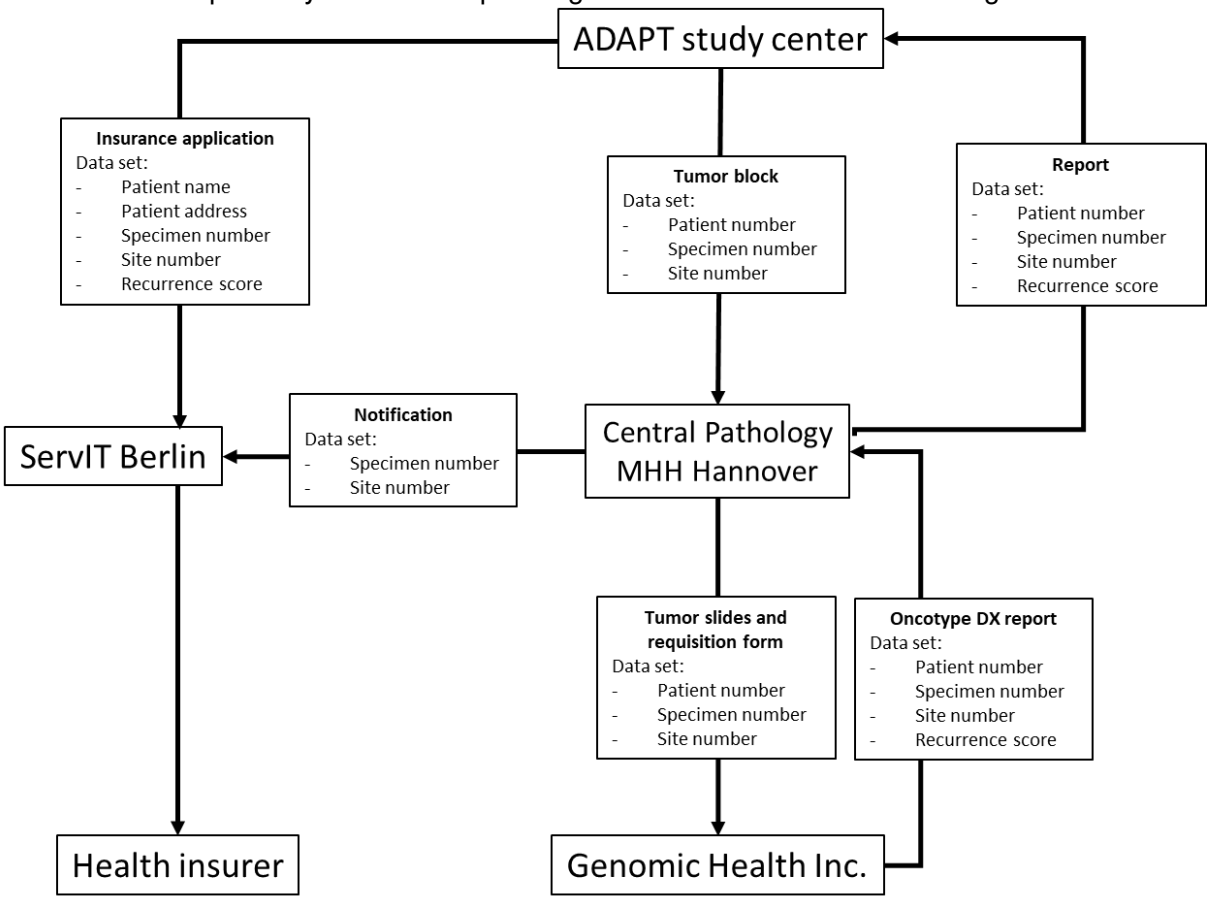
The individual centers will be informed about the RS results by the Institut für Pathologie an der Medizinischen Hochschule Hannover.

Process clarification of insurance applications for the reimbursements of the Oncotype DX test.

To initiate the Oncotype DX testing, the study site sends tumor samples to the central laboratory (MHH Hannover) after the patient has consented to the study participation. Subsequently, these samples will be sent to Genomic Health for testing and the results are communicated back to the study site by the central laboratory. In parallel, the study site applies for reimbursements of the Oncotype DX test using a third-party vendor (ServIT) who relays the application forms to the health insurer of the patient. In case the insurer rejects the reimbursement for the test, Genomic Health will be notified and will cover for the costs.

The process and the application forms are GDPR compliant. Data controller WSG and data processor Genomic Health along with its subsidiaries and subprocessors are bound by data protection agreements as well as corporate binding rules, respectively.

Communication pathways and corresponding data sets are listed the next Figure.



7.4 Central Pathology Review

The central pathology review will be compared to local histopathological results for all patients. For this purpose, the samples from the first diagnostic core biopsy/paraffin embedded primary tumor blocks and the samples from the second core biopsy (efficacy estimation) in patients with induction treatment will be shipped to Institute of Pathology, University Hannover, to the attention of Prof. Dr. Kreipe.

Prof. Dr. H. H. Kreipe
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E-Mail: Kreipe.Hans@mh-hannover.de

The following tests will be performed:

- Hormone receptor status
- HER2 expression
- Histology
- Tumor grade
- Proliferation index Ki-67
- Proliferation genes
- Apoptosis genes

Preferrably, in order to evaluate the tumors of all study participants, tissue microarrays (TMA) will be constructed. The TMAs remaining after central histopathological review will be stored at the central pathology tumor bank. After construction of TMAs, the remaining tumor blocks will stored by the Institute of Pathology In Hannover, if the tumor sample was donated by the patient.

7.5 Surgery; Axillary Lymph Node Involvement Assessment

Definitive surgical treatment must be either mastectomy with axillary lymph node dissection or breast conserving surgery with adequate surgical axillary lymph node staging according to current AGO guidelines, for operable breast cancer (T1-4, any nodal status, M0). Margins of the resected specimen from definitive surgery must be histologically-free of invasive carcinoma and/or ductal carcinoma in situ. Lobular carcinoma in-situ (except LN3) will not be considered a positive margin. For assessment of lymph node involvement sentinel node biopsy, axillary lymph node dissection must be performed in cases of at least one involved sentinel lymph node (pN1) with a minimum of 10 resected lymph nodes in clinically N+ patients. For clinically N0 patients, sentinel node biopsy may be performed. Only centers with established experience in sentinel lymph node biopsy are allowed to use such a procedure for the purpose of this study.
If the sentinel is involved, surgical approach based on the results of the ACOSOG[69] results is allowed, if conform to AGO guidelines[70].

7.5.1 Timing of Surgery

Within the sub-trials the timing of surgery will be different. For patients in the HR+/HER2- part I trial surgery is performed after 3 weeks of induction treatment. Opposingly, if downstaging is intended in the HR+/HER2- part 2 chemotherapy protocol and if neoadjuvant therapy is given in HER2+ and TN disease a sentinel lymph node biopsy is allowed in cN0 patients prior to

neoadjuvant (chemo)therapy. Surgery is completed three to five weeks after the last chemotherapy cycle.

7.6 Estrogen/Progesterone Receptor and HER2 Status

Patients must have a histopathological analysis of estrogen and progesterone receptor as well as HER2 on the primary tumor sample from the diagnostic core biopsy. Tumors are considered as HR positive in case of ≥1% positive cells for ER and/or PR. Percentage and intensity of scoring needs to be provided by local pathologists for inclusion of patients into the study.
HER2 status is considered as positive according to current AGO guidelines, if strong membranous staining in >10% of cells is present (3+) or in case of positive FISH/CISH analysis. All 2+ cases (<10% strong, or >10% moderate circular membranous staining) should be examined by FISH or CISH. One colour ISH positive if >6 signals in at least 20 cohesive cells, negative if <4 signals, re-testing is recommended if 4-6 signals, two-colour ISH bei ratio≥2.0 or ≥6 signals according to current ASCO/CAP guideline[71] and AGO guidelines. Central pathology review is obligatory in all cases with unclear receptor status from local pathology prior to registration. Any sample from a secondary core biopsy is not acceptable. Results must be known prior to randomization.

7.7 Definition of Study Medication

For the purpose of this study, study medication will be labelled study-specific, where applicable, which is defined according to the respective sub-protocols. Any other medication will be commercial ware. For further information, please refer to the respective sub-protocols.

7.8 End of Induction Treatment

End of induction treatment is defined as the completion of the induction treatment with either neoadjuvant endocrine therapy, neoadjuvant chemotherapy or targeted therapy.
At the end of induction treatment, the status quo will be captured and further treatment (endocrine monotherapy (if applicable) or randomization; responder or low responder (if applicable); etc.) will be documented. Reporting of (serious) adverse events ((S)AEs) will continue until end of therapy within the respective sub-protocols.

7.8.1 End of Treatment (EOT) Definition ADAPT

There will be no general end of treatment for the ADAPT trial, but only end of induction treatment, as described in the previous chapter. Therefore, end of treatment will be part of the ADAPT sub-trials. Please refer to the respective sub-protocol for further information.

7.9 Prophylactic Premedication Regimen for Treatment with Taxanes, Epirubicin and Cyclophosphamide

The premedication regimen that is to be administered for patients is dependent on the therapeutic agent. Please refer to the summary of product characteristics for further information about prophylactic premedication. Nonetheless, the administration of dexamethason is highly recommended (table 3.2 below).).There is no special premedication for nab-paclitaxel required.

Table 3: *Premedication Regimen for the Administration of Paclitaxel*

Medication	Timing	Total daily dose
Dexamethason	• Oral intake: 12 and 6 hours prior to **i.v. infusion of paclitaxel** • i.v. infusion: 30-60 minutes prior to **i.v. infusion of paclitaxel**	20mg p.o. **or** i.v.

7.9.1 Use of Prophylactic Antibiotics

Fluoroquinolone prophylaxis has been reported to lower the incidence of febrile neutropenia and all-cause mortality following the first cycle of myelo-suppressive chemotherapy for solid tumors.
Prophylactic use of antibiotics is anticipated in case of neutropenia grade 4 (ANC<500 cells/mm^3 (possible colonization of individuals by resistant organisms taken into account). Therefore, fluoroquinolone prophylaxis should be considered for high-risk patients with expected durations of prolonged and profound neutropenia (ANC ≤100 cells/mm^3 or for >7 days). Levofloxacin and ciprofloxacin have been evaluated most comprehensively and are considered to be roughly equivalent, although levofloxacin is preferred in situations with increased risk for oral mucositis-related invasive viridans group streptococcal infection. A systematic strategy for monitoring the development of fluoroquinolone resistance among gram-negative bacilli is recommended. Addition of a gram-positive active agent to fluoroquinolone prophylaxis is generally not recommended. Antibacterial prophylaxis is not routinely recommended for low-risk patients who are anticipated to remain neutropenic for <7 days[72].
Prophylactic antibiotics will not be routinely used in subsequent cycles for patients who had a prior episode of febrile neutropenia.
Primary prophylactic use of antibiotics is not allowed in this trial. Prophylactic use of antibiotics is recommended in subsequent treatment cycles for those patients who experienced a serious or life-threatening infection.
For patients who had a serious or life-threatening infection, a prophylactic antibiotic is required for all subsequent chemotherapy cycles. Ciprofloxacin is recommended at 500 mg orally twice daily for 10 days starting day 5 of each cycle for remaining chemotherapy cycles. If ciprofloxacin is not available or not tolerated, another oral antibiotic **must** be used. The choice of an antibiotic is at the discretion of the investigator.

7.9.2 Use of Prophylactic G-CSF with Chemotherapy

Primary G-CSF prophylaxis (i.e. from 1st cycle onwards) should be given in all 2-weekly scheduled (dose-dense) chemotherapy courses, according to current AGO guidelines.
Primary G-CSF prophylaxis with Pegfilgrastim according to current AGO guidelines (e.g. FN-risk >20%, dose-dense therapies, TAC q2w, etc.)
Secondary G-CSF prophylaxis according to current AGO guidelines (e.g. weekly with nab-Paclitaxel).

Use of Pegfilgrastim is recommended within the HR+/HER2- study due to to subevaluation of lipegfilgrastim within the dose-dense setting. Lipegfilgrastim use is allowed within the Elderly subprotocol
Treatment with ESF according to SmPC.

Secondary use of G-CSF is permitted only:

- As prophylactic treatment in patients with a prior episode of febrile neutropenia or significant infection in earlier cycle.
- As prophylactic treatment in patients with at least one of the following risk factors:
  - Age ≥ 65 years
  - Serious co-morbidity other than exclusion criteria
  - Open wound or active infections
  - Poor nutritional status
  - Hemoglobin prior to chemotherapy < 12g/dl

The aims of using G-CSF in this trial are to prevent febrile neutropenia, to reduce therapy related morbidity and to prevent dose delay or dose reduction in more than 10% of patients to optimize outcome parameters.

7.9.3 Use of Prophylactic Antiemetics with Chemotherapy

Antiemetic prophylaxis is mandatory for all patients receiving chemotherapy. Selection of antiemetics is at the discretion of the investigator.

7.9.4 Concomitant Treatment during Chemotherapy

Recommendations and restrictions for concomitant treatment during trial participation will be listed in the respective sub-protocols.

7.10 Follow-up

Patients will be followed every 6 months starting from month 6 after registration until 24 months after registration and every 12 months thereafter until year 5 (corresponding to German aftercare plan) or until relapse to document:

- Event-free survival
- Overall survival
- Further therapy (and/or endocrine treatment/treatment with Herceptin®)
- Longterm toxicities
- Relapse (local relapse)
- 2nd primary malignancy
- First treatment for metastatic breast cancer or 2nd primary malignancy
- Results for biopsy of distant metastases (if feasible)
- Yearly evaluation of lifestyle parameter (optional in a subset of patients)

Timing of follow-up visits is based on the date of registration. Follow-up visits will be scheduled at month 6, 12, 18, 24, 36, 48, and 60 after registration.
Patients who relapse or suffer from 2nd primary malignancy will only be followed for survival. Any distant metastasis occurring should be biopsied and the result should be reported in the CRF.
Patients completing follow-up month 60 may be followed half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study, provided that an additional informed consent regarding prolongation of the follow-up was signed.

7.11 Radiation Therapy

Radiotherapy will be mandatory in case of breast conserving surgery according to the policy at each participating site in accordance with current AGO guidelines.
After mastectomy according to the policy in use at each participating study site in accordance with current AGO guidelines. Boost radiation therapy (external or IORT) according to the policy at each participating site in accordance with current AGO guidelines.
If indicated, radiation therapy will begin 3 to 8 weeks after the chemotherapy is completed.

7.12 Therapy after Protocol Treatment is discontinued

Any treatment decision after study discontinuation is at the discretion of the investigator.
In patients with HER2 positive or triple negative tumors and significant tumor burden after 12 weeks of neoadjuvant therapy, the neoadjuvant therapy may be prolonged as **post-study**

treatment. The remaining tumor burden must be proven histologically, i.e. the tumor sample will be sent to the central pathology.

8 Study Evaluations

8.1 Prestudy Screening

All patients will be screened for participation in the ADAPT trial.

Table 3: *ADAPT Study Evaluations during Screening*

	INVESTIGATIONS	**TIMING**
Patient informed consent	Obtained	Prior to study entry[1]
Diagnostic core biopsy	Obtained	Prior to registration
ER/PR status	✔	Prior to registration
HER2 status	✔	Prior to registration
Ultrasound	✔	Prior to registration
History and physical exam	History including: • Diagnosis of unilateral primary invasive breast cancer from core biopsy • Assessment of cN and cT status • Receptor status (ER/PR/HER2) at diagnosis • Menopausal status • General medical history including cardiac history and allergy • Concurrent illness and existing signs and symptoms • Concomitant medications and their indication used within one month prior to study entry Physical examination including: • Height • Weight • Karnofsky index for performance status/vital signs Lifestyle parameter (optional in a subset of patients): • Smoking • Alcohol • Physical activity • Nutrition	≤ 3 weeks prior to registration
Imaging	Mandatory for all chemotherapy treated patients. In other patients only if indicated according to current AGO guidelines: • Contralateral mammography and/or ultrasound (mammogram is preferred), where applicable • Chest-X-Ray (PA and lateral), CT or MRI • Abdominal ultrasound and/or CT scan and/or MRI • Bone scan; additional bone X-ray in case of hot spots in bone scan in high risk patients Other instrumental examinations as indicated by radiologist.	≤ 3 months prior to registration[2]

[1]Informed Consent should be obtained prior to any tests specified in this clinical protocol that are not part of the patient's routine care

[2]Imaging can be done while induction treatment is given

Patients receiving chemotherapy will additionally be screened for the following parameter.

Table 4: *Study Evaluations during Screening for Patients Receiving Chemotherapy*

	INVESTIGATIONS	**TIMING**
Laboratory	**Hematology** • Leucocytes • Platelet count • Hemoglobin	≤ 14 days prior to randomization
	Biochemistry Liver function: • ASAT (SGOT) • ALAT (SGPT) • Total bilirubin Renal function: • Serum creatinine Electrolytes: • Na^+, K^+ • Cl^-	≤ 14 days prior to randomization Liver function tests are to be repeated within 3 days, if abnormal results
	Pregnancy test Urine or serum (if applicable)	≤ 7 days prior to registration
Evaluation during therapy	• Evaluation of risk factors of febrile neutropenia (HR+/HER2- patients only) • Ultrasound*	• Every chemotherapy cycle • HR+/HER2-: every 4 weeks • Elderly, TN, HER2+: After 3 weeks of induction therapy, 6 weeks and prior to surgery.
ECG	ECG	≤ 6 weeks prior to randomization
LVEF	Echocardiography	≤ 6 weeks prior to randomization

*only in patients receiving neoadjuvant chemotherapy

8.2 Evaluation during Induction Treatment (Endocrine Therapy or Neoadjuvant (Chemo) therapy)

During induction treatment, all patients must be examined according to the schedule outlined below until they undergo the second core biopsy (efficacy estimation).

Table 5: *Study Evaluations under Induction Treatment*

	INVESTIGATIONS	**TIMING**
History and physical examination	Clinical history since previous treatment Physical examination - including: • Weight • ECOG or Karnofski index for performance status • Clinical tumor assessment	Every cycle[1]
Hematology	• Hemoglobin • WBC • Neutrophils (optional) • Platelets count	Every week[1]
Biochemistry	• Alkaline phosphatase • ASAT (SGOT) • ALAT (SGPT) • Bilirubin • Serum creatinine • Electrolytes: Na^+, K^+, Cl^-	Every cycle[1]
ECG and LVEF	Echocardiography	As clinically indicated if clinical symptoms
Other investigations		As clinically indicated if clinical symptoms

Adverse events including cardiac toxicity	Investigations as clinically indicated	Serious Adverse Events must be reported within 24 hours anytime

[1]Within 1 day prior to treatment. **Not applicable for endocrine induction therapy.**

8.3 Evaluation at End of Induction Treatment

Work-up will include:

- Surgery/second core biopsy (efficacy estimation)
- Physical examination with Karnofsky index or ECOG (only in chemotherapy treated patients)
- Hematology, biochemistry, urine analysis (only in chemotherapy treated patients) Documentation of toxicity

8.4 Ultrasound assessment:

In accordance with the schedule of the respective sub-protocols the tumor (marker lesion) is measured in all three dimensions. The two longest diameters must be documented. Progressive Disease (PD) is defined as ≥20 percent increase of at least 5 mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameters recorded. In case of PD the therapy should be changed (or surgery performed) at discretion of the investigator. In case of PD the therapy should be changed (or surgery performed) at discretion of the investigator.

Response will be evaluated on an exploratory basis. The tumor needs to be marked with a clip before the first cycle of chemotherapy to be able to reliably identify the region of the former tumor at the time of surgery.

8.5 Evaluation at End of Treatment

For further information please refer to the respective sub-protocol.

8.6 Response Assessment for Neoadjuvant Therapy

Clinical assessment should be performed at baseline, at the time of core biopsy/breast MRI (week 3), after 6 weeks and at the end of therapy (week 12). Clinical assessment at the week 9 is optional.

Within HR+/HER2- protocol in patients treated by neoadjuvant chemotherapy response assessment should be performed after 4, 8, 12 and 16 weeks of therapy, prior to the next cycle.

The clinical response is typically assessed by bidimensional clinical measurements of the primary breast tumor (i.e. clinical palpation). The clinical complete response (cCR) is defined as complete disappearance of all clinically detectable disease in the breast and regional lymph nodes.

Assessment by ultrasound or mammography will be performed according to the following criteria.

- Progressive Disease (PD): ≥20 percent increase of at least 5 mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameter recorded. In case of PD the therapy should be changed (or surgerry performed) at discretion of the investigator.

Response will be evaluated on an exploratory basis. The tumor needs to be marked with a clip before the first cycle of chemotherapy to be able to reliably identify the region of the former tumor at the time of surgery.
Pathological response assessment: The tumor ypT is measured as the largest single focus of invasive tumor, not including areas of fibrosis within the tumor bed. Pathological complete

response (pCR) implies no histopathological evidence of residual invasive tumor cells, either in the breast or the axillary lymph nodes.

Recently von Minckwitz et al compared different definitions of pCR (e.g. ypT0/ypN+, with or without don-invasive lesions etc.). They found adverse impact of remaining in situ lesions on prognosis of patients[73] (in contrast to prior reports[74]).

9 Dose Delays and Reduction / Modification

Patients will be treated as per protocol or until disease progression or withdrawal from treatment due to an unacceptable adverse event or informed consent withdrawal. Prior to each chemotherapy cycle subjects have to be evaluated for evidence of drug-related adverse events.

9.1 Treatment Dose Adjustments and Treatment Delays

Toxicities will be graded using the NCI Common Toxicity Criteria (NCI CTC), version 4.0.
Any treatment dose adjustment and/or treatment delay has to be done in accordance to the applicable summary of product characteristic or the investigator's brochure, respectively. Please find the instructions on dose adjustment and delays attached in Appendix 1 – Treatment Dose Adjustments and Treatment Delays.

Treatment with chemotherapy may be delayed no more than 2 weeks (up to day 21 - 35) to allow recovery from acute toxicity.

10 Translational Research

10.1 Sample Collection

10.1.1 Performance of Genomic Profile (Oncotype DX®)

For all HR+/HER2- patients, Recurrence Score will be determined prior to endocrine induction therapy and in a subgroup of patients after the induction therapy. The evaluation will be done by Genomic Health Inc.
For testing, paraffin-embedded primary tumor block tissue will be shipped to the laboratory of Genomic Health (Genomic Health Inc., 301 Penobscot Dr, Redwood City, CA 94063, USA) by the Institut für Pathologie an der Medizinischen Hochschule Hannover.

Prof. Dr. H. H. Kreipe
Institut für Pathologie an der
Medizinischen Hochschule Hannover
Postfach 610140
30601 Hannover

A prerequisite for the first testing is its coverage as standard of care as well as a signed informed consent for risk assessment and follow-up.
Tumor blocks will be returned to the Westdeutsche Studiengruppe after Oncotype DX® testing. Further details can be found in the SOP manual.

10.1.2 Mandatory Tissue Samples

Each patient has to donate a part of the primary core biopsy for evaluation of prognosis (e.g. Ki-67, RS (where applicable), proliferation genes, apoptosis genes).
In patients with HR+/HER2- disease undergoing induction treatment one paraffin-embedded representative primary tumor block donated by the patient to the WSG is required from each

patient at time of the risk screening phase for the Oncotype DX® testing as well as central pathology (for further translational projects in paraffin-embedded tissue) prior to randomization. The tumor block should be clearly labelled with the patients screening number. The shipment of tumor blocks will be supplied by the supplement form indicating patients screening number and date of birth as well registration number of local pathology.
Each patient needs to give informed consent for shipment of tumor block.

On behalf of the Westdeutsche Studiengruppe GmbH, the paraffin blocks will be collected by (and finally stored by):

Prof. Dr. H. H. Kreipe
Institut für Pathologie an der
Medizinischen Hochschule Hannover
Postfach 610140
30601 Hannover

Tel. +49 511 5324580
Fax +49 511 5325799
E-Mail: Kreipe.Hans@mh-hannover.de

10.1.3 **Optional Samples**

Participating centers and patients are strongly encouraged to participate in all translational projects of the ADAPT sub-protocols. Therefore, the following optional samples are requested (samples may be donated either all together or separately to the WSG):

- Serum sample for pharmacogenetic evaluation
- 10 ml EDTA-blood sample for circulating tumor cells at 3 (- 4) time points (only in a subgroup of patients: before and at the end of chemotherapy (in initially circulating tumor cell positive patients, another sample will be taken in between); one year after end of the chemotherapy.

Results of central pathology review of Ki-67 in HR+/HER2- substudy will be routinely reported back to the centers, whereas those of optional translational research projects will not.

10.1.4. Objectives of translational research

- Evaluation of pre- and postmenopausal status as a predictive factor of therapy response with the following sub-studies: HR+/HER2- ; HR+/HER2+; HR-/HER2- ; HR-/HER2+
- Evaluation of PI3K mutations status, PD-L1, IL-8, bcl-2 and further molecular markers as predictors for response (in distinct subtypes: e.g. HER2+ and HR+/HER2-)
- Pharmacogenomic analysis
- cDNA analysis in blood sample
- Whole genome deep sequencing and methylation analysis in a representative cohort of patients in distinct substudies, this list will be updated according to further translational projects
    - E.g. to derive mutational profiles in endocrine sensitive and resistant breast cancer
    - Epigenetic changes in endocrine sensitive and resistant breast cancer by performing genome wide DNA methylation profiling
    - Genomic copy numbers associated with endocrine resistance/sensitivity
    - Characterization of miRNA profiles associated with endocrine sensitivity/resistance

- Within HR+ and HR-/HER2+ and HR-/HER2- substudies:
  - Evaluation of tumor infiltrating lymphocytes value as a predictor for therapy response
  - Evaluation of molecular subtypes by PAM50 plttform as predictors for therapy response and outcome of patients
- Within HR-/HER2- only:
  - Evaluation of tumor BRCA1 mutation status and/or BRCA1-ness as predictor for therapy response
  - Target gene analysis (25 gene panel) as predictor for response
  - Evaluation of family history of breast cancer as predictor for therapy response
  - AR measurement as a predictor for therapy response

11 Global Statistical and data analysis considerations

11.1 Specification of endpoints

Primary endpoints

As stated in the sub-protocols, primary endpoints for the individual sub-studies are specific to the patient groups considered:

- HR+/HER2-: Five-year EFS.
- HR+/HER2+: pCR
- TN: pCR
- HR+/HER2+: pCR
- Elderly: pCR

(Precise event definitions are specified below.)

In addition, for ADAPT umbrella, 5-year EFS will be a primary endpoint for comparisons involving all five sub-studies: Five-year EFS will be prospectively compared between two groups defined as follows:

- ADAPT Umbrella Test Group comprising
  - Patients with intermediate risk (RS 12-25) with early good response (and no chemotherapy);
  - Patients with pCR in HR+/HER2+ disease;
  - Patients with pCR in HR+/HER2- disease;
  - Patients with pCR in TN disease
  - Patients with pCR in the Elderly protocol

- ADAPT Umbrella Control Group comprising
  - Low-risk HR+/HER2- (RS< 12, N0-1) patients

Across the sub-protocols, we assume that adjuvant chemotherapy can be spared in HR+/HER2- disease and pCR be achieved in HER2+/TN in expected 1120 (HR+/HER2-) and at least 170 (HER2+ and TNBC and Elderly) patients within the main phase of the trial. The outcome of this group will be compared to the “control group” containing an expected 640 patients defined as low risk (by RS), HR+/HER2- and no chemotherapy. Again, assuming 94% 5-year survival in this control group, a one-sided test of non-inferiority at the 95% confidence level will have 80% power for a survival non-inferiority margin corresponding to 3.2% (i.e., 90.8% survival).
Under the stated 5-year EFS assumptions (i.e., 94% “true” 5-y), the power of this test with the stated non-inferiority margin will remain at least 80% if the total number of patients in the

control group is at least 640 and the total number in the ADAPT Umbrella Test Group is at least 1290; e.g., a smaller number of pCR (e.g. due to smaller number of recruited patients) in one of the subgroups of the ADAPT Umbrella Test Group will not reduce power as long as the total is at least 1290.

Secondary endpoints

In all sub-studies and for groups within the studies, the following secondary endpoints (defined below) will be prospectively evaluated[75]:

- Overall survival
- Relapse free survival
- Distant disease-free survival
- Local and regional relapse-free survival
- Quality of life
- Toxicity.

In the ADAPT Umbrella project, these endpoints will be utilized in analyses including

- Translational research/prognostic factor analysis
- Cost-effectiveness analysis
- Comparisons with historical, evidence based outcome estimates (e.g., using Adjuvant Online).

Toxicity and health economic issues in the main protocol will be evaluated when the results from the sub-protocols are available.

Additional ("Tertiary") endpoints and related research questions

Additional endpoints will be defined from the study data to assess and evaluate the following important questions.

- Impact of lifestyle factors (body mass index/change of weight), sport activity, alcohol and smoking on prognosis in a subgroup of patients
- Predictive and prognostic value of all molecular, pathological and clinical markers and their combinations.

Additional translational research questions occurring during the trial will be defined in sub-protocols.

11.2 Allocation, randomization, and stratification

Patients will be allocated to four different groups defined by hormone receptor and HER2 status: HR+/HER2-, HER2+/HR+, HER2+/HR- and TN; allocation to the trial will thus be performed in a non-randomized setting.

There are several instances of randomization to treatments as specified in the respective sub-protocols. In all such instances, randomization will be performed centrally according to a permuted block design.

Stratification will be performed by study center. and nodal status (p or cN0, N1, N2, N3). Further stratification parameters are defined in the sub-protocols.

11.3 Efficacy Evaluations

11.3.1 Definitions of primary efficacy parameters

The primary efficacy parameters are 5-year EFS for HR+/HER2- disease and pCR rates for HER2+ and TN disease. These are defined as follows.

Event-free survival (EFS):

Event-free survival (EFS) will be analyzed on the basis of any *event* (detailed event definitions see below). EFS is defined as the interval from the date of registration to the date of local, regional or metastatic invasive or both invasive/non-invasive relapse or the date of second primary cancer (with the exception of curatively treated non-melanoma skin cancer or in situ carcinoma of the cervix) or death from any cause, whichever occurs first.
This definition is according to the current guidelines recommended definition of invasive disease free survival[75,76].

Pathological Complete response (pCR):

The efficacy parameter pCR is defined at the time of surgery as absence of invasive tumor in the breast and lymph nodes. This will also be measured based on provision of data on size of the residual tumor, proportion of vital cells within invasive carcinoma, number of positive lymph nodes and size of the largest lymph node metastasis and ductal carcinoma in situ.

Remark: Based on these criteria, residual cancer burden (and other pCR classifications) will be measured for further analysis. Further chemotherapy can be omitted at the discretion of the investigator only in tumors with pCR defined as not invasive and DCIS patterns.

In all neoadjuvant sub-protocols other pCR definitions (ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypN0 and regression grades) as well rates of breast conserving therapy will be examined.

Clinical response (examination, mammography/sonography, MRI) will be compared to proliferation response and be correlated to pCR and therapy.

11.3.2 Further event definitions

Objective Relapse

Objective relapse is defined as any clinical or radiologic evidence of tumor relapse including the central nervous system.

1. Documented histological or cytological proof of failure is strongly recommended.
2. Detail on flow sheets the appearance of any evidence of malignant disease.
3. Follow-up for survival.

Local Relapse

Local relapse is defined as evidence of tumor (invasive or both invasive/non-invasive) in the breast surgical scar, ipsilateral breast (conservative surgery), or evidence of tumor in the ipsilateral anterior chest wall (mastectomy) or skin or soft tissues within the local area.

Histological or cytological proof is mandatory.

Regional Relapse

Regional relapse is defined as evidence of tumor (invasive or both invasive/non-invasive) in the axillary scar, ipsilateral nodal areas (axillary, internal mammary, infraclavicular and supraclavicular) as well as skin or soft tissues within the regional area.

Histological or cytological proof is mandatory.

Distant Relapse

Distant relapse is defined as evidence of tumor beyond the local-regional level. Distant relapse includes the following:

1. lymph nodes not included in the areas defined above (i.e. contralateral axilla, paratracheal, etc.)
2. skin not included in the areas defined above
3. liver
4. lung
5. bone
6. central nervous system
7. contralateral breast (similar biology as primary tumor).
8. other sites not defined above

Histological or cytological proof is preferred, especially in solitary lesions.
Elevation of serum markers such as CEA or CA15-3 alone will not constitute evidence of relapse without other objective evidence of relapse. These analyses are not recommended.

Second Primary Cancer
Second primary cancer is defined as any other histopathologically proven cancer including second invasive primary breast cancer in ipsilateral or contralateral breast.

11.3.3 Further efficacy parameters

Relapse free survival (RFS), Distant disease-free survival (DDFS), Local relapse free survival (LRFS) and overall survival (OS) and disease free survival (former EFS definition) are further efficacy parameters.
Relapse free survival will be analyzed on the basis of only local, regional or distant invasive relapse or death, but not secondary cancer.
Disease free survival (or DCIS-DFS according to the current STEEP criteria) is defined as the interval from the date of registration to the date of local, regional or metastatic invasive or both invasive/non-invasive relapse or the date of second primary or death from any cause, whichever occurs first.

DDFS will be analyzed on the basis of only distant metastases, deaths or secondary invasive cancers as event, and not local relapses or contralateral breast cancer.

11.3.4 Populations to be analyzed

- All patients: all patients enrolled in the study
- Intention-to-treat and per-protocol populations (ITT1 and PP1) in low and intermediate-risk HR+/HER2- disease treated with no chemotherapy.
- Intention-to-treat and per protocol populations (ITT2 and PP2) in high-risk HR+/HER2- (high risk and N0-1/intermediate with no response to endocrine therapy) disease treated with chemotherapy
- Intention-to-treat and per-protocol populations in HER2+/HR+ (ITT3 and PP3), HER2+/HR- (ITT4 and PP4) and TN (ITT5 and PP5) disease

- Safety population within low-risk HR+/HER2- (SP1), high-risk HR+/HER2- (SP2), HER2+/HR+ (SP3), HER2+/HR- (SP4) and TNBC (SP5), who have started their allocated treatment (at least one dose of the drug)

Analysis of EFS and of OS will be performed in the **Intent-to-Treat (ITT) population**, defined as the population of all randomized patients analysed in the treatment group they were assigned to. Analysis of EFS and OS will also be performed in the **eligible patients populations**, defined as the ITT population patients without patients who were randomized and started with therapy, but were not eligible for the trial according to the inclusion and exclusion criteria (modified IIT).

11.3.5 Time to event definitions:

In this protocol, time to event (EFS (currently iDFS), DCIS-DFS, RFS, DDFS, L(R)FS and OS) will be defined as follows:

- For all analyses related to endocrine-only patients (HR+/HER2-), time-to-event endpoints will start at the date of registration of patients
- For all analysis related to chemotherapy application, time-to-event endpoints will start at the date of registration for the trial
- For all HER2+, HER2+/HR+ and TNBC patients, time will start at the date of the registration for the trial

11.3.6 Timing of analyses

Final analysis (pCR) in ITT3-5 and PPP 3-5 will be performed after all patients within HER2+ and TN subgroups have completed surgery. Exploratory analysis in patients of ITT2 and PP2, who underwent neoadjuvant chemotherapy will be performed also after completion of surgery.

Prognostic factor analysis will be defined at the time of end analysis. Both local and central data will be used.

11.4 Safety Evaluations

11.4.1 Grading of Adverse Events

The National Cancer Institute Common Toxicity Criteria (NCI-CTC), version 4.0 and the corresponding grading system will be used to grade adverse events for recording in the CRF. For all adverse events not classified by the NCI-CTC a COSTART grading classification (FDA 1989) will be performed (severity as 1: mild, 2: moderate, 3: severe, and 4 life threatening).

11.4.2 Populations to be analyzed

The safety analysis will be conducted on all patients who started at least one infusion of the study treatment.

11.4.3 Interim Safety Analysis

Safety analyses will usually coincide with the end of the run-in phase (if applicable), unless stated differently in a particular subprotocol, and comprise the evaluation of AEs, SAEs, as well as cardiotoxicity (see appendix 2) where treatment consists of cardiotoxic therapies anthracycline-containing chemotherapy and/or anti HER2 therapies. All evaluations will be done by treatment arm. If a patient has more than one AE and at least one of the AEs was considered drug-related, the patient will be counted as having a drug-related AE. If a patient has more than one AE and at least one of the AEs was considered severe, the patient will be counted as having a severe AE. An overview table will be presented with the number (and percentage) of patients with at least one AE, with at least one SAE as well as with the number

of patients who died during the trial by treatment arm. Further, all AEs/SAEs of known severe intensity, all drug-related AEs/SAEs (according to the investigator), all actions taken with study medication as well as the outcome of all AEs/SAEs will be tabulated by treatment arm. The incidence of cardiac adverse events (cardiac deaths, CHF, grade 3 or grade 4 ischemia/infarction, grade 3 or grade 4 arrhythmias) will be calculated for each treatment arm. Further safety objectives may be defined in the respective subprotocols.

11.4.4 **Overall Safety Evaluation**

The DSMB of the ADAPT trial will be based on the expertise of at least 5 members. In general these members will represent the different specialties necessary for the trial. Beside members from national and international cancer centers and breast centers also a statistician and a pathologist will be asked to join the DSMB.
Data will be reviewed at least every 3 months during active treatment phase and 6 months uring follow up phase and additionally in case of any safety concerns.

11.5 General Statistical Considerations

11.5.1 **Statistical tests of primary endpoints**

Statistical analysis of primary endpoints includes both one-sided and two-sided testing as appropriate for the within the study populations and design in question. In particular, testing will generally be one-sided in the case of non-inferiority testing (in comparison to a low-risk control group) unless otherwise stated. (In the case of non-inferiority hypothesis testing involving a test treatment versus active treatment control, the non-inferiority margin is far less than the historical benefit of the control throughout the ADAPT trial.)

Significance levels (alpha) for primary endpoints are stated in the individual sub-studies (under sample-size calculation) and are usually taken at the 5% level.

11.5.2 **Statistical tests of secondary and further endpoints**

All confidence intervals regarding secondary and further endpoints will be reported at a nominal 95% confidence level.

11.5.3 **Univariate and multivariate survival analysis**

Time-to-event models will be estimated using survival analysis methods.

Survival curves will be computed by the product-limit method and will be displayed in Kaplan-Meier format. The log-rank statistic will be computed for all direct comparisons of subgroups. This statistic has been used as the basis for power and sample size calculations for survival analysis.

Hazard ratios will be estimated and reported in both univariate and multivariate analysis according to the Cox proportional-hazards model.

In exploratory analyses, assumptions of the proportional hazards model will also be tested and time-varying models will be estimated if appropriate. At the exploratory level, interactions including time-varying interactions will be considered.

As part of multivariate modeling, biomarkers such as clinical/pathological nodal status, age, clinical/pathological tumor size, locally and centrally measured Ki-67, ER, PR, HER2, local and central grade, lifestyle factors will be recoded as appropriate to allow optimal comparison of effect sizes and interpretation of the models.

11.5.4 Further exploratory univariate and multivariate survival analyses

Further advanced survival models based on statistical likelihood will be utilized in exploratory analysis in ADAPT umbrella and in the sub-studies.

In exploratory analysis, classifiers based on biomarkers will be investigated and constructed using established statistical methods. (A simple example of a classifier is a binary variable defined from a continuous biomarker according to an “optimal cutoff”.) The quality of these classifiers will be reported using appropriate statistics such as the Bayes information criterion and methods such as n-fold cross validation.

Further exploratory analysis could utilize multiple imputation for missing data if required.

Local and regional relapse-free survival (LRFS and RRFS) (overall and/or only invasive) will be analyzed taking into account local treatment (mastectomy/breast conserving therapy, type of radiotherapy (intra-operative vs. no), type of axillary treatment).

Overall survival will be also analyzed by sensitivity analysis, taking only cancer related deaths into account, for all patients and for single subgroups.

11.5.5 Statistical methods for pCR comparisons

Primary comparison of pCR of primary endpoints will be performed for large sample sizes by X^2 tests or by T-test using the normal approximation with continuity correction; when expected counts are low, Fisher’s exact test or one of its generalizations will be performed.

Models of pCR using explanatory factors will utilize logistic regression on the binary variable pCR.

If additional (continuous) measures of response are available as secondary endpoints, appropriate regression models for these will be utilized.

11.5.6 Statistical methods for safety evaluation

Adverse event comparisons will be carried out using two-tailed X^2 tests or Fisher’s exact test or one of its generalizations.

Descriptive statistics will be given on the number of patients in whom the study medication had to be replaced, delayed or permanently stopped.

In safety evaluation, a large number of statistical tests with formal p-values or confidence intervals will be reported; these safety evaluation tests serve to highlight differences worth further attention and therefore will not be corrected for multiple testing.

11.5.7 Health-economical Analysis

A health-economical analysis will be performed, taking into account the ratio of risk grouping by baseline Recurrence Score, clinico-pathological factors, (HR+/HER2-) and patients identified to be spared additional chemotherapy (in all sub-trials) or targeted therapy (HER2+/HR- or TNBC) by dynamic test, percentage costs and side-effects of chemotherapy administered, as well as patient outcome.

Quantification of health-economic parameters will be evidence-based and supported by expert assessments.

11.6 Power of ADAPT Umbrella

Five-year EFS will be prospectively compared between the ADAPT Umbrella Test Group and the ADAPT Umbrella Control Group defined above. A non-inferiority margin of 3.2% is considered clinically appropriate.

To estimate the statistical power of this comparison, we assume the following:

In the ADAPT Umbrella Test Group adjuvant chemotherapy can be spared in HR+/HER2- disease and pCR be achieved in HER2+/TN in expected 1120 (HR+/HER2-) and at least 170 (HER2+ and TNBC) patients within the main phase of the trial.

The outcome of the ADAPT Umbrella Test Group will be compared to that of the ADAPT Umbrella Control Group, which is expected to contain 640 patients.

Assuming 94% 5-year EFS in this control group, a one-sided test of non-inferiority at the 95% confidence level will have 80% power for a non-inferiority margin (delta survival) corresponding to 3.2% (i.e., 90.8% survival).
Under the stated 5-year EFS assumptions (i.e., 94% “true” 5-y), the power of this test with the stated non-inferiority margin will remain at least 80% if the total number of patients in the control group is at least 640 and the total number in the ADAPT Umbrella Test Group is at least 1290; e.g., a smaller number of pCR (e.g. due to smaller number of recruited patients) in one of the subgroups of the ADAPT Umbrella Test Group will not reduce power as long as the total is at least 1290.

12 Adverse Events

12.1 Adverse Event Monitoring

Subjects must be carefully monitored for adverse events. This monitoring includes clinical laboratory tests. Adverse events should be assessed in terms of their seriousness, intensity, and relationship to the study drug and reported according to the NCI Common Toxicity Criteria Version 4.0.
(Serious) adverse events that occur within 30 days following the last drug intake regardless of causal relationship or any (S)AE that occurs after 30 days that is considered related to the study medication will be followed until resolution.

12.2 Adverse Event Definitions

12.2.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The adverse event does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An adverse event occurring in the course of the use of a drug product in professional practice
- An adverse event occurring from an overdose whether accidental or intentional
- An adverse event occurring from drug abuse
- An adverse event occurring from drug withdrawal
- An adverse events where there is a reasonable possibility that the event occurred purely as a result of the subjects participation in the study (e.g.

adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an adverse event even if it is not related to the investigational product

"Progression of underlying disease" is NOT considered as (S)AE. Signs and symptoms related to disease progression should be graded. Objective documentation of the progression should always be sought.

12.2.2 **Serious Adverse Event**

A serious adverse event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is an important medical event

All grade IV CTC adverse events have to be reported as SAEs, if the investigator assesses that the event meets standard ICH criteria for an SAE.

Life-threatening:
The term "life-threatening" in the definition of "serious" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event that hypothetically might have caused death if it were more severe.

Hospitalization:
Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as serious, UNLESS at least one of the following exceptions is met:

- The admission results in a hospital stay of less than 12 hours or
- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study) or
- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care).

However it should be noted that invasive treatment during any hospitalization may fulfil the criteria of 'medically important' and as such may be reportable as a serious adverse event dependent on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event:
Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "WHO Adverse Reaction Terminology – Critical Terms List". These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention, because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

12.2.3 **Unexpected Adverse Event**

An unexpected adverse event or suspected unexpected serious adverse reaction (SUSAR) is any adverse drug event; the specificity or severity of that is not consistent with the current

SmPCs for docetaxel (Doc), epirubicin (E), cyclophosphamide (C), paclitaxel (Pac), trastuzumab (T) or investigator's brochure for T-DM1, pertuzumab (P) or nab-paclitaxel (nab-Pac). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected adverse events. For example, an event more specific or more severe than described in the Investigator Brochure would be considered "unexpected". Specific examples would be; (a) acute renal failure as a labelled adverse event with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

An expected adverse event with fatal outcome must be regarded as unexpected, if the IB or SmPC does not explicitly state the option of fatal outcome for this event.

12.2.4 **Relationship of Adverse Event to Investigational Product**

The assessment of the relationship of an adverse event to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of 'No' would include:
1. The existence of a clear alternative explanation e.g., mechanical bleeding at surgical site; or
2. Non-Plausibility e.g., the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of 'Yes' indicates that there is a reasonable suspicion that the adverse event is associated with the use of the investigational drug.
Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subjects response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question.
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

12.2.5 **Severity of the Adverse Event**

All adverse events will be graded using the NCI CTC version 4.0.

12.2.6 **Adverse Event Documentation**

All adverse events, except the ones listed below, occurring after the subject has started study treatment (day 1) must be fully recorded in the subject's case report form.

For all therapy arms where no experimental drug is in use, all adverse events that are graded CTC grade 1 or 2 and that are named in the SmPC need not to be documented in the e-CRF, unless the investigator deems it as clinically significant. Any adverse event that is graded CTC grade 1 or 2 and that is not named in the SmPC or any adverse event that is graded CTC grade 3, 4 or 5 has to be documented in e-CRF.

Documentation must be supported by an entry in the respective subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an adverse event. Each event should be described in detail along with start and stop dates, severity (CTC grade), relationship to investigational product, action taken and outcome.

12.3 Reporting of Serious Adverse Events/Pregnancy

Each serious adverse event must be followed up until resolution or stabilization, by submission of updated reports to the designated person. An isolated laboratory abnormality that is assigned grade 4, according to CTC definition, is not reportable as SAE; unless the investigator assesses that the event meets standard ICH criteria for an SAE. Abnormal baseline laboratory values that are part of the disease profile should not be reported as AE, specifically when they are allowed or not excluded by the protocol inclusion/exclusion criteria.
All SAE, whether or not deemed drug-related or expected, must be reported by the investigator to the following address within one working day (24 hours) of first becoming aware of the event by fax on the respective form of serious adverse event reporting:

Studienzentrale Bonn (SZB)
Institut für klinische Chemie und klinische Pharmakologie
Venusberg Campus 1
53105 Bonn
Germany
Tel: +49 228 287 16040
Fax: +49 228 287 9080 110
e-Mail: safety-SZB@ukbonn.de

The Sponsor will supply Celgene with a copy of all SAEs which involve *exposure* to a Celgene product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g. IB, SmPC). The Sponsor will provide Celgene with a copy of the annual periodic safety report e.g. Development Update Safety Report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committee."

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 30 days of the subject's last dose of IP, are considered immediately reportable events. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify WSG and Celgene immediately about the outcome of the pregnancy (either normal or abnormal outcome).

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE within 24 hours of the

Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

It is the duty of the Westdeutsche Studiengruppe GmbH to ensure that ethics committee, competent authority and participating investigators are informed of all suspected unexpected serious adverse reactions (SUSARs) and all other relevant safety information in accordance with legal requirements (§13 GCP-V, annual reports).

It is the duty of the Westdeutsche Studiengruppe GmbH to inform the marketing authorization holder of all study-specifically labelled study drugs according to stipulation. In case of non-study-specifically labelled drugs any possible effort will be taken to inform the respective authorization holder.

The marketing authorization holder will also be notified about all significant or safety-relevant results or recommendations of the study board, which may influence or impair the course of the study or the safety of the study participants.
Pregnancy occurring during a clinical investigation, although not considered a serious adverse event, must be reported to the Westdeutsche Studiengruppe GmbH within the same timelines as a serious adverse event on a Pregnancy Monitoring Form. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child must be reported.

13 Study Medication

13.1 Drug Packaging, Labelling, Dispensing and Storage

13.1.1 Packaging and Labelling

For the ADAPT trial commercial ware will be used. Investigational medicinal products (IMPs) which are used off-label will be labelled study-specific, the investigational medicinal products (IMP) used in-label will not be labelled study specific.

13.1.2 Dispensing and Storage

For preparation of the chemotherapy, which is commercial ware, solutions and storage, please refer to the SmPCs of the agents.

Storage and dispensation of study medication must be carefully documented by the investigator. The study drug will be directly sent to the study site. The investigator will confirm receipt of the first and all subsequent batches of study drugs in writing to the sponsor. All drug supplies must be stored in accordance with the manufacturer's instructions, and separately from normal clinic stocks present at the study site. The investigator is responsible for assurance of adequate storage, protected from exposure to any environmental changes. Moreover, the study medication must be stored in a lockable room or locker, so that only the investigator and specifically designated study personnel can have access.

13.2 Definition of Investigational Medicinal Product

The investigational medicinal product(s) (IMP) will be defined per sub-trial. For further information please refer to the respective sub-protocol.

14 Administrative Aspects

14.1 Monitoring, Auditing and Inspecting

The study will be monitored by regular site visits and telephone calls to the investigator by members of the sponsor or personnel designated by the sponsor WSG. During site visits, the monitor should review original patient records and document retention. Additionally, the monitor should observe study procedures and will discuss any problems with the investigator. During the course of the study WSG may conduct site audits. The investigator will provide direct access to source data/documents for trial related monitoring, audits, IRB/EC review and regulatory inspections.

14.2 Patient Identification

All patients registered for the study will have their personnel data entered on the patient log at the initial visit. In the event a patient is excluded from study participation, the reason is to be documented in the space provided on the patient log.
Each patient will be assigned a patient number on registration, consisting of 4 digits per patient. This number is to be entered on the case report form.

14.3 Recording of Data

The study will be conducted using e-CRFs in a web-based RDE system provided by Palleos CRO Services GmbH. Data entered into the forms should be verified against all original records before. All original data must be readily available for review during scheduled monitoring visits.

14.4 Record Retention

Copies of all pertinent information will be retained by the investigator for a period of at least 15 years from study completion. Additional considerations must be made in compliance with applicable local laws, guidelines, etc.
A study document binder will be provided by WSG for all required study documents.

14.5 Confidential Follow-up

The investigator will be responsible for retaining sufficient information about each patient (e.g. name, address, phone number and identity in the study) so that the monitor or regulatory agencies may access this information should the need to do so arise. These records should be retained in a confidential manner for as long as legally mandated according to local requirements.

14.6 Patient Informed Consent

Prior to the screening evaluation, the patient will be informed of the nature of the study drugs and will be given pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the patient will be exposed will be explained.
An approved informed consent statement will then be read and signed by the patient, and, when required, a witness, and the investigator. The patient will be provided with a copy of the signed informed consent statement. The patient might be withdrawn from the study at any time without prejudicing future medical treatment.

Prior to any documentation of prolonged follow-up assessments, the patient will be informed of the nature of the follow up and will be given pertinent oral and written information as to the intended purpose and possible benefits.

An approved informed consent for the prolongation of the follow-up assessments needs to be signed by the patient, and, when required, a witness, and the investigator. The patient will be provided with a copy of the patient information and signed informed consent. The patient may withdraw from the extended follow up at any time.

14.7 Ethics Committee/Institutional Review Board

The final approved protocol as well as the informed consent statement and any document handed over to the patients will be reviewed by a properly constituted Ethics Committee. The Ethics Committee's decision concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to every investigator.
The sponsor will agree to make required progress reports to the Ethics Committee, as well as report any serious adverse events, life-threatening problems or deaths. The sponsor will also inform the Ethics Committee about reports of serious adverse events. The Ethics Committee will be informed by the sponsor of the termination of the study.

14.8 Declaration of Helsinki

This study is to be performed in accordance with Appendix 4 – Declaration of Helsinki 48th General Assembly, Somerset West, Republic of South Africa, October 1996.

14.9 Insurance of Liabilities

The sponsor will forward the Ethics Committee and every investigator a copy of the insurance policy that the sponsor has to take out covering its and any other participating party’s liabilities.

14.10 Modification of the Protocol

Any modification to the protocol which may impact the conduct of the study, affect patient safety or potential benefit of the patient, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendment approved by the Ethics Committee prior to implementation and notified to the health authorities in accordance with local regulations.
Administrative changes and/or clarifications that have no effect on the way the study is to be conducted are minor corrections. These administrative changes will be documented in a memorandum. The Ethics Committee will be notified of administrative changes at the discretion of WSG.

14.11 Use of Information and Publication

It is planned to publish the trial results, in mutual agreement with the Coordinating Investigator, in a scientific journal and at German or international congresses. Publication of the results of the trial as a whole is intended. Any publication will take account of the ‘Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors’ (ICMJE) [JAMA 1997;277:927-34]).
The trial will also be registered in a public register in accordance with the recommendations of the ICMJE. Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the sponsor (WSG).
If necessary, this section should be used to list persons or bodies contracted by the sponsor who will receive data and will therefore be informed of the results of the trial.

Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the sponsor in advance, and the sponsor reserves the right to review and comment on such documentation before publication.
By signing the contract to participate in this trial, the investigator declares that he or she agrees to submission of the results of this trial to national and international authorities for approval and surveillance purposes, and to the Federal Physicians Association, the Association of Statutory Health Fund Physicians and to statutory health fund organizations, if required. At the same time, the investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical trial may be made known to these bodies.

15 ADAPT Sub-trials

According with the result of the first core biopsy, which evaluates the type of tumor, patients will be introduced to one of the ADAPT sub-trials (HR+/HER2-, HER2+/HR-, HER2+/HR+ or triple negative or Elderly) after 3 weeks of induction treatment (if applicable: endocrine therapy for HR+/HER2- disease; neoadjuvant chemotherapy + targeted therapy in HER2+/HR-, HER2+/HR+ and triple negative disease).

16 Investigator's Agreement

The investigator's agreement will be available in the Investigator Site File and has to be signed by the principal investigator of the site and any co-investigator, respectively. Any investigator in the ADAPT trial must have read the protocol prior to participation. The understanding of the trial and all requirements will be confirmed by signing the investigator's agreement.

Appendix 1 – Treatment Dose Adjustments and Treatment Delays

Dose reductions Table

mg/m^2 or AUC	Level 0	Level 1	Level 2
Nab-Paclitaxel mono	125	100	80
Paclitaxel q2w	175	130	100
Epirubicin	90	75	60
Cyclophosphamide	600	500	Stop
Paclitaxel q1w	80	60	50
Nab-Paclitaxel in combination with gemcitabine	125	100	75
Nab-Paclitaxel in combination with carboplatin	125	100	80
Gemcitabine	1000	800	650
Carboplatinum	AUC 2 (upper limit 300 mg)		

Toxicity	**Toxicity grade**		**Chemotherapy**
Hematotoxicity	**Neutrophils (x 10^9/L)**	**Platelets (x 10^9/L)**	
	>1.0-1,5	>100	EC q2w: Full dose Paclitaxel q2w: Full dose Paclitaxel q1w: Full dose, consider G-CSF prophylaxis (filgrastim) until recovery e.g. days 2-5 Nab-Paclitaxel Full dose, daily G-CSF prophylaxis (filgrastim) e.g. days 2-5 Gemcitabine: Dose reduction do level 1
	1.0-1.5 and/or	75-100	For all chemotherapies: Wait until recovery (not more than 2 weeks) than continue with full dose. Consider treatment with daily G-CSF until ANC ≥ 1.0 and platelets >100. Add G-CSF (if not given) in remaining cycles if, recovery occurred after day +7. If no recovery after 2 weeks after planned cycle, (ANC < 1.0 x 10^9/L), patient will go off chemotherapy. If toxicity occurs despite G-CSF use and/or after febrile neutropenia with subsequent G-CSF secondary prophylaxis then dose reduction to the next level.
	<1.0 and/or	75-100	For all chemotherapies: Wait until neutrophils >1.0 and then with G-CSF support (if not given) If toxicity occurs despite of G-CSF use and/or after febrile neutropenia with subsequent G-CSF secondary prophylaxis then dose reduction to the next level

			If ANC <500 start ciprofloxacin 2x500-750 mg/d)
	Any and	<75	Wait until recovery to >100 and then dose reduction to the next level, if grade 3-4 (<50000/µl) If no recovery within day of planned chemotherapy +14 patient should go off chemotherapy If 2. occur after dose reduction patient should go off chemotherapy Carboplatin: Omit for the next cycles Transfusions should be given if platelets <10000/µl
	Hemoglobin (CTC Grade)		
	I	LLN-10 g/dl	
	II	<10-8.0 g/dl	Start with ESF for all subsequent cycles (Consider use from Hb <11 depend on clinical symptoms). Iron use 200 mg/d. ESF should be stopped if HB>12. If rapid Hb increase (>2 g/dl in 4 weeks)→dose reduction of ESA 25-50%. If no response after 6-9 weeks→no further ESA treatment (Hb increase < 1 g/dl or reticulocytes <40.000/µl)
	III-IV	<8.0-6.5→<6.5 g/dl	Stop of chemotherapy until Hb >8.0. Blood transfusions until Hb >9.0. Continue with ESA treatment (see above). If despite of ESA use Hb drop <9.0 dose reduction to the next level. If again despite of ESA use no Hb > 8.0 g/dl, patient should go off chemotherapy
Febrile Neutropenia **Infections**	**ANC < 1.0 with fever ≥ 38.5°C (SAE)** III-IV		Discontinuation of all study treatments; hospital admission (omission allowed only in low risk cases) Bacteriology specimens during fever/infection prior to antibiotic therapy Complete blood count daily until ANC>1.0 and temperature <38.1°C If low risk ampicillin/clavulanic acid 2x875/125+ciprofloxacin 750 or 500 x2/d If high risk or severe infection (pneumonia, hypotension, multi organ sepsis, mucositis/diarrhea grade 4, lymphopenia, age >65 years old, fungal infection: consider piperacillin/tazobactam 3x4,5 g/i.v.; imipenem/Cilastin 4x500 mg i.v. or 3rd generation cephalosporin (Rocephin) plus aminoglycoside (Gentamicin 3-5 mg/kg i.v. Cave nephrotoxicity) If severe catheter sepsis, known MRSA or penicillin/cephalosporine resistant pneumococces combination with Vancomycin 2x100 mg i.v. Cave: No antibiotic therapy change before 3 days of persistant fever Treatment with daily G-CSF (if not given as Prophylaxis) should be considered in the high risk FN. **If no G-CSF prophylaxis was given begin of G-CSF prophylaxis in all subsequent cycles**
2nd Infection/febrile Neutropenia			If while on G-CSF prophylaxis dose reduction to the next dose level
Non-hematological	**CTC Grade**		
Nausea/Vomiting	I-II		Optimize antiemetic treatment
	III-IV		If despite optimization of antiemetic therapy delay chemotherapy until recovery and than next dose level
Renal (Creatinine Clearance)	I (creatinine clearance) <LLN - 60 ml/min/ (if 1.73 m^2)		Full dose

	II (creatinine clearance) 59 – 30 ml/min/(if 1.73 m^2)			Stop Carboplatin Reduce Cyclophosphamide by one dose level	
	III-IV (creatinine clearance) 29 – 15 ml/min/(if 1.73 m^2) or <15 ml/min			Patient should go off chemotherapy	
Hepatic (In case of liver toxicity >grade 2: liver imaging)	AST/ALT	I	AST/ALT (>ULN - 3.0 x ULN)	AP (>ULN -2,5 x ULN)	Full dose
				AP Grade II (>2,5 ULN - 5 x ULN)	Reduce by one dose level
		II	AST/ALT (>3.0 - 5.0 x ULN)	AP (>ULN -2,5 x ULN)	Reduce by one dose level
				AP Grade II (>2,5 ULN - 5 x ULN)	
		III	AST/ALT 5,0-20,0 ULT	AP Grade III (>5 xULN)	Dose delay by a maximum of 2 weeks, if no recovery patient should go off chemotherapy
	Bilirubin		I (>1,1 mg/dl - 1.5 x ULN)	Re-test every weeks, continue therapy	
			II (>1.5 - 3.0 x ULN)	Delay chemotherapy until improvement to grade 1, than next dose level	
			III	Stop treatment	
Mucositis / Stomatitis	II-III			Discontinue treatment until grade 1, than next dose level, If grade 3 despite of dose reduction, patient should go off chemotherapy	
Peripheral Neuropathy	II			Retreat Paclitaxel at the next dose level. If no further improvement patient should give of chemotherapy	
				Nab-paclitaxel after cycle 4: next cycle should be omitted. After one week off continuation of therapy with the next dose level	
	III-IV			Stop of paclitaxel/nab-paclitaxel treatment (as well combinations)	
Diarrhea	II			Continue study treatment with early begin of supportive care with loperamide In case of longer diarrhea grade >2 (>3 days) use next dose level	
	III			Hold therapy until recovery to grade ≤1 and use the next dose level in the subsequent cycles. If despite dose reduction, diarrhea still occurs at grade ≥ 3, the patient may go off chemotherapy	
	II-III			Delay treatment until resolution to grade 1 (maximum 14 days) and treat symptomatically. Than dose reduction to the next dose level	
	IV			Patient should go off chemotherapy	

All AE grade 3-4 not listed in the table requite delay of chemotherapy for maximum of 14 days and dose reduction to the next dose level

Taxane Anaphylactic Type / Hypersensitivity Reactions	

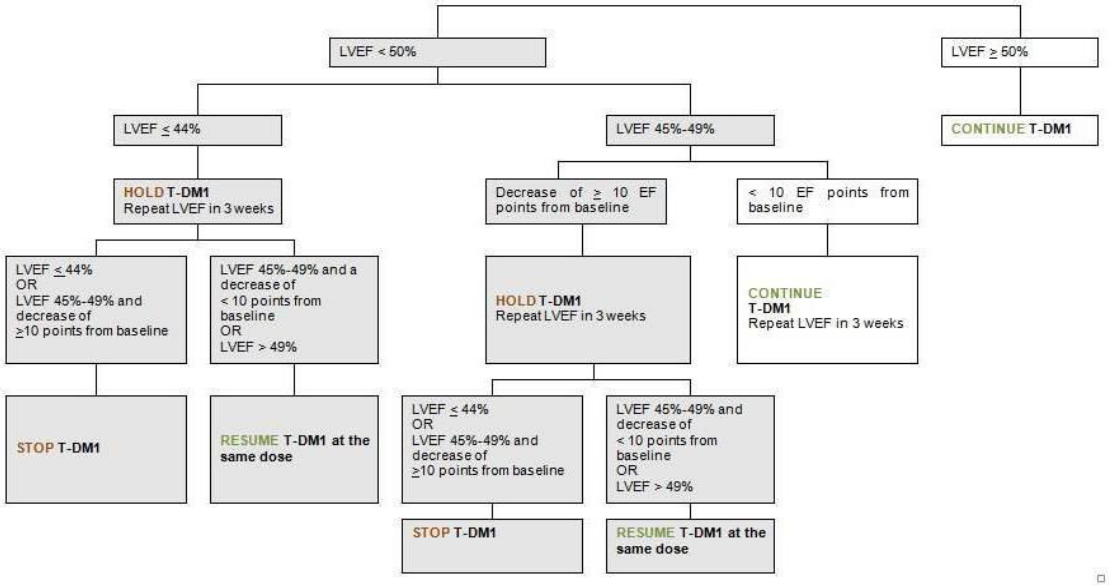
			Mild symptoms: Localized cutaneous reaction, such as: Pruritus, flushing, rash→consider the rate of infusion, than continue t at the planned rate. **Moderate symptoms:** Any symptom not listed above (mild symptoms) or below (severe symptoms), such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic blood pressure (BP) > 80 mm Hg →Stop study drug infusion. Give e.g. dexamethasone 8-10 mg i.v.. Re-Start infusion after recovery of symptoms. In the next cycles use the same procedure one hour prior to infusion, additionally to the planned premedication. **Severe symptoms:** Such as bronchospasm, generalized urticaria, hypotension with systolic BP ≤ 80 mm Hg, angioedema Stop study therapy, use dexamethasone 10 mg or diphenhydramine 50 mg i.v. (epinephrine if needed). Try to resume study drug within three hours after recovery. Alternatively infusion within 72 hours after infusion using dexamethasone 20 mg or diphenhydramine 50 mg i.v. Use similar schema in next cycles (dexamethasone 20 mg at the evening prior to therapy, than at the morning and one hour priot to taxane infusion
	Anaphylaxis (NCI CTC grade 4 reaction)	NA	**No further study drug therapy**

ADAPT HER2+/HR+ Dose Modifications and Reductions

Toxicity	Toxicity grade	T-DM1
Hematotoxicity	Grade III or IV	Patient should be checked at least **weekly** for recovery. If values do not recover to baseline or Grade ≤ I within **42 days** from the last dose received, the patient will be **withdrawn from study treatment**.
Thrombocytopenia	Patients who experience any of the following events for the **first time** may, after adequate recovery to a platelet count of Grade ≤ I (≥ 75,000/µL), continue treatment with T-DM1 at **one dose level lower** in subsequent treatment cycles (see chapter **9.1.1** of the ADAPT HER2+/HR+ sub-protocol). Patients who experience a **second event** may, after adequate recovery as defined above, continue treatment with T-DM1 at **two dose levels lower** (if that dose is not < 2.4 mg/kg) in subsequent treatment cycles. Patients who experience any event listed below at the 2.4 mg/kg dose will be **withdrawn from study treatment**. A **dose delay** of up to **42 days** from the last dose received is permitted.	

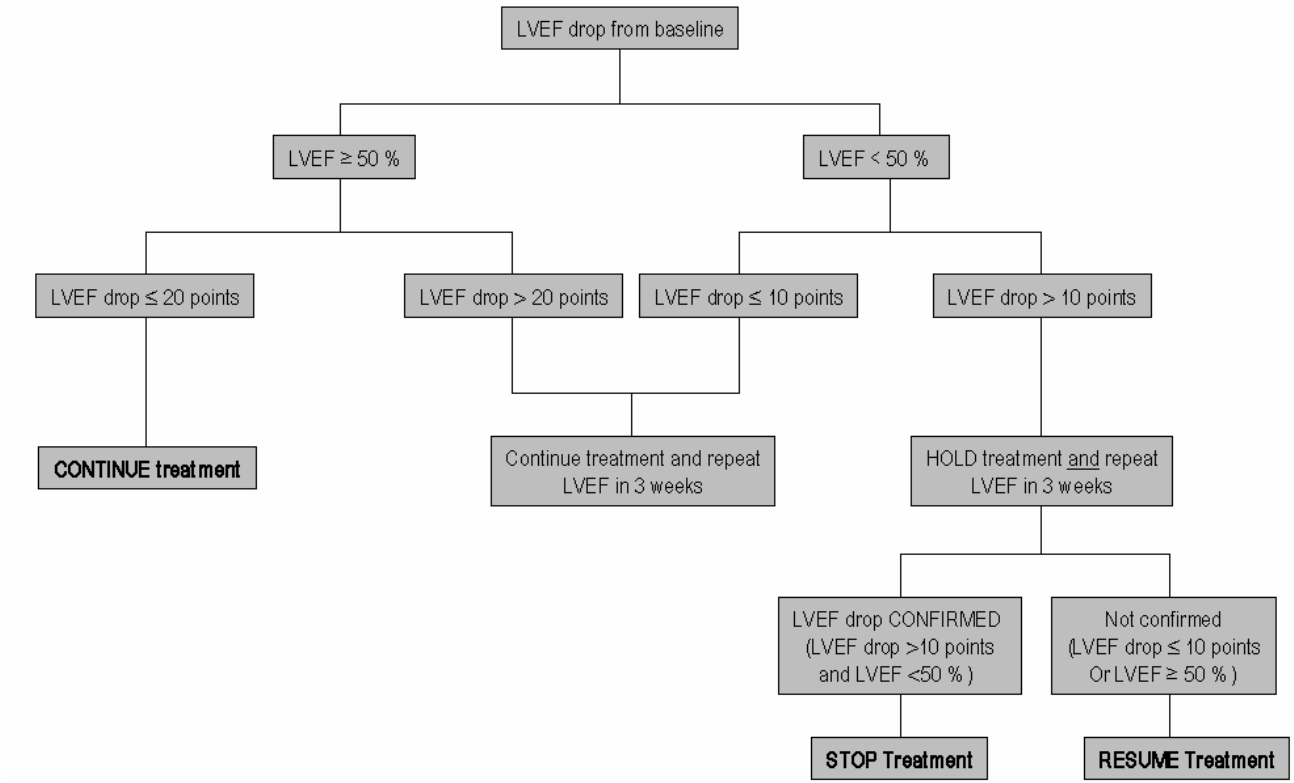
Toxicity	Toxicity grade	T-DM1
	Platelet counts should be obtained no less frequently than **every week** to evaluate recovery whenever any of the events listed below occurs. If platelet counts do not recover to Grade ≤ I within 42 days from the last dose received the patient will be withdrawn from study treatment. **No re-escalation of the T-DM1 dose is allowed**. Note: although CBCs with platelets are required within **72 hours** prior to study treatment administration at each cycle, the investigator may monitor platelet counts (or any other laboratory test) more frequently as clinically indicated. The following dose-reduction levels are applicable for treatment with T-DM1: **Dose level:** **− 0** 3.6 mg/kg (initial dose level) **− 1** 3.0 mg/kg **− 2** 2.4 mg/kg	
	Platelet count	
	< 75,000/μL (Grade ≥ II) on the scheduled day of T-DM1 administration (i.e., pre-dose on Day 1)	**Dose reduction** by one dose level. No re-escalation of the T-DM1 dose is allowed.
	< 50,000/μL (Grade ≥ III) for patients on anticoagulation therapy, platelet count of any duration.	**Dose reduction** by one dose level. No re-escalation of the T-DM1 dose is allowed.
	< 25,000/μL (Grade IV) that does not recover to Grade ≤ I after 7 days from the onset date of the Grade IV event	**Dose reduction** by one dose level. No re-escalation of the T-DM1 dose is allowed.
	< 10,000/μL of any duration	**Dose reduction** by one dose level. No re-escalation of the T-DM1 dose is allowed.
Hepatotoxicity	Patients receiving T-DM1, who experience for the **first time** a Grade III or IV transaminase elevation and/or a Grade ≥ II total bilirubin elevation (or > 1.5 × baseline elevation for patients with documented Gilbert's syndrome at enrollment) may, after adequate recovery to Grade ≤ II (transaminase levels) and/or Grade ≤ I (total bilirubin level) or baseline, continue treatment with T-DM1 at **one dose level lower** in subsequent treatment cycles.	

Toxicity	Toxicity grade	T-DM1
	Patients who experience a **second event** of Grade III or IV transaminase elevation and/or a Grade II or greater total bilirubin elevation may, after adequate recovery to Grade ≤ II (transaminase levels) and/or Grade ≤ I (total bilirubin level) or baseline, continue treatment with T-DM1 at **two dose levels lower** (if that dose is not < 2.4 mg/kg) in subsequent treatment cycles. Patients at the 2.4 mg/kg dose level who experience a Grade III or IV transaminase elevation and/or a Grade II or greater total bilirubin elevation will be **withdrawn from study treatment**. A dose delay of up to 42 days from the last received dose is permitted. If transaminases and/or total bilirubin do not recover to baseline or Grade ≤ II (transaminases) or Grade ≤ I (total bilirubin) within **42 days** from the last dose received, the patient will be discontinued from study treatment. **No re-escalation of the T-DM1 dose is allowed**.	
Neurotoxicity	Grade III-IV	If no recovery to Grade ≤ II within **42 days** after the last dose was received **treatment will be discontinued**.
Cardiac Events	NYHA I-II	T-DM1 therapy to be held, continued or resumed according to the figure below

Toxicity	Toxicity grade	T-DM1
		 **Figure 2 - Algorithm for Continuation and Discontinuation of T-DM1 Based on Left Ventricular Ejection Fraction Assessments in Patients** CHF = congestive heart failure; LVEF = left ventricular ejection fraction; T-DM1 = Trastuzumab-MCC-DM1; Note: LVEF assessment results must be reviewed before the next scheduled T-DM1 infusion. **a.** LVEF can be repeated within 21 days, and T-DM1should be discontinued if LVEF ≤ 44% is confirmed. T-DM1 should be held while the repeat LVEF is obtained. **b**. After a second consecutive confirmatory result, T-DM1 should be discontinued if the LVEF is confirmed to be ≥ 10% points below baseline or if medical management was required to correct the LVEF.
Other	If significant T-DM1-related toxicities (other than infusion reactions, thrombocytopenia, hepatotoxicity, neurotoxicity, and cardiotoxicity) have not recovered to Grade I or baseline, the next scheduled dose may be **delayed for up to 42 days** from the last dose received. "Significant" and "related" will be based on the **judgment of the investigator** (in consultation with the Sponsor's Medical Monitor or designee when appropriate). For example, alopecia even if considered related would most likely not be considered to be significant. Fatigue may or may not be considered either related or significant. In general, when the significant and related toxicity (or any other toxicity that the investigator chooses to delay dosing for) resolves to Grade I or baseline, the patients may **resume T-DM1**, if the delay has not exceeded **42 days** from the last received dose.	

Toxicity	Toxicity grade	T-DM1
	Patients should be **re-evaluated weekly** during the delay, whenever possible. If dosing resumes, the patient may receive T-DM1 either **at the same dose level** as before or at **one dose level lower**, at the discretion of the investigator. Subsequent cycles should remain **every 21 days**, and patients should be assessed for toxicity as described in chapter **10** of the ADAPT HER2+/HR+ sub-protocol. If a patient requires a dose reduction, dosing will be **reduced by one dose level**. **No dose re-escalation will be allowed**. If any toxicity does not resolve within **42 days** from the last dose received, the patient will **discontinue study treatment** and will be **followed for disease progression** and **survival outcome**.	

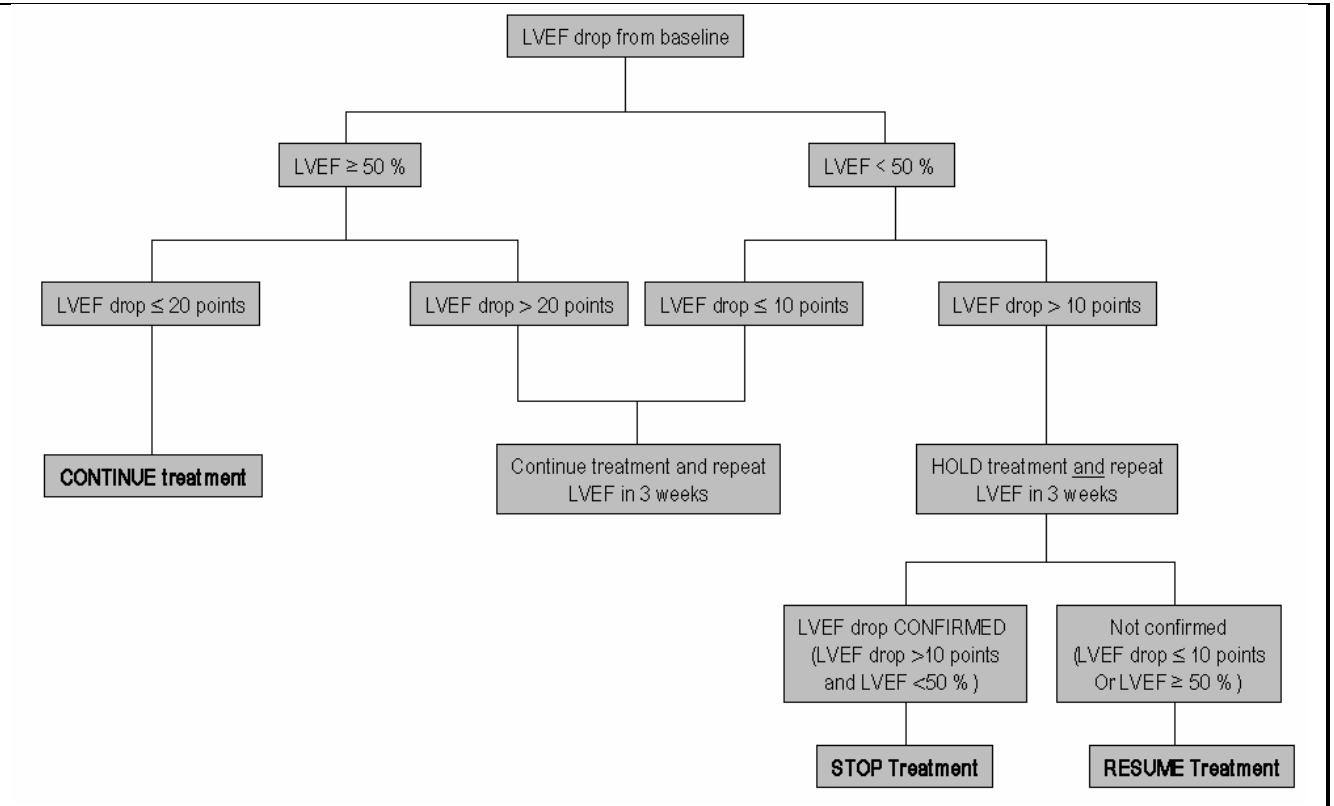
Toxicity	Toxicity grade	Trastuzumab
Non-hematological (excluding cardiac)	CTC I-II	Continue trastuzumab therapy.
	CTC III-IV and adverse events resolved to grade ≤ II within a maximum of 5 weeks from last administration	Hold trastuzumab therapy until recovery to Grade ≤II.
	CTC III-IV and adverse event **not** resolved to Grade ≤ II within a maximum of 5 weeks from last administration	Discontinue trastuzumab therapy.
	CTC III-IV upon re-challenge with trastuzumab	Discontinue trastuzumab therapy permanently.
Hematological	Any	Trastuzumab dose should not be held.

<table>
<tr><td rowspan="2">Cardiac Events</td><td>NYHA I-II</td><td>Trastuzumab therapy to be held, continued or resumed according to the figure below
 
</td></tr>
<tr><td>NYHA III-IV</td><td>Permanently discontinue Trastuzumab therapy.</td></tr>
</table>

ADAPT HER2+/HR+ Dose Modifications and Reductions

Toxicity	Toxicity grade	Pertuzumab
Any	Any	Dose reduction for toxicity is not permitted.

Toxicity	Toxicity grade	Trastuzumab
Non-hematological (excluding cardiac)	CTC I-II	Continue trastuzumab therapy.
	CTC III-IV and adverse events resolved to grade ≤ II within a maximum of 5 weeks from last administration	Hold trastuzumab therapy until recovery to Grade ≤II.
	CTC III-IV and adverse event **not** resolved to Grade ≤ II within a maximum of 5 weeks from last administration	Discontinue trastuzumab therapy.
	CTC III-IV upon re-challenge with trastuzumab	Discontinue trastuzumab therapy permanently.
Hematological	Any	Trastuzumab dose should not be held.
Cardiac Events	NYHA I-II	Trastuzumab therapy to be held, continued or resumed according to the figure below

		
	NYHA III-IV	Permanently discontinue Trastuzumab therapy.

Appendix 2 – Cardiac Safety Monitoring

1. Cardiac Safety Evaluation

One of the disadvantages of anthracycline-containing chemotherapy and Herceptin (trastuzumab) is cardiac toxicity. Hence, cardiac adverse events should be followed closely.

Cardiac safety evaluation will include evaluation of cardiac adverse events, measurement of LVEF by echocardiography and ECG. Cardiac assessments should be performed according to the current clinical guidelines. It is the responsibility of the investigator to ensure that adequate resources and technical equipment for performance of echocardiography and ECG are available. These examinations must be performed and evaluated by a cardiologist.

2. Definitions of Cardiac Toxicity

Cardiac toxicity will be classified as follows:

Cardiac death:
Cardiac death will be defined as death due to one of the following:

- Confirmed congestive heart failure
- Myocardial infarction
- Documented primary arrhythmia
- Probable cardiac death i.e. sudden death without documented etiology

An autopsy is preferred in cases where cause of death has a cardiac etiology.

Congestive Heart Failure (CHF):
Clinical signs and symptoms suggesting congestive heart failure (dyspnoea, tachycardia, cough, neck vein distension, cardiomegaly, hepatomegaly, paroxysmal nocturnal dyspnoea, orthopnoea, peripheral edema, etc.) must be investigated.
The suspicion of congestive heart failure, based on the signs and symptoms mentioned above, must be confirmed by a LVEF decrease in echocardiography, with a chest X-ray. LVEF assessment should be repeated 4 to 7 days afterwards to confirm a diagnosis of congestive heart failure.

Cardiac Arrhythmias, Grade 3 or Grade 4:
The NCI Common Toxicity Criteria, version 3.0 will be used to classify an arrhythmia as grade 3, which is symptomatic and requiring treatment, or grade 4 which is an arrhythmia considered to be life-threatening e.g. an arrhythmia associated with CHF, hypotension, syncope, shock.

Cardiac Ischemia / Infarction, Grade 3 or Grade 4:
The NCI Common Toxicity Criteria, version 3.0 will be used to classify the severity of cardiac ischemia/infarction. Grade 3 ischemia is defined as angina without evidence of infarction. Grade 4 is defined as an acute myocardial infarction.
Patients showing one of those symptoms will consult a cardiologist and will be followed as defined by the institution's routine.

3. Cardiac Safety Analysis

The incidence of cardiac adverse events (cardiac deaths, CHF, grade 3 or grade 4 ischemia/infarction, grade 3 or grade 4 arrhythmias) will be calculated for each treatment arm.

4. Reporting of Cardiac Toxicities

Cardiac toxicities will be documented in the CRF at each visit during treatment and follow-up.

Appendix 3 – Fluid Retention Severity Grading

Edema	Severity grading	Effusion
• Asymptomatic *and/or* • Very well tolerated *and/or* • Dependent in evening only	MILD 1	• Asymptomatic • No intervention required
• Moderate functional impairment *and/or* • Pronounced and well tolerated *and/or* • Dependent throughout day	MODERATE 2	•Symptomatic : - exertional dyspnoea *and/or* - chest pain *and/or* • ECG changes *and/or* • Abdominal distension • Drainage may be required
• Significant impairment of function *and/or* • Pronounced and not well tolerated *and/or* • Generalized anasarca	SEVERE 3	• Symptomatic effusion - dyspnoea at rest *and/or* - tamponade *and/or* - pronounced abdominal distension • Drainage urgently required

Appendix 4 – Declaration of Helsinki 48th General Assembly, Somerset West, Republic of South Africa, October 1996

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly,Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on

experimentation involving human subjects.
In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.
Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.
3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE
In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, reestablishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.
3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)
1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research

if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Appendix 5 – Method for Breast MRI

Method for breast MRI:

Standard operating procedure for breast MRI

1. Necessary equipment

- 1.5T or 3.0T MR systems
- Dedicated open breast multichannel surface coil
- should have system for breast immobilisation in phase encoding direction (cranio-caudal direction for axial imaging)
- Power injector
- Vacuum Biopsy system for biopsy under MR guidance

Patient is placed on the MR system's couch in a prone position. Arms are securely placed along the body or – in some set ups – in front of the head. Head should be placed on a special head rest. If patient suffers from claustrophobia, sedation with i.v. diazepam should be administered generously. Common radiological standards with respect to monitoring of vital signs during and patient care after conscious sedation procedures must be adhered to.

2. Pulse sequence protocol:

2.1 Survey:
Fast imaging in at least 4 planes: axial, coronal sagittal over left breast and sagittal over right breast

2.2 T2 weighted TSE imaging

- 2D multislice Fast/Turbo Spin Echo
- axial orientation
- left-right phase encoding direction
- foldover suppression
- FOV to cover the breast (not: chest) adjusted to breast size, typically between 290 and 350 mm
- 512 x 512 acquisition matrix (true acquisition, not interpolated)
- Section thickness $\leq$ 3 mm
- SENSE or other parallel imaging factors $\leq$ 2
- no fat saturation
- effective TR $\leq$ 5000 ms
- one echo; TE between 80 and 110 ms

2.3 T1 weighted dynamic series

at 1.5T:

- 2D multislice Gradient Echo
- axial orientation
- left-right phase encoding direction
- no foldover suppression
- FOV exactly matching the FOV of T2 weighted pulse sequence, i.e. between 290 and 350 mm.
- no “rectangular field of view”
- acquisition matrix at least 512 x 470 or higher true acquisition, no interpolation
- Section thickness ≤ 3 mm, matching the section thickness of the T2 TSE
- SENSE or other parallel imaging with acceleration factors ≤ 2
- No fat saturation
- TR ≤ 320 ms
- TE 4.6 ms
- Flip Angle 90°
- temporal resolution: ≤ 90 seconds per dynamic acquisition
- regular central to peripheral k-space read out.

Dynamic imaging is acquired before and at least 5 times after bolus injection of 0,1 mmol Gadobutrol (Gadovist) / kg body weight (this is 0.1 ml gadobutrol 1,0 per kg body weight) followed by a 20 cc bolus of saline via a power injector set at 3 ml/sec.

Scanning is paused during the injection of the contrast agent. Contrast agent is injected through an i.v. line placed in an antecubital vein before the patient is moved into the scanner. If venous line is placed in a more peripheral vein, amount of saline must be increased to account for the longer distribution volume. After complete injection of the contrast agent and of about 10 cc of the saline chaser, the first post contrast acquisition is started.

at 3.0T:

- 3D Gradient Echo
- axial orientation
- left-right phase encoding direction
- no foldover suppression
- FOV exactly matching the FOV of T2 weighted pulse sequence, i.e. between 290 and 350 mm.
- no “rectangular field of view”
- acquisition matrix at least 512 x 470 or higher true acquisition, no interpolation
- Section thickness ≤ 3 mm, matching the section thickness of the T2 TSE
- SENSE or other parallel imaging with acceleration factors ≤ 2
- fat saturation allowed
- TR ≤ 20 ms
- TE 2.3 ms
- Flip Angle ≤ 45°
- temporal resolution: ≤ 90 seconds per dynamic acquisition
- regular central to peripheral k-space read out.

Dynamic imaging is acquired before and at least 5 times after bolus injection of 0,1 mmol Gadobutrol (Gadovist) / kg body weight (this is 0.1 ml gadobutrol 1,0 per kg body weight) followed by a 20 cc bolus of saline via a power injector set at 3 ml/sec.

Scanning is paused during the injection of the contrast agent. Contrast agent is injected through an i.v. line placed in an antecubital vein before the patient moves into the scanner. If venous line is placed in a more peripheral vein, amount of saline must be increased to account for the longer distribution volume. After complete injection of the contrast agent and of about 10 cc of the saline chaser, the first post contrast acquisition is started.

2.4 Diffusion weighted imaging

- Multi-Shot Echo Planar
- axial orientation
- left-right phase encoding direction
- FOV matching to FOV of T2 weighted pulse sequence
- 128 or higher acquisition matrix;
- Section thickness 3 mm or higher
- SENSE or other parallel imaging with acceleration factors as needed
- Fat saturation

b-values 0, 300, 800, 120

ADAPT Hormone Receptor Positive/HER2 Negative Breast Cancer Sub-trial

Adjuvant **D**ynamic marker-**A**djusted **P**ersonalized **T**herapy trial optimizing risk assessment and therapy response prediction in early breast cancer - **H**ormone **R**eceptor **positive**/**HER2 negative** breast cancer

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Final Version 5.0, 11 November 2021

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Protocol Title: Adjuvant **D**ynamic marker-**A**djusted **P**ersonalized **T**herapy trial optimizing risk assessment and therapy response prediction in early breast cancer - **H**ormone **R**eceptor **positive/HER2 negative** breast cancer

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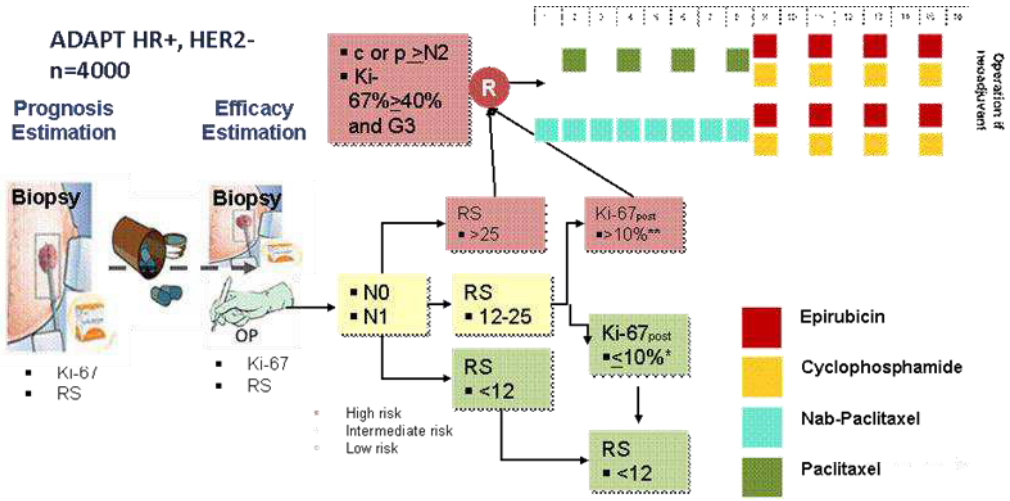
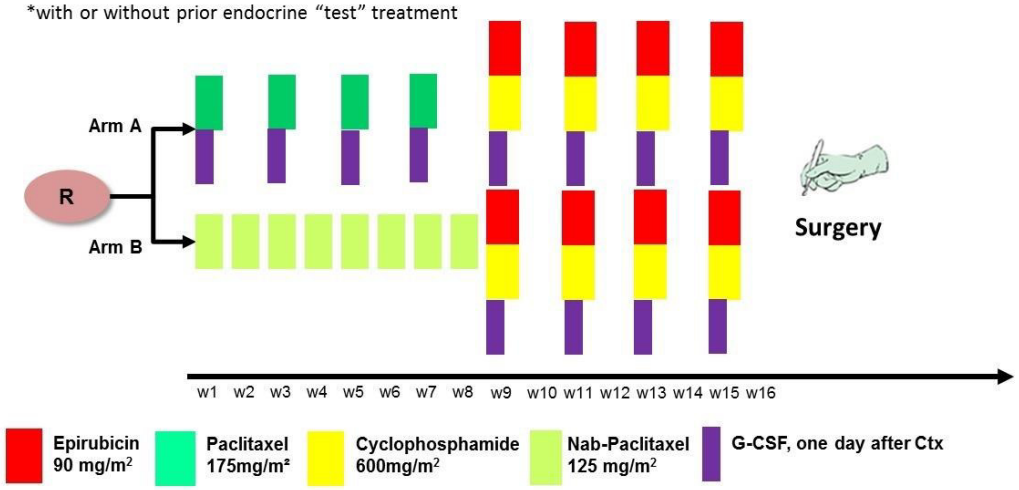
1 Study Summary ADAPT HR+/HER2- Breast Cancer

ADAPT HR+/HER2-	**A**djuvant **D**ynamic marker-**A**djusted **P**ersonalized **T**herapy trial optimizing risk assessment and therapy response prediction in early breast cancer – **H**ormone **R**eceptor **positive/HER2 negative** breast cancer
Study Overview	Hormone receptor positive breast cancer is probably the entity where the largest proportion of over-treatment with chemotherapy must be suspected. Over, under and –mistreatment with endocrine therapy is much better tolerated by the scientific community because it causes less toxicity and lower costs. Modern prognostic and predictive markers such as uPA/PAI1 and Oncotype DX have been integrated to a new generation of trials (NNBC-3, TAILORx, planB), which aim at the reduction in the number of patients who are treated with adjuvant chemotherapy. In N0-1/HR+ breast cancer **Oncotype DX** identifies a high risk group of patients who have a high likelihood of significant benefit from chemotherapy and a low risk group with minimal, if any benefit of chemotherapy. In addition an intermediate risk patient segment is identified where the benefit of chemotherapy is unclear. Within the **TAILORx** trial these patients (N0, intermediate risk) are randomized to chemotherapy and sequential endocrine therapy versus endocrine therapy alone. The trial is conducted with more than 11 000 patients to detect potentially small survival differences. Data are expected in 2015. Besides optimized baseline prognostic assessment **ADAPT** tries to integrate early treatment response to decision making. All HR+ patients receive a 3 week endocrine induction treatment with sequential evaluation of RS and Ki-67. Numerous trials have shown that Ki-67 is a good predictor for outcome after endocrine therapy (tamoxifen, aromatase inhibitors). A Ki-67 drop after short term pre-surgical endocrine therapy was found to be more important for outcome prediction than Ki-67 baseline values[25]. On the basis of the sequential assessment ADAPT trialists hope to separate a group of responders and of low-responders to endocrine therapy (dynamic test). Differently from TAILORx, ADAPT spares chemotherapy to not only N0, but also to N0-1 patients with a Recurrence score ≤11. In the intermediate risk group – and this is the major difference to TAILORx strategy – those patients with potentially maximum benefit (responders after endocrine induction therapy) are spared chemotherapy, because they are considered to be sufficiently treated by endocrine therapy alone (**ADAPT HR+/HER2- part I).** Future intertrial comparison to TAILORx thus may help to identify a potentially small subgroup, which is overtreated. Intermediate risk patients, who are suspected to have low benefit from endocrine therapy on the basis of low response to endocrine induction treatment as well as high risk patients (N0-1/RS≥ 26, all N2/3 with or without endocrine "test" treatment) receive chemotherapy within the **ADAPT HR+/HER2- part II** trial. The chemotherapy protocol (ADAPT HR+ part II) previews randomization to weekly nab-paclitaxel for eight weeks compared to paclitaxel at two week intervals for the same time followed by four courses of rapidly cycled EC.
Rationale	The adjuvant chemotherapy indication in HR+/HER2- BC today is mainly based on the individual prognostic profile as defined by clinical-pathological factors (tumor size, nodal status, grade, age) at the baseline, i.e. the risk profile. Definition of this profile allows identification of a subgroup being at a low risk of recurrence for which absolute reduction of risk of recurrence by chemotherapy is only marginal. However, even if modern molecular risk stratification tools are used, there remains a large group of patients at intermediate risk with unclear benefit from chemotherapy, especially in the HR+ group. ADAPT includes all

	HR+ patients, who are candidates for chemotherapy on the basis of conventional prognostic factors according to current German guidelines. Beyond these criteria ADAPT HR+ identifies on the basis of the genomic profile Oncotype DX additional information about the prognostic profile of these patients. Responsiveness to endocrine therapy is not included in the decision-making procedure so far. Proliferation response to a short course of primary endocrine therapy on the other hand is an excellent (dynamic) predictor of endocrine therapy outcome. On the basis of an early assessment of endocrine responsiveness ADAPT tries to identify good and low responders to endocrine therapy. The hypothesis would be that good responders are sufficiently treated by endocrine therapy only, whereas patients with low response need other treatments such as chemotherapy. The classification of endocrine response is primarily made on the basis of sequential Ki-67 evaluation. The design also allows identification of further molecular markers/profiles correlating stronger. The chemotherapy protocol (ADAPT HR+ part II) previews randomization to weekly nab-paclitaxel for eight weeks compared to paclitaxel at two week intervals for the same time followed by four courses of rapidly cycled EC. Beyond TAILORx this may give another opportunity to allocate patients to appropriate treatment in the heterogeneous intermediate risk group in N0 and N1 patients. Early results show that about 70% of patients will have a good response to endocrine therapy, so that our assumption is to correctly reduce use of adjuvant chemotherapy in HR+/HER2- early BC (0-3 positive lymph nodes) by approximately 50% without any negative survival effect by combination of baseline and response data. Thus, in summary ADAPT HR+/HER2- uses genomic profiling as an add-on to conventional pathology/IHC and invents prediction as another determinant for adjuvant chemotherapy indication. ADAPT renounces to compare conventional pathology to genomic profiling in a randomized phase III trial due to the pending results from the first generation trials (MINDACT/TAILORx) which will be mature by 2015. Another criterion has been the limited reproducibility of conventional local pathology/IHC results by central testing experienced in WSG and important international trials.
Objectives	<u>Primary objectives</u> **Run-in Phase:** ▪ Analysis of reproducibility of each biomarker ▪ Assessment of dropout rate ▪ Assessment of proportions of marker responders vs. non-responders ▪ Central/local pathology ▪ Central/local Ki-67 assessment ▪ Ki-67 change after endocrine induction therapy ▪ Comparison of changes in RS, Ki-67, quantitative ER and proliferation group within the RS ▪ Assessment of distribution of responders/low responders in low (RS≤11), intermediate (RS 12-25) and high-risk (RS≥26) patients with the aim to allow early adjustment of the statistical plan ▪ Identification of other proliferation markers that drop significantly **Run-in phase + main phase** ▪ ADAPT HR+/HER2- part I:

	○ Prospective comparison of EFS in patients with intermediate risk by RS (12-25)/response vs. patients with low risk by RS (RS≤11; N0-1); both groups receiving endocrine therapy only ▪ ADAPT HR+/HER2- part II: ○ Prospective comparison of 5-year EFS of nab-paclitaxel 125mg/m² q1w x 8 versus Paclitaxel 175mg/m² q2w x 4 both followed by conventionally dosed $E_{90}C_{600}$ x 4 q2w chemotherapy regimens; patients with intermediate risk by RS (12-25)/low response or high risk patients by N0-1/RS ≥26, all N2/3, or Ki-67≥40%, >pT1b, and G3 will be treated with chemotherapy Secondary objectives: • Evaluation of 5-year EFS in patients classified as "clinical high risk*" and selected by ADAPT strategy for treatment by endocrine therapy alone (this group comprises patients with low or intermediate risk by Oncotype Dx) • To determine if an additional baseline biomarker (or change in biomarker) can improve upon the combination of baseline RS and Ki-67 response, by evaluating the association between baseline biomarker (or change in biomarker) and EFS in the following groups of patients (HR+): ○ patients with intermediate risk by RS (12-25) with Ki-67 response to neoadjuvant therapy, who are treated without chemotherapy and ○ patients with intermediate risk by RS (12-25) without Ki-67 response to neoadjuvant endocrine therapy, who are treated with chemotherapy * For the purposes of secondary objective a patient is classified as having a "clinical high-risk" if one or more of the following criteria (A-E) are satisfied: A. Node positive B. G3 by central grading C. Age<35 years D. (if N0): G2 AND (Ki-67≥20% OR T2-3) E. (if N0): G1 AND tumor size >3 cm. These criteria are based on current guidelines (St. Gallen, S3, ESMO) or Adjuvant Online (as criterion used in the MINDACT study). For the substudy, clinical prognostic factors vs. genomic vs. ADAPT-guided approach (as pooled analysis of planB and ADAPT trials) • Prognostic/predictive impact of conventional prognostic markers will be evaluated in exploratory analysis within distinct genomic subgroups; prognostic/predictive impact of dynamic testing (along with conventional prognostic criteria) will be assessed within a pooled analysis of the ADAPT and planB (historical control) trials. • Prognostic impact of classical prognostic criteria and prognostic and predictive impact of dynamic testing regarding indication for adjuvant chemotherapy will be evaluated. • Prospective analysis of dynamic testing (i.e., proliferation course measured by Ki-67 after 3 weeks induction pre-surgical endocrine therapy) regarding its prognostic impact in homogeneously treated

	patients (with respect to chemotherapy) from the PlanB and ADAPT study (low and high risk). • Prospective analysis of dynamic testing regarding its predictive impact in intermediate risk disease (pN0-1) based on the Main/Run-In phase ADAPT study (assumed only 1/3 treated by chemotherapy based on dynamic testing in overall n=1600) vs. planB study (all treated by adjuvant chemotherapy; n=1232) • Subgroup RS≤11: pooled analysis (ADAPT + planB) of 5-year EFS for clinically high risk patients. • Subgroup RS ≤11: pooled analysis (ADAPT + planB) of 5-year EFS of clinical low vs clinical high risk. **ADAPT HR+/HER2- part II:** • Safety interim analysis in first 120 patients and in 1000 patients treated by chemotherapy • In patients receiving chemotherapy prior to surgery: ▪ Comparison of pCR rates (defined as ypT0/ypN0). ▪ Other pCR definitions (ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypN0 and regression grades). ▪ Rate of breast conserving therapy. ▪ Clinical response (examination, mammography/sonography). • In all patients: ▪ Superiority testing for EFS of the nab-paclitaxel-EC vs. paclitaxel-EC ▪ Evaluation of genomic profile correlating with response to nab-paclitaxel treatment. ▪ Prospective evaluation of febrile neutropenia rates in patients treated by dose-dense EC and Paclitaxel q2w and pegfilgrastim as well use of G-CSF in the nab-paclitaxel arm.
Trial design	Prospective, multi-center, controlled, non-blinded, randomized phase III 

	ADAPT HR+/HER2- Part II • More than 3 involved lymph nodes (c/pN2-3)* • N0-1 and RS ≥ 26* • N0-1 and RS 12-25 with Ki-67post > 10% • G3 with Ki-67 ≥40% in tumors >1cm * *with or without prior endocrine "test" treatment  **Chemotherapy**: A: Paclitaxel 175 mg/m² q2w x 4 → E_{90} C_{600} q2w x 4 versus B: nab-paclitaxel 125 mg/m² q1w x 8 → $E_{90}C_{600}$ q2w x 4 Patients with incomplete information for risk classification, i.e. missing RS, Ki-67pre/post, etc. will be randomized within ADAPT HR+/HER2- Part II. Patients, who decide to take chemotherapy despite low or intermediate risk/response can receive chemotherapy within ADAPT HR+/HER2- Part II. **Bisphosphonates after induction phase** (optional according to AGO guidelines): Zoledronic acid 4 mg every six months for three years Clodronate 1600 mg/d p.o. for two years
Induction Treatment	**Endocrine therapy** (according to current AGO guidelines): Premenopausal: Tamoxifen Postmenopausal: Aromatase inhibitors
Timing of Surgery	Breast surgery can be either done after 3 weeks of induction treatment (+/- 1 week due to organizational reasons[27]) or after the completion of neoadjuvant chemotherapy at the discretion of the investigator (ADAPT HR+/HER2- part II). When neoadjuvant chemotherapy is intended SLN in cN0 cases can be performed prior to chemotherapy start.
Supportive treatment	G-CSF prophylaxis according to AGO guidelines (primary G-CSF prophylaxis (Peg-Filgrastim) within the dose-dense chemotherapy)
Selection of patients	**ADAPT HR+/HER2-:** • ER and/or PR positive and HER2 negative • Central pathology available (Grading, Ki-67, RS) • All patients should be recommended to be treated by adjuvant chemotherapy in the daily routine practice by one of the current guidelines (St. Gallen, AGO Mamma, S3, ESMO) or to be high clinical risk by AdjuvantOnline (breast cancer specific survival of ≤88%)

	▪ Clinically N+ or cN0 with one of following features: G3 or <35 years old or Ki-67>14% or cT2-4c, If G1 only if clinical tumor size >3 cm ▪ If Clinical decision is based on AdjuvantOnline patients should derive more than 5% 10-year relapse-free survival benefit by use of chemotherapy (3rd-generation anthracycline/taxane-based) additional to standard endocrine therapy (using clinical T and N status) **ADAPT HR+/HER2- Part II:** • More than 3 involved lymph nodes (c/pN2-3)* • N0-1 and RS ≥ 26* • N0-1 and RS 12-25 with Ki-67post > 10% • G3 with Ki-67 ≥40% in tumors >1cm* • Strong candidate for chemotherapy based on clinical risk irrespective of induction treatment (e.g. heterogenous tumor, multifocal tumor etc.) *with or without prior endocrine "test" treatment **Additional inclusion criteria for patients receiving chemotherapy (ADAPT HR+/HER2- Part II):** • Patients with tumors ≥cT2 and/or cN+ are strongly recommended to be treated by neoadjuvant chemotherapy • Laboratory requirements for patients receiving chemotherapy (within 14 days prior to randomization): o Leucocytes ≥ 3.5 x 10^9/L o Platelets ≥ 100 x 10^9/L o Hemoglobin ≥ 10 g/dL o Total bilirubin ≤ 1 x ULN o ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 x UNL o Creatinine ≤ 175 µmol/L (2 mg/dl) • LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization) **Additional exclusion criteria for HR+/HER2- patients:** • Patients with clinical low risk tumors, who are not treated by adjuvant chemotherapy in the daily practice (e.g. cT1 and G1 and cN0) **Additional exclusion criteria for patients receiving chemotherapy (ADAPT HR+/HER2- Part II):** • Known polyneuropathy ≥ grade 2 • Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study • Uncompensated cardiac function • Inadequate organ function including: o Leucocytes < 3.5 x 10^9/l o Neutrophils <1.5 x 10^9/l o Platelets < 100 x 10^9/l o Bilirubin above normal limits o Alkaline phosphatase ≥ 5 x UNL o ASAT and/or ALAT > 2.5 x UNL

Efficacy evaluation	An intention to treat (ITT) analysis will be conducted for all randomized comparisons. Analyses that are not randomized comparisons will be conducted among the eligible patients (per protocol)
Statistical considerations	**ADAPT HR+/HER2- Part I:** Primary endpoint **Prospective comparison of EFS in "intermediate-RS" N0-1 dynamic responders vs. "low-RS" N0-1 patients (RS ≤ 11 AND N0-1)** "Intermediate-RS N0-1 dynamic responders" are defined as N0-1 patients with baseline RS between 12 and 25 AND good response to endocrine treatment. Sample Size We assume 94% 5-year EFS in the N0-1, RS ≤ 11 group and consider this as a "control" group. We intend to test for non-inferiority of the "experimental group" defined as N0-1/RS 12-25/dynamic responders. The "control group" has expected size of 16% (n=640) of all 4000 HR+/HER2- patients randomized to the trial. The experimental group has an expected size of 28% of HR+/HER2- patients (n=1120). We allow for 5% dropouts lost to follow-up. Recruitment for the respective group will be continued until the required patient number is achieved, i.e. 640 low-risk patients ("control group"), 1120 patients in the "experimental group" (N0-1/RS 12-25/dynamic responders) and 2240 patients have been randomized to the chemotherapy arms (Part II). Secondary endpoints Please refer to chapter 11.1 of the ADAPT HR+/HER2- sub-protocol. **ADAPT HR+/HER2- Part II:** Primary endpoint • **Prospective comparison of EFS in nab-paclitaxel vs. paclitaxel based chemotherapy followed by dose dense EC** EFS definition see above. Sample size The aim of the chemotherapy randomization sub-study in early, high-risk HR+ breast cancer is to *compare invasive disease-free survival (iDFS) in nab-paclitaxel vs. paclitaxel based chemotherapy followed by dose dense EC. The trial aims to demonstrate superiority of nab-paclitaxel-EC in a two-sided test and to report a 95%, 2-sided confidence interval for the EFS treatment difference.. The arms are randomized 1:1. Assuming alpha=.05, 80% power leads to the criterion of at least 317 observed invasive events for the hypothesis test of superiority*. Exploratory Analysis In further exploratory analysis, the study will report point estimates and formal 95% 2-sided confidence intervals for survival differences due to neo-adjuvant vs. adjuvant chemotherapy in each chemotherapy arm separately and as a whole.

In further exploratory analysis, confidence intervals for survival differences in neoadjuvantly treated patients achieving pCR versus all others (adjuvant treatment and neoadjuvant treatment without pCR) will also be reported.

This exploratory work is not designed to detect all clinically relevant differences, but confidence intervals could be useful for future study design or for meta-analysis.

Secondary endpoints

Interim 1. safety analysis
Run-In: An interim safety analysis is planned after recruitment of 120 patients in both study arms (i.e., 60 patients in each chemotherapy arm).

Approximately 8.3% of the patients (n=5) in the Paclitaxel (Taxol) - EC arm will be expected to suffer SAE including neuropathia grade 3-4 and/or febrile neutropenia and/or neutropenia grade 4 during the paclitaxel part. The purpose of the interim safety analysis is to test the hypothesis that the percentage of patients with such SAE in the nab-paclitaxel part is higher. It is assumed that an incidence of 25% (n=15) would lead to consideration of a dose reduction. Under these assumptions, a one-sided test of these proportions at a 95% level of significance will have approximately 80% power.
Interim 2. Safety analysis: Exploratory second safety analysis will be performed after n=1000 patients treated by chemotherapy with focus on neutropenia, febrile neutropenia and infections to ensure the safety profile of the drug.

- **pCR rates in the neoadjuvant treatment of dose dense paclitaxel-EC vs. nab-paclitaxel-EC arms**

For the secondary endpoint pCR (defined as no invasive tumor ypT0/ypN0) in neo-adjuvantly treated patients, we estimate that about 400 patients in each arm will receive their treatment as neo-adjuvant therapy.

We expect about 17% pCR in the neoadjuvant dose dense paclitaxel-EC patients and consider an improvement to 25.3% in the neoadjuvant nab-paclitaxel-EC arm (125mg/m²) as a clinically relevant response. If there are 800 patients, this number is adequate to detect the difference of pCR proportions between 25.3% and 17% by a one-sided test with 80% power. (alpha error 0.025).
Further secondary and exploratory endpoints in patients treated by chemotherapy:

- pCR rates by other defintions (ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypN0) and regression grades
- Clinical response (examination, mammography/sonography)
- rate of breast conserving therapy

- Prospective evaluation of febrile neutropenia in patients treated by dose-dense EC and Paclitaxel q2w with primary pegfilgrastim prophylaxis as well use of G-CSF in the nab-paclitaxel arm.

- Prospective evaluation of incidence of febrile neutropenia with primary pegfilgrastim prophylaxis in the nab-paclitaxel-EC arm (n=1120) and in the paclitaxel-EC arm (n=1120) with secondary use of G-CSF. With

	expected n=1120 and expected incidence of 3% in each arm, the 2-sided confidence intervals will extend from about .02 to .04 in each arm. • Impact of use of daily G-CSF during nab-paclitaxel treatment in exploratory analysis.
Patient number/ enrolment period	Run-in phase: 400 patients Main phase: 3600 patients In total: expected 4000 patients (per group: minimum of 640 low risk and 1120 intermediate risk/responders and 2240 high risk (treated as per protocol versions after 1.2) Number of sites: 60-80 (12 run-in phase) Maximum patients per site: 15% of randomized patients Enrolment start: Q2 2013 Enrolment stop: Q4 2019 Follow-up period: 60 months, may be prolonged half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study

2 Introduction and Background ADAPT HR+/HER2- Breast Cancer

Adjuvant treatment decision making based on conventional clinical and pathological prognostic markers is a field where systematic over- and under-treatment is tolerated by clinicians due to the substantial and continuous improvement of outcome data during the past decades. Especially in HR positive patients with low tumor load, who make up for nearly 30,000 cases per year in Germany, a large cohort (up to 50-70%) is over-treated, if current German (AGO) and international guidelines are respected.

Prognosis: molecular risk stratification tools

With regard to prognostic factors, a number of molecular recurrence risk stratification tools (such as 21-Gene-Recurrence Score RS (Oncotype DX®)[8], Genomic Gene Index (MammaQuant DX®, GGI)[77], 70-Gene-profile (Mammaprint®)[78], or uPA/PAI-1(Femtelle®)[11]) have been developed for patient stratification for (adjuvant) systemic therapy.

The **RS assay** has been developed to predict recurrence in patients with node-negative, hormone receptor (HR)-positive, tamoxifen-treated breast cancer (BC). The RS assay includes 16 cancer-related and five reference genes measured by real-time, reverse-transcriptase–polymerase-chain reaction (RT-PCR), using formalin-fixed paraffin-embedded tissue. The list of genes and algorithm were designed based on data from 447 patients from three independent trials including the tamoxifen (T)-only treated group of the NSABP B20 study and 250 candidate genes from the literature and previous experiments. The 16 cancer-related genes, which correlated most strongly with relapse-free interval, consistently across the study populations (including ER, PR, HER2, Ki-67 and genes related to apoptosis, invasion and proliferation) were selected to build the algorithm which renders a score from 0 to 100 (highest risk) that can be divided into three prognosis groups (score 0–17: low, 18–30: intermediate and ≥31 high risk)[8]. RS was consecutively validated as a prognostic marker in node-negative HR positive Tam -alone treated patient populations from randomized NSABP B14 (about 25–30% of original study population)[9] and in a nested case-control study in a community health setting: Later evaluation refers to N+ patients from the SWOG 8814 trial (367 pts HR+, node positive BC patients treated by T vs. T + CAF)[14] and to 465 HR+ patients with 0-3 positive nodes from the E2197 trial comparing equally effective adjuvant chemotherapy by doxorubicin with docetaxel (AT) or cyclophosphamide (AC) (2885 node-positive and high risk node-negative BC)[13]. 40% to 55% of patients have been assigned to the low-risk group in these trials. In the NSABP B14 study, in the tamoxifen group low-risk patients carried a risk of distant recurrence at 10 years of only 6.8% compared to 30.5% in those 20–30% of patients identified as high-risk based on the RS[8]. These differences were fairly similar for the untreated group as well as for most other treated patient collectives[12,13].

Retrospective analyses from Trans-ATAC confirm these results for endocrine therapy with aromatase inhibitors. RS is an independent prognostic factor with a hazard ratio (HR) of 5.25 (per 50 point increase) for distant recurrence in contrast to central tumor grading (HR poor vs. well = 2.06, ns) in both N+ and N0 BC irrespective of endocrine treatment.[12]. Notably, for any RS-value, the risk of distant recurrence was higher for N + than N0 patients and higher in patients with four positive nodes than patients with 1-3 positive nodes[14]. In addition, in the NSABP B14 as well as B20 trial, RS was significantly associated with risk of local relapse in all treatment groups and independent of patient age. In the tamoxifen group, risk of local relapse was 4.3% for low RS vs. 15.8% for high RS[79].

In the NSABP B20 trial, RS was also significantly predictive of benefit from adjuvant chemotherapy[9]. While chemotherapy was associated with an overall 10% lower risk of distant recurrence for all patients, there was a hazard ratio of 0.26 for Tam + CMF vs. Tam-alone in the high-risk group compared to a hazard ratio of 1.31 in the low-risk group representing 54% of study population. Similarly for node positive patients, in the SWOG 8814 trial after adjustment for number of positive nodes, CAF chemotherapy was only beneficial in patients with high RS (32% of pts), while no benefit was observed in the low-risk group (40% of pts.). The predictive impact of RS was independent of nodal groups[14]. These predictive data are also supported by neoadjuvant data.

Notably, in Trans-ATAC the risk of recurrence was rather low (e.g. 3.3% in 0–1 positive LN and 7.9% in the subgroup of 2–3 positive LN) in patients with intermediate risk BC with 1–3 positive lymph nodes and low RS treated by endocrine therapy alone (tamoxifen or anastrozole) and similar survival rates in this subgroup were reported by other trial used chemoendocrine therapy[12-14].
All studies revealed no apparent benefit from adjuvant chemotherapy in patients with low Recurrence Score, but could not exclude some benefit in patients with intermediate Recurrence Scores.
Impact of chemotherapy in patients with RS 12-25 node-negative BC is currently under investigation within the TAILORx trial (compared with endocrine treatment alone). PlanB is a prospective multi-center randomized phase-III trial run by the West German Study Group comparing taxane based chemotherapy +/- anthracycline in HER2- BC. Based on a low RS in the primary tumor about 50% of patients with node-negative and 1-3 positive LN disease can be spared chemotherapy, if traditional definition of low RS is used (0-17). In the planB study, the intermediate risk interval is defined as 12-25, however leading to a higher proportion of patients in the intermediate risk segment. Within the translational research program of planB uPA/PAI1, Ki-67, central pathology and RS are compared.
The interim analysis of the planB trial revealed moderate correlation between RS and central grading. With 24% of low risk ≤11) by RS, 31% of intermediate (RS 12-25) and *80% of* high risk being centrally G3[80]. There was a weak positive correlation between Ki-67 and RS (Spearman's coefficient r_s=0.336, p<0.001). Clinical impact of the discordance remains unclear, but may indicate substantial heterogeneity within both pathomorphological and molecular groups.
The recently updated St. Gallen Consensus recommends evaluating single proliferation markers to further separate HR+ tumors with high proliferation (luminal B) from tumors with low proliferation (luminal A). Ki-67 ,a protein expressed in all cell cycle phases except G0, is a marker of proliferation and is a strong prognostic factor in BC[16]. It is proposed to be used for discrimination of luminal A vs. B subtypes. If a cut-off of 13,25% is used it strongly correlates with the differentiation done by PAM 50 signature[15]. In the MA14 trial the same genomic signature is better than IHC measurement of Ki-67 as prognostic factor in tamoxifen treated patients.[19].

Therapy outcome prediction depending on proliferative activity
Single agent anthracyclines and taxanes in luminal subtypes showed lower sensitivity than HR negative subtypes. No significant differences between luminal A and B subtypes was reported from these trials.[81] Several other reports suggest limited efficacy of chemotherapy in patients with highly HR positive/HER2 negative and low grade[82,83] and/or luminal A low proliferating tumors[32] especially in postmenopausal patients[4]. These data are in line with data published by von Minckwitz et al, demonstrating need for longer polychemotherapy in luminal subtypes as overall[84]. Alba et al. presented data on similar response rates for neoadjuvant hormonal (HT) and polychemotherapy (EC-Doc) in low proliferating luminal BC as defined by low Ki-67 ≤10% (response rate CT vs. HT: 63% vs. 58%) in contrast to higher proliferating tumors (67% vs. 42%)[20]. Although there are conflicting data[17,81] luminal B subtype may be associated with increased benefit of addition of taxanes to anthracycline-based chemotherapy.[18,21,22]
Within our own WSG-AGO EC-Doc trial there is significant improvement of EFS (hazard ratio = 0.71) in favor of the EC-Doc, if compared to 6 cycles FEC in 2011 patients with 1-3 involved lymph nodes. Large benefit from taxanes in this trial was restricted to luminal B tumors in multivariate interaction analysis. Central grade 3 and younger age were identified as negative prognostic factors and luminal A subtype (defined by negative HER2 status and low Ki-67 <20%) as a favorable marker. Patients with luminal A tumors have 5 year EFS >95% in both study arms.
In summary strong data support the role of Ki-67 as prognostic tool, but the role in prediction of chemotherapy outcome as well as the relevant cut-off levels remain to be defined[17].
Regarding endocrine response in the neoadjuvant setting, several studies revealed higher efficacy of aromatase inhibitors compared to tamoxifen[25,85] in postmenopausal patients. The Z 1031 trial revealed no significant differences between different aromatase inhibitors and similar

activity of endocrine therapy in both luminal subtypes[28], as also shown previously by Dowsett et al. earlier (response in luminal A and B groups: 77% vs. 76% [86]), although these data are still controversial.[87]

Therapy outcome prediction based on dynamic measurement of tumor cell proliferation
Recently, neoadjuvant endocrine and/or tailored therapies have been suggested as an important tool for evaluation of response to a given systemic therapy *in vivo*. Clinical response measured by sequential evaluation of different proliferation markers (such as Ki-67) following of a 2-4-week-course of endocrine therapy has been demonstrated to significantly correlate with increased benefit from aromatase inhibitor- or tamoxifen-based endocrine therapy[25,88]. Ellis et al. reported improved survival for stage 2 or 3 patients after 4 months neoadjuvant endocrine therapy with aromatase inhibitors or tamoxifen and a low-risk biomarker profile (including lower Ki-67[26]) in the surgical specimen. Furtherly, excellent EFS was reported after neoadjuvant endocrine therapy in patients with Ki-67 values of ≤10% following 2-4 weeks of endocrine therapy. However, no prognostic impact could be demonstrated for baseline Ki-67-values[27]. Similar data have been reported for genomic grade index (GGI) as a (dynamic) proliferation marker. Singahl et al. reported a significant association between response rates to neoadjuvant letrozole and GGI values measured on days 10-14. Again, no prognostic information could be demonstrated for baseline Ki-67 (mRNA) or GGI values[87]. It remains unclear which method of proliferation measurement is the optimal marker for early response evaluation regarding endocrine therapy. The ADAPT trial will be the the first large trial evaluating baseline proliferation markers and change in proliferation markers after a three week endocrine treatment and the association with EFS.

Optimal taxane and anthracyline based chemotherapy
Sequential (dose-dense EC-Paclitaxel, EC-Doc, EC-paclitaxel weekly, FEC-Doc) or combined (e.g. TAC) taxane and anthracycline containing chemotherapy regimens have been shown to be highly effective[89-91] and are thus considered one possible standard in adjuvant BC therapy. However there is still no consensus about a optimal standard adjuvant chemotherapy in the early breast cancer. So 4xEC→4xDoc (overall duration of 24 weeks) or 4xEC→12xPaclitaxel (24 weeks) have been shown to be superior to conventional dosed 4xEC→4xPaclitaxel[91]. Standard sequential treatment of 4xEC→4xDoc is also equieffective to 6 cycles of TAC (18 weeks)[90] and high-dosed Canadian CEF (18 weeks)[92]. But all these regimens associated either with significant toxicity (febrile netropenia/infection rates, myalgia (4xEC→4xDoc/6xTAC) and/or also substantial rates of second malignancies (Canadian CEF).
On the other hand dose-dense and/or dose-intensive concepts have been shown to be highly effective in comparison to standard anthracycline-taxane regimens, particularly in in high risk disease with high tumor load[93] and/or in aggressive node-positive disease[94]. Furthermore a recent meta-analysis shows significantly better DFS in favor of dose-dense vs. conventionally dosed chemotherapy in early breast cancer.
Dose-dense EC-Paclitaxel (overall duration of 16 weeks) has been recently shown to be equieffective as “gold standard” 6xTAC (with trend to better 5 year DFS, HR= 0,87, p=0,074), but was associated with significantly less febrile neutropenia (9% vs. 3%)/infections, diarrhea grade 3 (7% vs. 2%), trend to less treatment related deaths (0,9% vs. 0,3%), but significantly more neuropathy (7% vs. 1%) and anemia grade 2 (with similar rate of transfusions (4% vs. 2%)[95]. However further modification of short rapidly scheduled chemotherapy regimens addressing high proliferation rate and/or high tumor load (in patients with more than 4 LN) in high risk disease would be of immediate clinical relevance.

Optimal sequencing of taxane and anthracyline based chemotherapy
However, reverse or dose-dense scheduling of taxanes before standard anthracycline-containing courses resulted in better toxicity and higher dose-intensity in several small trials[96, 94,97,98]. Neoadjuvant trials with the reverse scheduling suggest that pCR rates are even higher[96]. So Alvarez et al. reported higher pCR and significantly better 5 year RFS (88 vs. 79.5%) and overall survival (93% vs. 83%) in 1596 patients treated by verse vs. standard sequence[99].

ADAPT HR+/HER2- part II uses this approach in selected HR+ patients. This part of the protocol is allowed to be given in an adjuvant or neoadjuvant setting and prefers the reverse sequence and introduces a new taxane compound nab paclitaxel. In the HER2+ and TN protocols 4 x Paclitaxel followed by four courses of EC are also the standard chemotherapy backbone, so that within the sub-protocols response can be compared.

Use of Nab-paclitaxel

Nab-paclitaxel (Abraxane) is a new formulation of albumin-bound paclitaxell. This results in potentially higher intracellular concentrations of taxane and significantly less hypersensitivity reactions associated with cremophor in conventional paclitaxel (175 mg/m^2).

In metastatic breast cancer nab-paclitaxel is approved for use at 260mg/m^2 q3w based on results of a phase III trial, showing better efficacy (overall response rate 33% versus 19%; p = 0.001, time to progression (PFS) 23.0 versus 16.9 weeks; hazard ratio (HR) = 0.75; p = 0.006 and non-significantly better overall survival 65.0 versus 55.7 weeks; P = 0.374) compared to conventional paclitaxel q3w. Abraxane q3w is associated with less myelotoxicity (5-9% grade 4 neutropenia), but greater incidence of grade 3 neuropathy (10% vs. 2% for paclitaxel q3w). However, significantly less premedication (only 8% due to emesis, myalgia/arthralgia) was required for use of abraxane compared to 99%, if conventional paclitaxel is used[100].

In a phase II trial weekly regimen of abraxane for three weeks with an one week therapy-free interval (150mg/m^2) resulted in longer PFS of 12.9 versus 7.5 months (p = 0.0065) compared to standard docetaxel 100 mg/m^2 q3w. Survival analysis demonstrated significantly longer overall survival for the 150mg nab-paclitaxel regimen versus 100mg/m^2 nab-paclitaxel. It was superior on a non-significant level to docetaxel 100mg/m^2 q3w[101]. Response was earlier (best response after 2. cycle). Dose limiting toxicity was peripheral neuropathy with 22% of patients suffering from grade 3 (no grade 4) peripheral polyneuropathia at a median onset of symptoms after 23 weeks of treatment. Similar efficacy was observed in patients treated by reduced dose of nab-paclitaxel, so that dose of 125 mg/m^2 can be used as a tolerable and effective option.

Nab-paclitaxel at 100mg/m^2 weekly over a period of 12 weeks within a phase II trial (NSABP/M.D. Anderson) was well tolerated (dose reduction in 2% of cycles, 3 drop outs 2 due to progressive disease, PNP °2 → 11%, PNP °3 → 5%) and generated in a sequential design followed by three cycles of FEC a pCR rate of 26%.

Recently interim results from a phase III trial tested bevacizumab + nab-paclitaxel (150 mg/m^2 or paclitaxel 90 mg/m^2 or ixabepilone 16 mg/m^2 d 1+8 q3w in first line therapy of metastatic breast cancer. 44% of the patients had previous taxane treatment in the adjuvant situation. In combination with bevacizumab nab paclitaxel at a weekly dose of 150 mg/m^2 had to be discontinued in 45% of patients at the time of the third course mainly due to neutropenia and neurotoxicity. Progression – free survival after paclitaxel and nab paclitaxel did not differ significantly, but there was an significant difference for the comparison of paclitaxel versus ixabepilone in favor of paclitaxel[102].

So taking into account data for paclitaxel weekly as “gold standard” therapy in the adjuvant setting or promising PFS/OS data for nab-paclitaxel in the metastatic setting, it would be of clinical interest to combine these with dose-dense approach for development of short tolerable and highly effective treatment for optimally pre-selected high risk HR+ disease. Dose of 125 mg/m^2 was chosen based on the data from metastatic setting and early data from the GeparSepto trial, which reduced dose from 150 to 125 mg/m^2 due to >20% dose reduction in the previous dose.

In the meantime results of two large randomized neoadjuvant trials (both not powered for survival) used nab-paclitaxel vs. paclitaxel in the adjuvant setting have been released.

GeparSepto has shown a significant improvement in pCR rates after nab-paclitaxel use (38% vs. 29%, p<0.001 in the overall cohort and 16% vs. 12% p=.23, in the HR+/HER2- disease respectively) and significantly improved 4-year iDFS (84% vs 76%, hazard ratio 0.66) in the overall population as well as in the HR+/HER2- cohort (hazard ratio 0.67, p=0.03)[103,104].

Furthermore Gianni et al. reported a non-significantly lower pCR in HR+/HER2- disease in the ETNA trial after solvent based paclitaxel compared to nab-paclitaxel (14 vs. 10% (odds ratio 0.67). In this trial 5 year EFS was non-significantly improved (and mostly pronounced

compared to TN disease) by use of nab-paclitaxel in the HR+/HER2- cohort (80.3 vs. 72.1%)[105,106].
These results are also in line with the recently published meta-analysis, included further trials, but all associated also with worse toxicity profile related to the nab-paclitaxel use[107]

3 Rationale ADAPT HR+/HER2- Breast Cancer

The adjuvant chemotherapy indication in HR+/HER2- BC today is mainly based on the individual prognostic profile as defined by clinical-pathological factors (tumor size, nodal status, grade, age) and/or genomic signatures (e.g. Recurrence Score) at the baseline, i.e. the risk profile. Definition of this profile allows identification of a subgroup being at a low risk of recurrence for which absolute reduction of risk of recurrence by chemotherapy is more than marginal. However, even if modern molecular risk stratification tools are used, there remains a large group of patients at intermediate risk with unclear benefit from chemotherapy. Responsiveness to endocrine therapy is not included in the decision-making procedure so far. Proliferation response to a short course of primary endocrine therapy on the other hand is an excellent (dynamic) predictor of endocrine therapy outcome. On the basis of an early assessment of endocrine responsiveness ADAPT tries to identify good and low responders to endocrine therapy. The hypothesis would be that good responders are sufficiently treated by endocrine therapy only, whereas patients with low response need other treatments such as chemotherapy.
The classification of endocrine response is primarily made on the basis of sequential Ki-67 evaluation. The design allows identification of further molecular markers/profiles correlating stronger. Within the chemotherapy part of the trial optimization of the dose-dense concepts of chemotherapy is evaluated. So the standard arm consists of modified highly effective dose-dense concept by Paclitaxel-EC q2w. The experimental arm incorporates a new nab-paclitaxel compound followed by dose-dense anthracycline part. So two short rapidly cycled regimens with expected high antitumor efficacy will be compared in optimally selected patients with high risk HR+ disease.
Based on the current evidence from the smaller, not powered for survival trials, all showing numerically better prognosis, but also worse toxicity profile after nab-paclitaxel use, it appears reasonable to test superiority of nab-paclitaxel vs. Paclitaxel treatment in the high-risk HR+/HER2- disease.
Beyond TAILORx this may give another opportunity to allocate patients to appropriate treatment in the heterogeneous intermediate risk group in N0 and N1 patients. Early results show that about 70% of patients will have a good response to endocrine therapy, so that our assumption is to correctly reduce use of adjuvant chemotherapy in HR+/HER2- early BC (0-3 positive lymph nodes) by approximately 50% without any negative survival effect by combination of baseline and response data.

ADAPT and other trials evaluating genomic signatures
The first generation of trials integrating information from genomic signatures follow two different philosophies. MINDACT is a classical phase III design comparing classical pathology/IHC versus decision making on the basis of the 70 gene signature in N0-1 BC. On the other hand TAILOR X substitutes conventional pathology/IHC by Oncotype DX® in the HR+, pN0-1 population.
PlanB and ADAPT combine classical pathology/IHC and Oncotype DX®. PlanB in a population identified to be candidate for chemotherapy on the basis of conventional pathology/IHC identifies by Oncotype DX® a subgroup, which does not need chemotherapy on the basis of a very good prognosis.
Beyond these two landmark trials ADAPT HR+/HER2- is a second generation trial integrating Oncotype DX® in the same way as TAILOR X. Other than TAILOR X within the intermediate risk group decision making is not done by random, but on the basis of early response to endocrine test treatment evaluated by sequential ki-67 testing. Early in the conduct of the trial data from a safety population consisting of the observational arm of PlanB will be available. PlanB and ADAPT will allow retrospective comparison of adjuvant decision making on the basis of conventional pathology/IHC and Oncotype DX® and early response.

4 Study Objectives ADAPT HR+/HER2- Breast Cancer

A total of 4000 patients will be introduced to the ADAPT HR+/HER2- breast cancer sub-trial, which will have two phases, a run-in phase (400 patients) and a main phase (3600 patients; whole trial). The objectives of both phases are listed below:

Primary objectives

Run-in Phase:

- Analysis of reproducibility of each biomarker
- Assessment of drop out rate
- Assessment of proportions of marker responders vs. non-responders
- Central/local pathology
- Central/local Ki-67 assessment
- Ki-67 change after endocrine induction therapy
- Comparison of changes in RS, Ki-67, quantitative ER and proliferation group within the RS
- Assessment of distribution of responders/low responders in low (RS≤11), intermediate (RS 12-25) and high-risk (RS≥26) patients with the aim to allow early adjustment of the statistical plan
- Identification of other proliferation markers that drop significantly

Run-in phase + main phase

- ADAPT HR+/HER2- part I:
  - Prospective comparison of EFS in patients with intermediate risk by RS (12-25)/response vs. patients with low risk by RS (RS≤11; N0-1); both groups receiving endocrine therapy only
- ADAPT HR+/HER2- part II:
  - Prospective comparison of 5-year EFS of nab-paclitaxel 125mg/m² q1w x 8 versus Paclitaxel 175mg/m² q2w x 4 both followed by conventionally dosed E90C600 x 4 q2w chemotherapy regimens; patients with intermediate risk by RS (12-25)/low response or high risk patients by RS (≥26; N2/3) or by G3/KI-67≥40% and tumor size >1 cm will be treated with chemotherapy

Secondary objectives:

- Evaluation of 5-year EFS in patients classified as “clinical high risk*” and selected by ADAPT strategy for treatment by endocrine therapy alone (this group comprises patients with low or intermediate risk by Oncotype Dx)
- To determine if an additional baseline biomarker (or change in biomarker) can improve upon the combination of baseline RS and Ki-67 response, by evaluating the association between baseline biomarker (or change in biomarker) and EFS in the following groups of patients (HR+):
  - patients with intermediate risk by RS (12-25) with Ki-67 response to neoadjuvant therapy, who are treated without chemotherapy and
  - patients with intermediate risk by RS (12-25) without Ki-67 response to neoadjuvant endocrine therapy, who are treated with chemotherapy

* For the purposes of secondary objective a patient is classified as having a “clinical high-risk” if one or more of the following criteria (A-E) are satisfied:

A. Node positive
B. G3 by central grading
C. Age<35 years
D. (if N0): G2 AND (Ki-67>20% OR T2-3)
E. (if N0): G1 AND tumor size >3 cm.

These criteria are based on current guidelines (St. Gallen, S3, ESMO) or Adjuvant Online (as criterion used in the MINDACT study).

<u>For the substudy clinical prognostic factors vs. genomic vs. ADAPT-guided approach (as pooled analysis of PlanB and ADAPT trials)</u>

- Prospective analysis of the prognostical/predictive impact of conventional prognostic markers will be evaluated by exploratory analysis in distinct genomic subgroups as well as prognostic/predictive impact of dynamic testing (along with conventional prognostic criteria) within a pooled analysis of the ADAPT and planB (historic control) trials
- Evaluation of prognostic impact of classical prognostic criteria and prognostic and predictive impact of dynamic testing regarding indication for adjuvant chemotherapy
- Prospective analysis of dynamic testing (i.e., proliferation course measured by Ki-67 after 3 weeks induction pre-surgical endocrine therapy) regarding its prognostic impact in homogeneously treated patients (regarding chemo) from the PlanB and ADAPT study (low and high risk)
- Prospective analysis of dynamic testing regarding its predictive impact in intermediate risk disease (pN0-1) based on the Main/Run-In phase ADAPT study (assumed only 1/3 treated by chemotherapy based on the dynamic testing in overall n=1600) vs. PlanB study (all treated by adjuvant chemotherapy; n=1232)
- Subgroup RS≤11: pooled analysis (ADAPT + PlanB) of 5year EFS of clinical high risk patients
- Subgroup RS ≤11: pooled analysis (ADAPT + Plan B) of 5 year EFS of clinical low vs clinical high risk

ADAPT HR+/HER2- part II:

- 1. Interim safety analysis in first 120 patients treated by chemotherapy
- 2. Interim safety analysis after n=1000 chemotherapy-treated patients
- In patients receiving chemotherapy prior to surgery:
  - Comparison of pCR rates (all definitions)
  - Rate of breast conserving therapy
  - Clinical response (examination, mammography/sonography)

In all patients:

- Superiority testing for EFS of the nab-paclitaxel-EC vs. paclitaxel-EC
- Evaluation of genomic profile correlating with response to nab-paclitaxel treatment
- Prospective evaluation of febrile neutropenia rates in patients treated by dose-dense EC and Paclitaxel q2w and pegfilgrastim as well use of G-CSF in the nab-paclitaxel arm

5 Study Design ADAPT HR+/HER2- Breast Cancer

The ADAPT HR+/HER2- breast cancer sub-trial is a modern biomarker-based adjuvant, prospective, multi-center, non-blinded, randomized phase III trial. After baseline assessment of receptor status, patients with tumors responsive to therapy are given a pre-surgical endocrine induction treatment with either tamoxifen or aromatase inhibitors according to menopausal status.

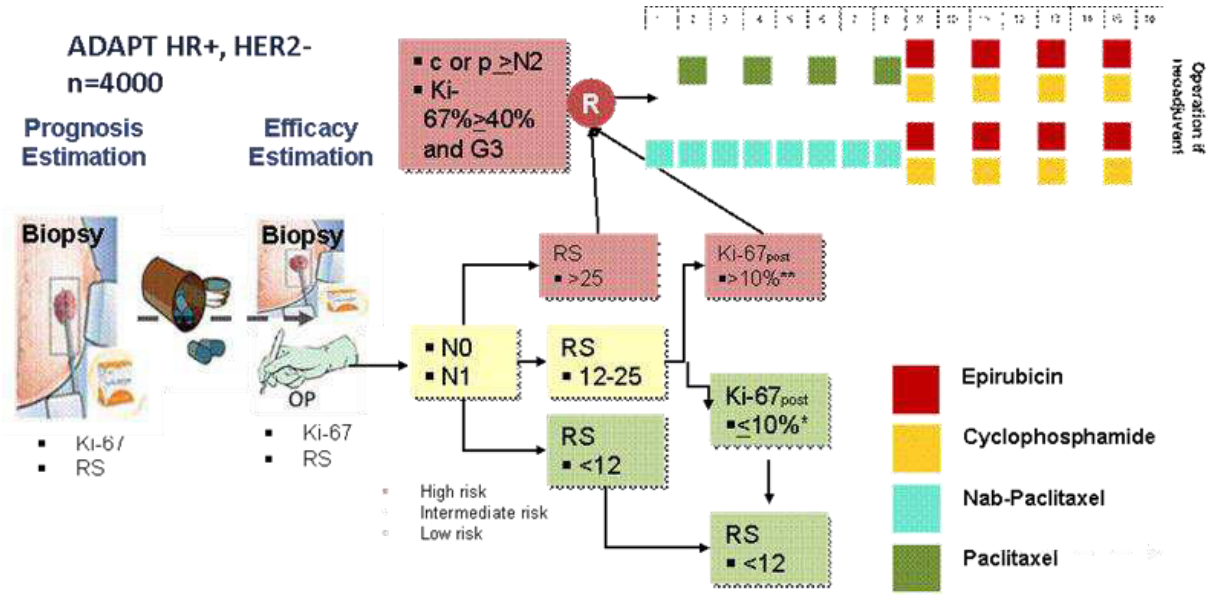


Figure 1: *Patient selection ADAPT HR+/HER2-Breast Cancer*

Following surgery or SLN biopsy/axillary dissection + second core biopsy early endocrine response will be evaluated. Patients with low baseline risk and intermediate-risk/good response patients will be allocated to endocrine therapy only (remain in the ADAPT-HR+/HER2- part I). The remaining HR+/HER2- patients (intermediate-risk/low response and high-risk patients) will be randomized with the WSG study coordinator to one of the treatment arms of the ADAPT HR+/HER2- part II (arm A nab paclitaxel 125mg/m² q1w x 8 versus arm B: Paclitaxel 175mg/m² q2w x 4 both followed by conventionally dosed $E_{90}C_{600}$ x 4 q2w (see 6.5 and figure 1). The study design for the chemotherapy part of the trial is depicted in figure 2 below.

Patients with incomplete information for risk classification, i.e. missing RS, Ki-$_{67pre/post}$, etc. will be randomized within ADAPT HR+/HER2- Part II. Patients, who decide to take chemotherapy despite low or intermediate risk/response can receive chemotherapy within ADAPT HR+/HER2- Part II.

If chemotherapy is given in the neoadjuvant setting surgery should be performed 3 to 5 weeks after the last chemotherapy cycle.

After completion of chemotherapy all HR+ patients will receive endocrine treatment according to current AGO guidelines.

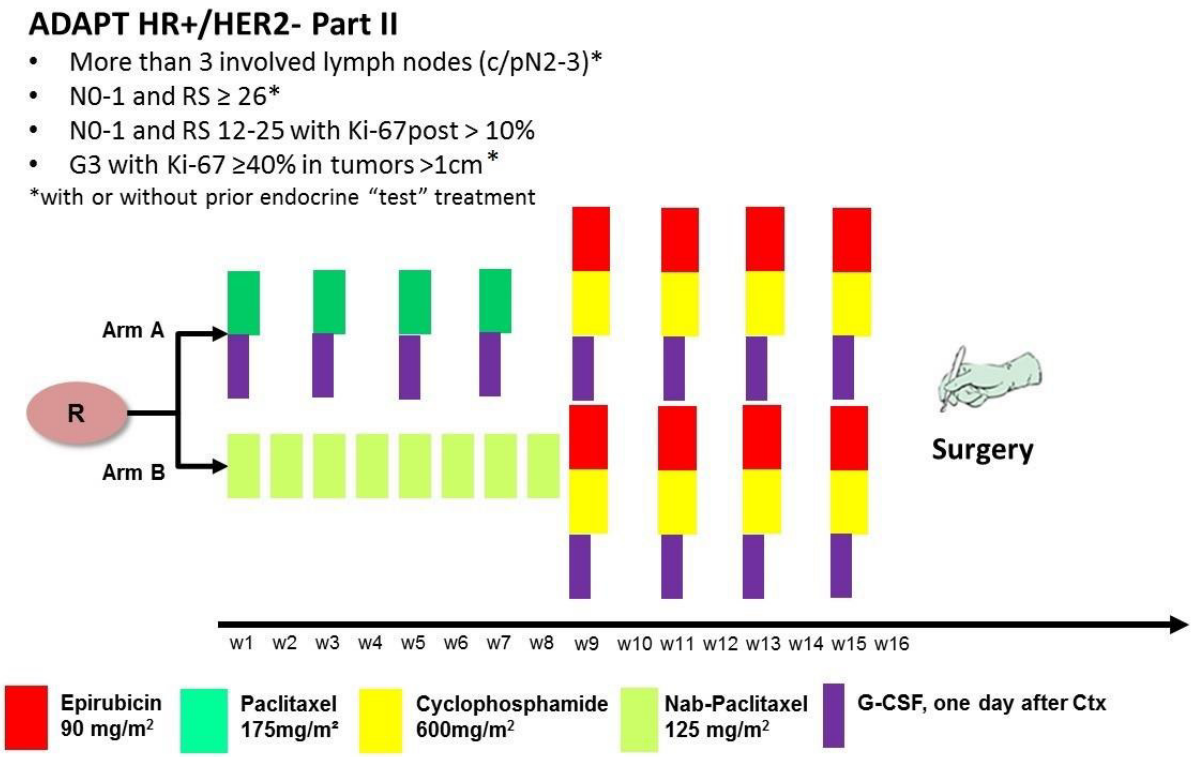


Figure 2: *Treatment Schedule ADAPT HR+/HER2- Breast Cancer*

5.1 Run-in Phase and Main Phase

For further information please refer to the ADAPT umbrella protocol, chapter 5.1. The run in phase of the HR+/HER2- protocol will include 400 patients and the main phase 3600 patients.

5.2 Timing of Surgery

Surgery is not part of the protocol but is recommended to be performed within 3-5 weeks after day of the last chemotherapy cycle. Breast surgery can be either done after 3 weeks of induction treatment or after the completion of neoadjuvant chemotherapy at the discretion of the investigator (ADAPT HR+/HER2- part II). When neoadjuvant chemotherapy is intended SLN in cN0 cases can be performed prior to chemotherapy start.

6 Patient Enrollment ADAPT HR+/HER2- Breast Cancer

Following three weeks of pre-surgical endocrine treatment and after adequate surgical treatment or second core biopsy (if applicable) with nodal assessment, the patients will be allocated to the HR+/HER2- breast cancer part of the ADAPT trial if they meet the additional inclusion/exclusion criteria (please refer to chapter 6.1 for additional inclusion/exclusion criteria).

The following examinations are recommended prior to randomization:

Table 1: Study Evaluations for Participation in ADAPT HR+/HER2- Breast Cancer Trial

	INVESTIGATIONS	TIMING
Surgery/second core biopsy (efficacy estimation)	Obtained: • Central pathological review* RS*	After end of induction therapy*
Positive ER/PR status **confirmed by central pathology***	✔	After end of induction therapy*
Negative HER2 status **confirmed by central pathology***	✔	After end of induction therapy*
Nodal status	Must be known	After end of induction therapy*
Grading **confirmed by central pathology**	Must be known	After end of induction therapy*
Recurrence Score (not applicable, if c/pN2/3 or G3 with Ki-67$_{pre}$ ≥40% in tumors >1cm)	Tumor sample obtained from diagnostic core biopsy of primary tumor	Prior to registration*
	Tumor sample obtained from surgery/second core biopsy (efficacy estimation)	After end of induction therapy*
Ultrasound	✔	At BL,after 4, 8, 12 and 16 weeks)+/- 2 weeks prior to the next chemotherapy cycle**.
History[1] and physical exam for patients receiving chemotherapy	Physical examination including: • Height • Weight • Karnofsky index for performance status/vital signs	≤ 7 days prior to registration

[1]Within 3 weeks prior to registration
* only in patients with induction treatment, not applicable to patients with clinical high risk disease (c/p N2-3; Ki-67 40% and G3 in tumors >1 cm)
**Only in patients treated by neoadjuvant chemotherapy

6.1 Additional Inclusion Criteria ADAPT HR+/HER2- Breast Cancer

In order to be eligible for the participation in the ADAPT HR+/HER2- breast cancer trial, patients who meet the general inclusion/exclusion criteria of the ADAPT trial also have to meet the following additional inclusion criteria:

- ER and/or PR positive and HER2 negative
- Central pathology available (Grading, Ki-67, RS)* (only in patients with induction treatment)
- All patients should be recommended to be treated by adjuvant chemotherapy in the daily routine practice by one of the current guildeines (St. Gallen, AGO Mamma, S3, ESMO) or to be high clinical risk by AdjuvantOnline (breast cancer specific survival of ≤88%)
    - Clinically N+ or cN0 with one of following features: G3, <35 years old, Ki-67 >14%, cT2-4c, If G1 only if clinical tumor size >3 cm

- If Clinical decision is based on AdjuvantOnline patients should derive more than 5% 10-year relapse-free survival benefit by use of chemotherapy (3rd generation anthracycline/taxane-based) additional to standard endocrine therapy (using clinical T and N status)

6.2 Additional Inclusion Criteria ADAPT HR+/HER2- Part II

To be eligible for the participation in the ADAPT HR+/HER2- trial part II (neo)adjuvant chemotherapy question) the patients have to meet one of the following inclusion criteria:

- More than 3 involved lymph nodes (c/pN2-3)*
- N0-1 and RS ≥ 26*
- N0-1 and RS 12-25 with Ki-67post > 10%
- G3 with Ki-67 ≥40% in tumors >1cm*
- To be a candidate for chemotherapy treatment due to high clinical risk irrespective of induction treatment (e.g. by heterogeneous tumor, multifocal tumor etc.)

*with or without prior endocrine "test" treatment

- Patients with tumors ≥cT2 and/or cN+ are strongly recommended to be treated by neoadjuvant chemotherapy
- Laboratory requirements for patients receiving chemotherapy (within 14 days prior to randomization):
  - Leucocytes ≥ 3.5 x 10^9/L
  - Neutrophils ≥1.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Hemoglobin ≥ 10 g/dL
  - Total bilirubin ≤ 1 x ULN
  - ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 x ULN
  - AP<5.0 ULN
  - Creatinine ≤ 175 µmol/L (2 mg/dl)
- LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization)

6.3 Additional Exclusion Criteria ADAPT HR+/HER2-

- Patients with clinical low risk tumors, who are not treated by adjuvant chemotherapy in the daily practice (e.g. cT1 and G1 and cN0)

6.4 Additional Exclusion Criteria ADAPT HR+/HER2- Part II

- Known polyneuropathy ≥ grade 2
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study
- Uncompensated cardiac function
- Inadequate organ function including:
  - Leucocytes < 3.5 x 10^9/l
  - Neutrophils <1.5 x 10^9/l
  - Platelets < 100 x 10^9/l
  - Bilirubin above normal limits
  - Alkaline phosphatase ≥ 5 x UNL
  - ASAT and/or ALAT > 2.5 x UNL

These patients will be randomized to one of the adjuvant chemotherapy arms. On the opposite, patients identified as low risk or intermediate risk with good response will remain on endocrine therapy only.

6.5 Randomization to ADAPT HR+/HER2- Part II Breast Cancer

Each eligible patient (intermediate-risk/low response or high-risk) will be randomized to receive either (neo)-adjuvant:

Arm A (Paclitaxel → EC dose dense),
vs.
Arm B (nab-paclitaxel → EC dose dense).

The taxane treatment consists of either:

1. paclitaxel (175 mg/m²) q2w x 4.

or

2. nab-paclitaxel (125 mg/m²) q1w x 8

The anthracyclin treatment consist of:

3. Epirubicin (90 mg/m²) and cyclophosphamide (600 mg/m²) q2w x 4

The randomization forms have to be filled in online in the e-CRF. After completion it has to be printed, signed by an investigator and faxed to the coordinator of the study:

Fax: +49 (0)611 160248 - 29

The following information will be requested:

- Institution name
- Investigator's name
- Patient's identifiers (site number, patient code)
- Patient's birth date (month/year)
- Date start of treatment planned

A patient who was not randomized prior to the first treatment administration will not be accepted for the study at a later date.
Investigators will be notified via the eCRF within 24 hours after complete information has been received from the site as per the randomization form.

Stratification
Patients will be stratified by

- Treatment (neoadjuvant/Adjuvant)
- Study center
- Nodal status N3 vs. N2 vs. N1 vs. N0
- RS group (high risk vs. intermediate/low endocrine response)

6.5.1 **Arm A: Paclitaxel→EC**

Paclitaxel
Dose: 175 mg/m², day 1

Route: 3 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule: Every two weeks
This is called a cycle of treatment and is to be given 4 times.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

If neoadjuvant treatment: if progressive disease during taxane treatment consider immediate switch to the anthracycline treatment or surgery.

6.5.2 **Arm B: nab-paclitaxel→EC**

Nab-Paclitaxel
Dose: 125 mg/m², day 1
Route: 30min intravenous infusion.
Schedule: Every week
This is called a cycle of treatment and is to be given 8 times.

Method of administration for nab-paclitaxel: Administer reconstituted Abraxane suspension intravenously using an infusion set incorporating a 15 µm filter. Following administration, it is recommended that the intravenous line be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure administration of the complete dose.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

6.5.3 **Anthracycline Segment:**

Epirubicin
Dose: 90 mg/m², day 1
Route: 5 - 15 minute intravenous bolus injection (as per hospital policy)
Schedule: Every 2 weeks

followed by

Cyclophosphamide
Dose: 600 mg/m², day 1
Route: 5 to 60 minutes intravenous bolus injection (as per hospital policy)
Schedule: Every 2 weeks

If neoadjuvant treatment: if progressive disease during anthracycline treatment, perform immediate surgery.

In all dose dense cycles G-CSF prophylaxis (pegfilgrastim) on day 2. G-CSF prophylaxis can be withdrawn only in cases of ANC>1000 during paclitaxel treatment.

7 Study Plan ADAPT HR+/HER2- Breast Cancer

7.1 Definition of Study Medication ADAPT HR+/HER2- Breast Cancer

For the purpose of this sub-trial, endocrine therapy with tamoxifen or aromatase inhinibitors, Paclitaxel, Epiribicin, Cyclophosphamide and pegfilgrastim will be commercial ware and will not be labelled study-specific. Nab-paclitaxel will be study medication and will be labeled study-specific accordingly. Documentation of preparation and distribution of the chemotherapy has to be done according to the study site's local guideline.

7.2 Study Treatment ADAPT HR+/HER2- Breast Cancer

In the "test" phase patients will be treated with endocrine therapy (tamoxifen in premenopausal and aromatase inhibitors in postmenopausal women) for 3 weeks.

After completion of the 3 week "test" treatment and the second core biopsy (efficacy estimation) further treatment decision will be based on the results for Recurrence Score and central pathological review. Patients will either continue on endocrine therapy only (low risk or intermediate risk/good response) or they will be randomized to chemotherapy part (intermediate risk/low response or high risk).
Not more than 14 days should elapse between the date of randomization and the start date of the first cycle of adjuvant chemotherapy.
Chemotherapy doses will be calculated according to body surface area (BSA) for all cycles. The weight will be determined at cycle 1 of chemotherapy. If there is a 10% or greater decrease in body weight compared to cycle 1, the BSA will be recalculated. If the calculated BSA of the patient is > 2.0 m^2, no dose adjustment is recommended (but can be used by clinical practice)

Dose adjustments and/or treatment delay and treatment discontinuation are planned for each arm in case of severe hematological and/or non-hematological toxicities.
In the event of relapse during treatment, unacceptable toxicities, withdrawn consent, treatment shall finish earlier.

7.2.1 End of Treatment (EOT) Definition ADAPT HR+/HER2- Breast Cancer

End of treatment is defined as 21 days after the last application of study drug. Work-up will include:

- Physical examination with Karnofsky Index or ECOG
- Hematology, biochemistry, urine analysis (only in chemotherapy treated patients)
- Documentation of toxicity

EOT for patients remaining on endocrine therapy only will be the date of registration, i.e. allocation to endocrine treatment.

7.2.2 Prophylactic Premedication Regimen for Taxanes, Epirubicin and Cyclophosphamid

Please refer to the ADAPT trial (chapter 7.9) for further information on prophylactic premedication, including use of antibiotics, G-CSF and antiemetics.
In case of dose dense q2w EC and Paclitaxel (q2w), G-CSF prophylaxis with Pegfilgrastim is recommended. In all other patients use secondary G-CSF according to current AGO guidelines.

7.2.3 Concomitant Treatment during Chemotherapy

For permitted prophylactic premedication please refer to the previous chapter.

Ancillary treatments will be given as medically indicated. Any concomitant medication must be documented in the Case Report Form. (Nab-)paclitaxel should not be given together with CYP2C8 and CYP3A4 inhibitors or inducers. Please refer to the SmPC.

7.3 Follow-up

For the follow-up please refer to the ADAPT protocol, chapter 7.10.

7.4 Post-Chemotherapy Treatment

After completion of chemotherapy the patients can be treated with bisphosphonates at the discretion of the investigator (according with AGO guidelines):

- Zoledronic acid 4 mg every six months for three years
- Clodronate 1600 mg/d p.o. for two years

7.4.1 Indication for Antihormonal Therapy

Every patient from the ADAPT HR+/HER2- trial must receive an antihormonal therapy according to current national standards as defined by AGO guidelines.

7.4.2 Therapy after Protocol Treatment is discontinued

Except for study chemotherapy, antihormonal therapy and radiotherapy as per protocol, no further antitumor therapy is allowed (surgery, chemotherapy, immunotherapy, etc.) before tumor relapse is documented.
If patients are removed from the study because of disease relapse, further treatment is at the discretion of the investigator. The metastatic regimen(s) used will be documented in the Case Report Form.

8 Study Evaluations ADAPT HR+/HER2- Breast Cancer

8.1 Evaluation during endocrine Induction Therapy

day	-21 to 0 (BL)	1	22
Medical history (incl. concomitant medications)	x		
Central pathology review of diagnostic core biopsy	x		
Core biopsy	x		x[1]
Physical Examination	x		x
Serum sample (biomarker analysis)	x[1]		x[1]
Radiology: • Chest X-ray • Bone scan • Liver imaging	X[2]		
• Mammography	x		
Breast MRI	x[1]		x[1]
Breast Ultrasound	x		x[1]
Clinical assessment	x		x
Pregnancy test	x		
ECG and LVEF	x[2]		
Laboratory: • Hematology • Biochemistry	x[2]		
(Serious) Adverse Event		continuosly	
Concomitant medication	x	continuosly	

[1] optionally
[2] only if indicated (e.g. in patients later to be treated by chemotherapy)

8.2 Chemotherapy

While under chemotherapy, all patients must be examined according to the schedule outlined below until they come off chemotherapy.

Table 2: Study Evaluations before each Cycle of Chemotherapy

	INVESTIGATIONS	TIMING
History and physical examination	Clinical history since previous infusion Physical examination - including: • Weight • ECOG or Karnofsky index for performance status • Clinical tumor assessment (only if neoadjuvant treatment)	Prior to any chemotherapy application[1]
Hematology	• Hemoglobin • WBC • Neutrophils • Platelets count	Prior to any chemotherapy application [1]
Biochemistry	• Alkaline phosphatase • ASAT (SGOT) • ALAT (SGPT) • Bilirubin • Serum creatinine • Electrolytes: Na^+, K^+, Cl^-	Prior to any chemotherapy application [1]
ECG and LVEF	Echocardiography	As clinically indicated
Other investigations		As clinically indicated
	Evaluation of risk factors of febrile neutropenia	Prior to any chemotherapy application [1]

Adverse events including cardiac toxicity	Investigations as indicated	Serious Adverse Events must be reported within 24 hours anytime

[1]Within 3 days prior to chemotherapy.

Only applicable for chemotherapy part.

week	-3 to 0 (BL)[2]	1	4	8	12	16 (EOT)	18-21 (Surgery)
Medical history (incl. concomitant medications)	x[2]						
Central pathology review of diagnostic core biopsy	X[1,2]						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x	x	x	x	x	x	
Serum sample (biomarker analysis)	x[1,2]		x[1]			x [1]	
Radiology: • Chest X-ray • Bone scan • Liver imaging	x[2,]						
• Mammography[3]	x					x	
Breast MRI[3]	x[1,2]		x[1]			x[1]	
Breast Ultrasound[3]	x		x	x	x	x	
Clinical assessment	x[2]		x	x		x	
Pregnancy test	x						
ECG and LVEF	x[2]						
Laboratory: • Hematology • Biochemistry	x	x	x	x	x	x	
Surgery							x
(Serious) Adverse Event		continuously					
Concomitant medication	x[2]	continuously					

[1]optionally
[2] Only applicable, if patient was included without induction therapy for ADAPT HR+/HER2- part II (chemotherapy)
[3] Only in patients treated by neoadjuvant chemotherapy

8.3 Evaluation at End of Induction Treatment

Please refer to chapter 7.8 of the ADAPT protocol for further information.

8.4 Evaluation at End of Treatment (EOT)

To be performed 21 days after the last treatment. Work-up will include:

- Physical examination with Karnofsky Index or ECOG
- Hematology, biochemistry (only in chemotherapy treated patients)
- Documentation of toxicity

EOT for patients remaining on endocrine therapy only will be the date of randomization, i.e. allocation to endocrine treatment.

8.5 Evaluation in Follow-up after End of Treatment

Patients will be followed every 6 months for one year starting from month 6 after registration and every 6 months thereafter until year 2. and then once yearly (corresponding to German aftercare plan) or until relapse to document:

- Event-free survival
- Overall survival
- Further therapy (and/or endocrine treatment/treatment with Herceptin)

- Long term toxicities
- Relapse (local relapse)
- 2nd primary malignancy
- First treatment for metastatic breast cancer or 2nd primary malignancy
- Results for biopsy of distant metastases
- Yearly evaluation of lifestyle parameter (optionally in a subset of paients)

Follow-up visits will be scheduled at month 6, 12, 18, 24, 36, 48, and 60 after registration. Patients who relapse or suffer from 2nd primary malignancy will only be followed for survival. For any distant metastasis occurring, if biopsied, IHC should be reported in the CRF.

Patients completing follow-up month 60 may be followed half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study, provided that an additional informed consent regarding prolongation of the follow-up was signed.

8.6 Response Assessment for Neoadjuvant Chemotherapy

Please refer to the ADAPT Umbrella protocol chapter 8.5.

9 Dose Delays and Reduction/Modification ADAPT HR+/HER2- Breast Cancer

9.1 Treatment Dose Adjustments and Treatment Delays

Toxicities will be graded using the NCI Common Toxicity Criteria (NCI CTC), version 4.0.

Dose reduction is planned for each treatment arm in case of severe hematological and/or non-hematological toxicities. Chemotherapy dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. In case of several toxicities in one patient and conflicting recommendations, the most conservative dose adjustment has to be followed. Doses which have been reduced for toxicity must not be re-escalated.

Treatment with chemotherapy may be delayed no more than 2 weeks (up to day 35) to allow recovery from acute toxicity.

9.1.1 Dose Adjustments and Treatment Delays – Endocrine Therapy

In case of non-tolerability of endocrine therapy any dose adjustment, switch of endocrine medication or treatment delay is at the discretion of the investigator. Any delay, switch or dose reduction must be documented in both the patient's file and the e-CRF.

9.2 Toxicity Related Guidelines for Dose Reduction and Dose Modification of Taxanes and Anthracyclines

Please refer to the ADAPT protocol, Appendix 1 – Treatment Dose Adjustments and Treatment Delays for further information.

10 Safety Monitoring

10.1 Safety Plan

Overall safety will be assessed on an ongoing basis during the conduct of the study. The DSMB (IDMSC) will monitor cumulative safety data at least once every 6 months during the course of the study. In addition, data on serious adverse events and deaths will be monitored by the DSMB (IDMSC) at least once every 3 months.

10.2 Cardiac Safety Monitoring

There will be no specific recommendations for the cardiac safety monitoring for HR+/HER2- patients. Please refer to the ADAPT protocol, Appendix 2 – Cardiac Safety Monitoring for further information.

11 Data Analysis and Statistical Considerations ADAPT HR+/HER2-

11.1 Primary endpoints and hypothesis testing

The primary endpoint of the ADAPT HR+/HER2- study is EFS, defined as the time from registration to any event (relapse, death without any evidence of disease, second malignancy).

Intention to treat (ITT) analysis will be conducted for all randomized hypothesis tests and will include the entire study population of recruited patients. Analyses that are not randomized comparisons will be performed among the eligible patients (per protocol)

11.1.1 **Primary endpoints ADAPT HR+/HER2- Part I:**

Clinical design considerations: Patients within “intermediate-risk” subgroups and 0-3 positive lymph nodes have long-term (e.g. 9-year) relapse risk of 10 to 20%. Data from pre-surgical trials has shown excellent survival in patients experiencing proliferation drop-off after a short course of anti-hormonal therapy. Based on these data, in a group selected by combining both prognostic information and dynamic assessment, long-term relapse-free survival without chemotherapy is expected to exceed 90%; a survival rate that would not justify the use of adjuvant chemotherapy.

Primary endpoint

Prospective comparison of EFS in “intermediate-RS” N0-1 dynamic responders vs. “low-RS” N0-1 patients (RS ≤ 11 AND N0-1).

“Intermediate-RS N0-1 dynamic responders” are defined as N0-1 patients with baseline RS between 12 and 25 AND good response to endocrine treatment.

Sample Size

We assume 94% 5-year EFS in the N0-1, RS ≤ 11 group and consider this as a “control” group. We intend to **test for non-inferiority** of the “experimental group” defined as N0-1/RS 12-25/dynamic responders. The “control group” has expected size of 16% (n=640) of all 4000 HR+/HER2- patients randomized to the trial. The experimental group has an expected size of 28% of HR+/HER2- patients (n=1120). We allow for 5% dropouts lost to follow-up.

Recruitment will be continued until the required patient number is achieved, i.e.640 low-risk patients (“control group”) and 1120 patients in the “experimental group” (N0-1/RS 12-25/dynamic responders) and 2240 patients have been randomized to the chemotherapy arms (after protocol version 1.2).

With an accrual of 36 months and a minimum follow-up of 60 months in at least 1760 patients treated by endocrine therapy only, a one-sided test with alpha = .05 (the 95% confidence level) has 80% power to reject the null hypothesis of 5-year EFS of 90.7% in the experimental group, i.e., delta=3.3%. Equivalently, the analysis may be performed after 134 EFS events whatever occurs first Sample size calculations will be reviewed after completion of the run-in phase, if the statistical assumptions are not met or if data from TAILORx demand it.

Remarks:

- A positive result would imply a confirmation that dynamic assessment adds meaningful information to baseline risk assessment of tumors.
- A strategy utilizing dynamic assessment could help to spare chemotherapy in an additional 20% of patients (estimated).
- The 5-year EFS survival difference (delta=3.3%) in the statistical design corresponds to approximately a five-percent 10-year survival advantage. This advantage is comparable to typical cut-offs used by clinicians for adjuvant chemotherapy recommendations in a low-to-intermediate risk situation (estimated for example using adjuvant-online).

11.1.2 **Primary endpoints ADAPT HR+/HER2- Part II**

Clinical design considerations: Anthracycline and taxane based chemotherapy regimens are a widely accepted standard. The original regimens tested the sequence anthracyclines → taxanes. Reverse [96]or dose-dense scheduling of taxanes before or with standard anthracycline-containing courses resulted in better toxicity and higher dose-intensity in several small trials. Neoadjuvant trials with the reverse scheduling suggest that pCR rates are even higher[99] Nab-paclitaxel (Abraxane) is a new formulation of paclitaxel in human serum albumin. In metastatic breast cancer nab-paclitaxel was superior to 3 weekly paclitaxel. The design previews the comparison of nab-paclitaxel 125mg/m² q1w x 8 versus paclitaxel 175mg/m^2 q2w + G-CSF x 4

Primary endpoint

- Prospective comparison of EFS in nab-paclitaxel vs. paclitaxel based chemotherapy followed by dose dense EC.

EFS definition see above.

Sample Size

The trial aims to test superiority of nab-paclitaxel-EC in a two-sided test and to report a 95%, 2-sided confidence interval for the EFS treatment difference. The arms are randomized 1:1.
To estimate a criterion for final evaluation, we assume 5y-EFS 81.7% in the control arm and hazard ratio 0.73 of Arm B compared to Arm A, in accordance with recent studies[103-106]. Corresponding 5y-EFS in Arm B is 86.3%, and 5y-EFS in the chemotherapy trial as a whole is 84.0% under these assumptions. Using a two-sided criterion for superiority (alpha=.05, 80% power) leads to the criterion **317 observed invasive events** for this hypothesis test.

Exploratory Analysis
In further exploratory analysis, the study will report point estimates and formal 95% 2-sided confidence intervals for survival differences due to neo-adjuvant vs. adjuvant chemotherapy in each chemotherapy arm separately and as a whole.
In further exploratory analysis, confidence intervals for survival differences in neoadjuvantly treated patients achieving pCR versus all others (adjuvant treatment and neoadjuvant treatment without pCR) will also be reported.

Remarks:

- This exploratory work is not designed to detect all clinically relevant differences, but confidence intervals could be useful for future study design or for meta-analysis.

11.2 Secondary endpoints ADAPT HR+/HER2- Part I & II

11.2.1 Patients treated by chemotherapy

Interim safety analysis

Run-In: An interim 1, safety analysis is planned after recruitment of 120 patients in both study arms (i.e., 60 patients in each chemotherapy arm).
Approximately 8.3% of the patients (n=5) in the Paclitaxel (Taxol) - EC arm will be expected to suffer SAE including neuropathia grade 3-4 and/or febrile neutropenia and/or neutropenia grade 4 during the paclitaxel part. The purpose of the interim safety analysis is to test the hypothesis that the percentage of patients with such SAE in the nab-paclitaxel part is higher. It is assumed that an incidence of 25% (n=15) would lead to consideration of a dose reduction. Under these assumptions, a one-sided test of these proportions at a 95% level of significance will have approximately 80% power.

Interim 2. Safety analysis: Exploratory safety analysis will be performed after n=1000 chemotherapy treated patients in Part II with focus on febrile neutropenia, neutropenia and infections.

- **pCR rates in the neoadjuvant treatment of dose dense paclitaxel-EC vs. nab-paclitaxel-EC arms**

For the secondary endpoint pCR (defined as no invasive tumor ypT0/ypN0) in neo-adjuvantly treated patients, we estimate that about 400 patients in each arm will receive their treatment as neo-adjuvant therapy.

We expect about 17% pCR in the neoadjuvant dose dense paclitaxel-EC patients and consider an improvement to 25.3% in the neoadjuvant nab-paclitaxel-EC arm (125mg/m²) as a clinically relevant response. If there are 800 patients, this number is adequate to detect the difference of pCR proportions between 25.3% and 17% by a one-sided test with 80% power. (alpha error 0.025)

Further secondary and exploratory endpoints in patients treated by chemotherapy:

- pCR rates by other definitions (ypT0/is ypN0; ypT0 ypN0/+; ypT0/is ypN0/+; ypN0) and regression grades.
- Clinical response (examination, mammography/sonography).
- Rate of breast conserving therapy.

- Prospective evaluation of incidence of febrile neutropenia in patients treated by dose-dense EC and Paclitaxel q2w with primary pegfilgrastim prophylaxis as well use of G-CSF in the nab-paclitaxel arm.
- Prospective evaluation of incidence of febrile neutropenia with primary pegfilgrastim prophylaxis in the nab-paclitaxel-EC arm (n=1120) and in the paclitaxel-EC arm (n=1120) with secondary use of G-CSF. With expected n=1120 and expected incidence of 3% in each arm, the 2-sided confidence intervals will extend from about .02 to .04 in each arm.
- Impact of use of daily G-CSF during nab-paclitaxel treatment in exploratory analysis.

11.2.2 **Prospective biomarker analysis within ADAPT trial**

Prospective sub-study regarding prognostic and predictive impact of conventional markers (tumor size, age, nodal status, centrally determined Ki-67) vs. genomic subgroups with/without dynamic response assessment in early HR+ breast cancer.

Clinical design considerations: As reviewed in Table 1, current international guidelines are neither concordant nor definitive regarding factors to be included in selection of patients with early HR+ breast cancer for chemo-endocrine therapy vs. endocrine therapy alone (Table 1).

	S3 (Germany) 2012	*St. Gallen 2011*	*NCCN 2012*	*ESMO 2011 (St. Gallen 2009)*	*AGO 2012****	*Adjuvant Online 8.0 or 9.0 (MINDACT study)*
Cht strongly recommended	*All pN+ pN0 high risk** Age <35 G3*	*Luminal B (Ki-67≥14% or G3) or pN≥2*	*All pN+ All pN0 if pT≥1b and High RS* All pN0 if pT≥1c Cht recommended (particurarly if G2/3)*	*≥pT3 ≥pN2 G3 Ki-67>30% ER/PR<50%*	*Ki-67 (+) Grade, uPA/PAI-1 (+/-) Gene expression*****	*Breast cancer specific survival ≤88%: All pN0 if: ≥pT2; G2-3 If G1 pT2 (>3,0 cm) All pN+ except pT1/pN1, G1)*
Cht optional	*All other risk algorithms (St. Gallen 2011/09/07 uPA/PAI-1; Ki-67****)*		*pT≥1b intermediate RS*	*pN1 pT2 G2 Ki-67 15-30%*		

**If performed*
*** not precisely defined*
****predictive factors for chemotherapy*
*****study participation*
*****If histology not tubular or mucinious*

Limitations of clinical prognostic factors for use as indication for adjuvant chemotherapy and rationale for our analysis are:

- *No predictive data for CT-ET vs. ET for G3 status in the HR+ disease*

(data from Oxford meta-analysis)

- *Ki-67 failed as predictor for chemo-endocrine therapy vs endocrine therapy alone within the IBCSG IX study*
- *High discordance rates in grade assessment (up to 40% within WSG and American trials (E2197, NSABP B20)*
- *No standardized method for Ki67 measurement*

- *Up to now only OncotypeDx/Recurrence Score is reported to be predictive for the use of CT-ET vs. ET alone in N0 (NSABP B-20) and N+ disease (SWOG 8814), with most benefit addressed to the high risk subgroup (level of evidence 1b)*
- *Impact of CT within the large intermediate risk group (40-60% of patients) is unclear*
- *However no data are available for modern regimens (anthracycline/taxane based, dose dense), so actually most of these patients are recommended to be treated by CT, as done within the PlanB trial (n=3200, 2009-2011)*
- *TailorX and RxPonder trials are randomizing patients with N0 and N1 breast cancer respectively to CT+ET vs ET alone within the intermediate risk group*
- *TailorX results are expected in 2015; however there is a high likelihood for significant mistreatment within this large heterogeneous group, so that randomization may be a suboptimal instrument for assessing effects of therapy.*

Inclusion of clinical factors within the RS model led to the reduction of the intermediate risk group and higher prognostic impact, but also to the loss of interaction effect significance.
In conclusion, there are no prospective data regarding a prognostic and predictive effect of classical prognostic factors when taking into account genomic subgroups. A dynamic marker approach (proliferation response to endocrine therapy) will be evaluated within the WSG-ADAPT trial as a clinical solution of the problem of potential over- or undertreatment within the intermediate-risk RS subgroup.

Rationale: Prospective comparison of risk-groups based on either clinical prognostic factors (using current guidelines: S3, AGO, St. Gallen, NCCN or AdjuvantOnline 8.0/9.0), on genomic RS subgroups or on dynamic testing (ADAPT).

11.2.3 5-year EFS in patients classified as clinical high/ADAPT low risk with no chemotherapy: Comparison with 91% LCL

Based on results from the Run-In Phase of the ADAPT trial, chemotherapy can be spared in about 63% of all patients included in the study by the ADAPT strategy.

Within the "ADAPT-low risk group" (this group comprises N0-N1 patients with EITHER low risk by RS (≤11) OR intermediate risk by RS (12-25) and Ki-67 response to neoadjuvant endocrine therapy selected for endocrine therapy only), an estimated 65% of patients would be classified as “clinical high-risk” by the following criteria:

A. Node positive
B. G3 by central grading
C. Age<35 years
D. (if N0): G2 AND (Ki-67>20% OR T2-3)
E. (if N0): G1 AND tumor size >3 cm.

The sample size of the group "(clinical high risk/ADAPT low risk)” is thus estimated at 1144 patients.

5-y EFS in this group (clinical high risk/ADAPT low risk) will be assessed and a non-inferiority hypothesis (compared to a fixed threshold) will be tested as follows:

1. Compute 90% CI of 5-y EFS
2. Reject null hypothesis if lower confidence limit (LCL) > 91%, accept otherwise.

If true 5-y EFS in this group were 93% (which would be clinically relevant), then we would expect to reject the null hypothesis at 80% power with this sample size.

This comparison is similar to the analysis performed within the MINDACT trial for a similar question. A positive outcome would support omission of adjuvant chemotherapy for this “clinical high risk/ADAPT low risk” group.

The size of the “clinical high risk/ADAPT low risk” group (including pooled analysis with the PlanB trial, as mentioned below), will allow further subgroup analysis by different Oncotype Dx risk categories.

11.2.4 **Assessment of the association between baseline biomarkers and their changes after a short endocrine induction therapy and EFS.**

In particular, analysis to demonstrate the association between continuous values of any marker and EFS will be performed in the following groups of patients:

1) Patients receiving only endocrine therapy but no chemotherapy (ITT) (ADAPT low risk)

2) Patients receiving endocrine therapy and chemotherapy (ITT): (ADAPT high risk: this group includes all N2 patients, patients with G3 and Ki-67 ≥40% in tumors >1cm, as well as those N0-N1 patients with EITHER high risk by RS (≥26) OR intermediate risk by RS (12-25) and no Ki-67 response to neoadjuvant endocrine therapy.

In each of these groups, multivariate survival analysis including a Cox proportional hazard model will be performed taking the following factors into account: age, lymph node involvement, tumor size, baseline markers (Ki-67 & RS), marker dynamics (Ki-67 and RS), and one or more additional biomarkers to be determined.

As exploratory analysis, samples 1.) and 2.) will be combined and analyzed (per protocol) by multivariate survival modeling including chemotherapy as a treatment variable and taking into account the propensity for chemotherapy treatment based on the treatment selection criteria.

1) In those patients with intermediate risk by RS and Ki-67 response to neoadjuvant endocrine therapy, a Cox proportional hazards regression model will be fit to EFS with the continuous marker as the sole independent variable. With 520 patients and assuming a 5-year EFS of 88%, there will be 83% power to detect a standardized hazard ratio of 1.4 at a two-sided alpha level of 0.05.
2) In the patients with intermediate risk by RS without Ki-67 response to endocrine therapy, a Cox proportional hazards regression model will be fit to EFS with the continuous marker as the sole independent variable. With 280 patients and assuming a 5-year EFS of 85%, there will be 82% power to detect a standardized hazard ratio of 1.5 at a two-sided alpha level of 0.05.
   - prospective analysis of the prognostical/predictive impact of conventional prognostic markers will be evaluated by exploratory analysis in distinct genomic subgroups as well as prognostic/predictive impact of dynamic testing (along with conventional prognostic criteria) within a pooled analysis of the ADAPT and planB (historical control) trials (see sub-study).
   - evaluation of genomic profile, correlating with response to nab-paclitaxel treatment.

11.2.5 **Pooled analysis of the ADAPT and planB trials**

Objective: Evaluation of the prognostic impact of classical prognostic criteria and the prognostic and predictive impact of dynamic testing with respect to the indication for adjuvant chemotherapy.

1) **Prospective analysis of dynamic testing** (i.e., proliferation course measured by Ki-67 after 3-week induction pre-surgicalpresurgical endocrine therapy) **regarding its *prognostic* impact** in homogeneously treated patients (with respect to chemotherapy) from the PlanB and ADAPT trials: low-risk (PlanB: n=340; ADAPT: n=640) and high-risk (all treated by Cht: PlanB: n=605; ADAPT estimated n=1760). In total: n=3345 (n=945 with no pre-surgicalpresurgical endocrine therapy vs. n=2400 with induction therapy).

   Non-inferiority of 3-week presurgicalpre-surgical endocrine therapy (n=2400) vs. control (no presurgicalpre-surgical endocrine therapy; n=945) will be tested. 5-year EFS in the homogeneously treated (with respect to chemotherapy), genomically low and high-risk populations (ADAPT and planB) is taken as 89% in the control group. A one-sided test with alpha=.05 will have 80% power for a clinically relevant non-inferiority margin of delta = 3.0%.

2) **Prospective analysis of dynamic testing regarding its *predictive* impact** in intermediate-risk disease (pN0-1) based on the ADAPT Main/Run-In phase (assumed only 1/3 treated by Cht based on dynamic testing; total n=1600) vs. PlanB study (all treated by adjuvant Cht; n=1232).

   5-year EFS in a control group (n=1232) of genomically intermediate-risk patients with chemotherapy from WSG-planB is taken as 89%. The test group (n=1600) of genomically intermediate-risk patients in ADAPT will have a different treatment strategy resulting in about 1/3 receiving Cht. A one-sided test with alpha=.05 will have 80% power for a clinically relevant non-inferiority margin of delta = 3.0%.
3) **Prospective exploratory analysis of the prognostic and predictive impact of conventional prognostic markers** within distinct genomic subgroups by means of a pooled analysis of the ADAPT and planB (historical control) trials (n=3345), in particular evaluation of clinical risk assessment in homogeneously treated patients:
   - low-risk (no Cht, n=980): PlanB: n=340; ADAPT n=640)
   - high-risk (all treated by Cht, n=2365): planB: n=605; ADAPT: n=1760).

a) Genomic low-risk subgroup: Prognostic impact of classical prognostic subgroups will be evaluated by constructing 95% confidence intervals for clinical high risk vs. low/intermediate risk within the genomic low-risk subgroup from the PlanB and ADAPT studies (PlanB: n=340; ADAPT n=640).

Depending on the method of risk allocation to clinical markers, 45-85% of patients will be classified as “clinically high-risk”, and 55-15% as “clinically low-risk”. 5-year EFS in the clinical high/genomic low risk group (expected n= 700) is assumed as 93% vs. 97% in the clinical low/genomic low (expected n=280). A two-sided test with alpha 5% would have 80% power to detect this difference.

b) Genomically high-risk subgroup: Prognostic impact of classical prognostic subgroups within this subgroup will be evaluated by estimating the hazard ratio of low to high clinical risk. A hazard ratio <1 (associated with low clinical risk) could signal possible overtreatment.

About 85% (n=2010) of the 2365 genomically high-risk patients are expected also to be clinically high-risk vs. 15% (n=355) clinically low-risk. Taking 5-year EFS in the clinically high-risk sub-group of genomically high-risk patients to be about 81%, a hazard ratio of 0.7 (low vs. high clinical risk) can be detected by a test with two-sided alpha = .05 and 80% power. The

survival improvement corresponding to this hazard ratio would be about 5.25%. A 5-year EFS difference as large as 10% is almost certain to be seen.

c) Overall: Regarding overall analysis of classical prognostic subgroups within the genomic high-risk and genomic low-risk subgroups in ADAPT and planB, 80% (n= 2676) are expected to have clinically high risk and 20% (n=669) clinically low risk. Confidence intervals for 5-year EFS will be estimated in these sub-groups in exploratory analysis.

11.3 Tertiary objectives

Further objectives include

- Assessment of impact of lifestyle factors (body mass index/change of weight), sport activity, alcohol and smoking on prognosis in a subset of patients.
- Evaluation of further molecular, pathological and clinical markers and their combinations in terms of predictive and prognostic value.

Additional translational research questions occurring during the trial will be defined in sub-protocols.

11.4 Ethical Considerations ADAPT HR+/HER2-

All participants will give written informed consent for participation in the trial. All participants will be protected by the insurance cover as standard in clinical trials. Possible undertreatment should be excluded by the data from several trials. Donating a tumor block to the central tumor bank is planned for further research purposes.

11.5 Allocation/Randomization

For **HR+/HER2- patients,** the results of the efficacy estimation of induction treatment will support subsequent treatment decisions. After evaluation of proliferation changes and Recurrence Score from the surgical tissue sample by central pathology (and, if adequate material for both classifiers, RS and Ki-67, has been obtained), all *eligible* patients will be allocated by the WSG study coordinator to the corresponding treatment arms.

Low-risk (RS≤11; N0-1) and intermediate-risk (RS 12-25; N0-1) good-response patients will be allocated to endocrine therapy alone.
High risk (RS≥26 or N2 or G3/Ki-67≥40% and tumor size >1 cm) or intermediate risk (RS 12-25; N0-1)/poor-response will be randomized for one of two chemotherapy arms (anthracyclines-taxane (classical) or taxane-anthracycline sequence (experimental)).

11.6 Efficacy Evaluation

11.6.1 Efficacy Parameters

The primary efficacy parameter will be 5-year EFS for HR+/HER2- disease. EFS is defined as in the umbrella protocol.

11.7 Summary of statistical methods

Statistical tests for particular endpoints were described above. Survival methods include product limit (Kaplan-Meier) estimation, log-rank statistics and proportional hazards (Cox) analysis. Descriptive statistics, tests of proportions, distribution-free tests, and bootstrap analysis (as required for exploratory analyses, secondary endpoints, and tertiary endpoints) will also be provided. In exploratory analysis involving survival, non-proportional hazards testing and (if indicated) modeling will be performed.

For further information, please refer to the umbrella protocol chapter 11.5.

11.7.1 HealthEconomics Analysis

A health economics analysis will be performed to estimate key measures including incremental cost-effectiveness ratios (ICER) of ADAPT chemotherapy selection strategies, based on patient outcome vs. costs and side-effects of chemotherapy administered. The analysis will take into account risk assessment by clinico-pathological factors and baseline Recurrence Score and also utilize efficacy, survival, and other data obtained in ADAPT. In particular, cost-effectiveness of dynamic testing to identify patients to be spared chemotherapy will be estimated.

11.8 Safety Evaluations

11.8.1 Interim Safety Analysis

Interim safety analysis in chemotherapy arms was described under Secondary Endpoints above (Section 11.2). For further information, please refer to the umbrella protocol chapter 11.4.3

12 Translational Research

Please refer to the ADAPT protocol, chapter 10 for further information.

13 Adverse Events

The Sponsor will supply Celgene with a copy of all SAEs which involve *exposure* to a Celgene product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g. IB, SmPC). The Sponsor will provide Celgene with a copy of the annual periodic safety report e.g. Development Update Safety Report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committee.

Please refer to the ADAPT protocol, chapter 12 for further information.

14 Definition of Study Medication

14.1 Study Medication

For the purpose of this sub-trial, nab-paclitaxel is the investigational medicinal product (IMP or IP), which will be labeled study-specific.

15 Administrative Aspects

Please refer to the ADAPT protocol, chapter 14 for further information.

ADAPT HER2 Positive/Hormone Receptor Positive Breast Cancer Sub-trial

(Recruitment for substudy stopped)

A prospective, randomized multicenter, open-label comparison of pre-surgical trastuzumab emtansine (T-DM1) with or without standard endocrine therapy versus trastuzumab with endocrine therapy given for twelve weeks in patients with operable HER2+ and HR+ breast cancer within the ADAPT protocol.

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Final Version 5.0, 11 November 2021

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Protocol Title: ADAPT HER2 Positive/Hormone Receptor Positive Breast Cancer Sub-trial

A prospective, randomized multicenter, open-label comparison of pre-surgical trastuzumab emtansine (T-DM1) with or without standard endocrine therapy versus trastuzumab with endocrine therapy given for twelve weeks in patients with operable HER2+ and HR+ breast cancer within the ADAPT protocol.

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Signature Page ADAPT HER2+/HR+ Biostatistics

Protocol Title: ADAPT HER2 Positive/Hormone Receptor Positive Breast Cancer Sub-trial

A prospective, randomized multicenter, open-label comparison of pre-surgical trastuzumab emtansine (T-DM1) with or without standard endocrine therapy versus trastuzumab with endocrine therapy given for twelve weeks in patients with operable HER2+ and HR+ breast cancer within the ADAPT protocol.

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1 Study Summary ADAPT HER2+/HR+ Breast Cancer

ADAPT HER2+/HR+	A prospective, randomized multicenter, open-label comparison of pre-surgical trastuzumab emtansine (T-DM1) with or without standard endocrine therapy vs. trastuzumab with standard endocrine therapy given for twelve weeks in patients with operable HER2+/HR+ breast cancer within the ADAPT protocol.
Study Overview	HER2 over-expressing breast cancer with its aggressive biology remains a major clinical challenge. Over-expression of the HER2 gene is reported in about 10-20% of breast cancers. It is associated with poor prognosis[108], with good response to neoadjuvant chemotherapy[109,110], decreased sensitivity to endocrine therapy[85] and response to targeted therapy such as trastuzumab[33,111]. In about half of the cases there is a co-expression of hormone receptors (ER and/or PR) and HER2 receptor (so called HER2+/HR+ cases). Trastuzumab is a monoclonal antibody against the HER2 receptor. Its use leads to activation of antibody-dependent cellular cytotoxicity, inhibition of extracellular domain cleavage, abrogation of intracellular signaling, reduction of angiogenesis, and decreased DNA repair. These effects are increased by combination with a wide range of anti-cancer agents. The use of trastuzumab changed the perception of HER2+ metastatic breast cancer as it rendered prognosis of HER2+ patients treated with trastuzumab-based chemotherapy comparable to that of patients with HER2- disease[112]. In the adjuvant setting, the use of trastuzumab (for one year[34] or shorter[113]) sequentially[34] or simultaneously[35] to an adjuvant chemotherapy backbone is associated with a reduction of the relapse risk by about 50%. In HER2+ early breast cancer (eBC), adjuvant trastuzumab (T) therapy for 52 weeks in combination with chemotherapy is considered gold-standard. Up to now HER2+/HR+ BC and HER2+/HR- disease have not been looked at separately. There is a large body of evidence for poor prognosis of HER2+/HR+ BC compared to HER2 negative cases[114]. Nevertheless, prognosis of HER2+/HR+ BC is essentially better than that of HER2+/HR- controls[45,46]. **Relative endocrine resistance/chemotherapy responsiveness of HER2+/HR+ BC** Several studies reported reduced response of HER2+/HR+ tumors to endocrine therapy particularly in the metastatic setting[115]. These reports are supported by preclinical evidence for ER independent growth pathways triggered by HER2/HER1 receptors[116]. However, these data are conflicting and not fully supported by data from adjuvant and neoadjuvant studies. Ellis et al. reported substantial response to letrozole, but reduced response to tamoxifen in HER2+/HR+ tumors[117]. Other adjuvant trials revealed poor outcome for both tamoxifen- and aromatase inhibitors treated HER2+/HR+ tumors[114,118] and similar response of aromatase inhibitors in both HER2+ and HER2- tumors[118]. With respect to chemotherapy responsiveness, the large adjuvant trastuzumab trials reported similar risk reduction ratios for both HR positive and negative disease[46], even though in the neoadjuvant setting pCR rates seem to be lower in HER2+/HR+ than in HER2+/HR- tumors[44]. **Role of pCR in HER2 over-expressing BC (HR+/HR-)** Similar to triple negative (ER/PR/HER2 negative) BC, achievement of pathological complete response (pCR) in patients with a HER2+ subtype is associated with significantly better long-term survival as compared to those patients without pCR[30].

Trastuzumab (T)-containing neoadjuvant chemotherapy has been reported to increase the probability of pathological complete response (pCR) in HER2+ disease up to 67%[36,110,119].
In the NOAH trial, the neoadjuvant use of trastuzumab was associated with improved disease-free survival[36].
The TECHNO trial is the first trial reporting a significant association between pCR after neoadjuvant anti-HER2 therapy (together with chemotherapy) and improved survival in HER2+ disease[31].
Thus, pCR in HER2 over-expressing BC is a validated surrogate parameter for patient outcome and survival.
For **HER2+/HR+ breast cancer,** these data have to be confirmed. A recent meta-analysis presented by von Minckwitz et al. revealed a differential prognostic impact of pCR in HER2+/HR- and HER2+/HR+ tumors. pCR was prognostically significant in HR- tumors, but not in HR+ tumors[120]. These data are not supported by other reports[121].

Dynamic measurement (breast MRI/tumor cell proliferation) as an early surrogate marker for pCR
Recently, neoadjuvant cytotoxic and/or tailored therapies have been suggested as an important tool for evaluation of response to a given systemic therapy *in vivo*. Clinical response measured by sequential evaluation of different proliferation markers (such as Ki-67) following a course of neoadjuvant chemotherapy has been demonstrated to correlate significantly with an increased risk of relapse in patients not achieving pCR[122]. Summing up divergent effects of several anti-HER2 therapies on proliferation, it would be clinically relevant to evaluate such proliferation tools for early prediction of combination therapy efficacy (chemotherapy and HER2 targeted therapy). So far, it remains unclear which method of proliferation measurement is the optimal marker for response evaluation regarding combined chemo-anti-HER2 therapy.
However, measurement of proliferation and apoptosis as well as assessment of changes in PI3K/AKT, IGF and stem cell signaling after a short course of therapy could provide a unique signature for *dynamic* response evaluation and selecting patients for mono vs. combined targeted treatment.
Another way to assess early response could be **molecular imaging** by breast MRI (or other functional dynamic imaging), given the strong evidence, particularly in HER2+ and triple negative breast cancer[52,53]
Changes in contrast medium kinetics in contrast-enhanced MRI (DCE-MRI) or of the ADC (apparent diffusion coefficient) in the diffusion-weighted MRI or drop of the chlin peak in the ^{1}H-MR-Spektroskopy already after short induction therapy are possible measurement instruments for an imaging approach as an alternative non-invasive and complimentary method for dynamic patient stratification within the trial. A further advantage of breast MRI is an analysis of whole tumor (and not only a single biopsy area) and better evaluation of tumor heterogeneity.

Blockade of HER2 pathway in HER2+/HR+ and HER2+/HR- disease
Combination of trastuzumab with other HER2-targeted therapies (e.g. HER2/HER1 tyrosine kinase inhibitor lapatinib or HER2/HER3 dimerization inhibitor pertuzumab) is reported to improve significantly efficacy of therapy in both HER2+/HR- and HER2+/HR+ disease.
For a 12 weeks dual anti-HER2 therapy (Pertuzumab + Trastuzumab) without chemotherapy, the NEOSPHERE trial reports a pCR rate of 6% (in HER2+/HR+) and 29% in HER2+/HR-[43].

Blockade of HER2 pathway + chemotherapy in HER2+/HR+ and HER2+/HR- disease

Pathological CR rates up to 74% are reported for combination of standard chemotherapy and dual blockade by trastuzumab and lapatinib[123]. Comparable pCR rates of 39%[43] and 47%[38] are reported for even shorter taxane monochemotherapy duration in combination with dual blockade by T + lapatinib or pertuzumab.

Pathological CR rates in HER2+/HR+ tumors are generally lower compared to HR negative tumors. They vary from 15-25% for trastuzumab or lapatinib in combination with (ECx4→Docx4) [31] or 12-week taxane therapy[38,43]. For dual blockade (trastuzumab + pertuzumab or lapatinib) pCR rates from 25[43]-40%[38,124] have been reported.

Interestingly, Bianchini et al. reported different pathways responsible for achieving pCR after combination of chemotherapy with trastuzumab in HR+ and HR- tumors[125].

Due to short follow-up of the studies, no data on a survival impact of increased pCR rates from combination anti-HER2-therapy are available so far.

Blockade of HER2 pathway + endocrine therapy (ET) in HER2+/HR+ tumors

Combinations of anti-HER2 targeted therapies with endocrine therapies have mainly been reported for metastatic breast cancer. The combination of anastrozole with trastuzumab has been reported to prolong progression free survival from 3.8 to 5.6 months[126] . The same is true for the combination of lapatinib + letrozole, which increases PFS from 3.0 to 8.3 vs. letrozole alone[127]. The combinations are generally well tolerated, while toxicity is significantly lower than reported for the corresponding combinations with chemotherapy.

Recently presented neoadjuvant trials provide further evidence for the subgroup of HER2+/HR+ patients. Combination of trastuzumab and lapatinib with endocrine therapy seems to add further significant activity to targeted therapy and to produce pCR rate after 14 weeks of 21% in HR+ and 46% in HR- disease using an anti-HER2 combination alone[128].

Trastuzumab Emtansine (T-DM1) in HER2+ BC

T-DM1 is composed of the following components: DM1, an anti-microtubule agent derived from maytansine; and succinimidyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate (SMCC), a thioether linker molecule used to conjugate DM1 to trastuzumab. It provided excellent tumor response and preliminary better PFS data (compared to standard docetaxel + trastuzumab combination) in a phase II study with excellent toxicity profile [129]. Currently, the EMILIa study provided further excellent data on T-DM1 offering significant advantage in EFS and OS over standard capecitabine + lapatinib in the second-line treatment of BC with moderate toxicity profile[130].

In summary, HER2+/HR+ tumors remain a not well-defined subgroup of BC, where numerous questions have to be answered to guide the next generation of adjuvant trials:

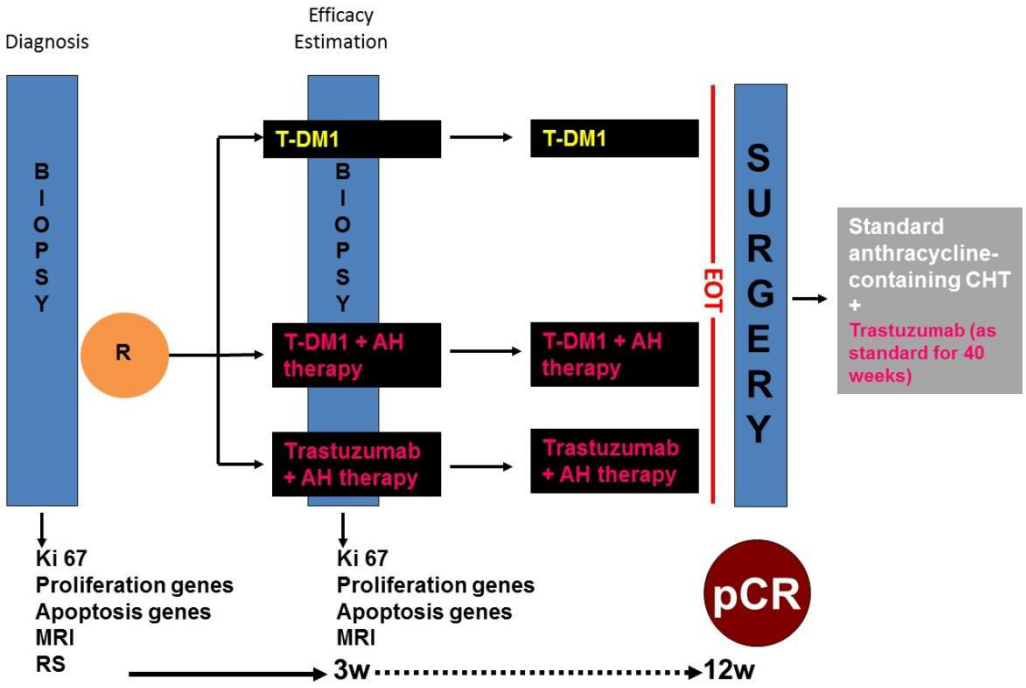
- direct comparison of standard (T + taxane) vs. T + endocrine therapy
- direct comparison of standard (T + taxane) vs. dual blockade/optimal anti-HER2 therapy + endocrine therapy
- direct comparison of standard (T + taxane) vs. new compounds like T-DM1
- direct comparison of standard (T + taxane) vs. T + endocrine therapy
- direct comparison of standard (T + taxane) vs. new compounds like T-DM1 +/- P

The ADAPT philosophy – A combined static and dynamic model

	Early response assessment in eBC may be essential to separate sub-populations with large or marginal benefit from therapy. Drop of proliferative activity after a short course of endocrine therapy (2 weeks to 4 months) as measured by proliferation marker Ki-67 is an excellent predictor for local as well as systemic outcome in HR+ disease. It allows to identify groups of patients with excellent outcome in both low and higher risk groups independently from chemotherapy application[25-27]. ADAPT applies this dynamic model to all early breast cancer subtypes. First step is a broad baseline assessment (conventional central pathology, RS, biomarker) of prognosis. Sequential tissue sampling is realized (3 week interval, core biopsies and surgery) after a short induction anti-HER2/cht/endocrine- treatment. Thus, besides baseline prognosis estimation (***static* assessment**), therapy efficacy is evaluated at an early time of treatment (***dynamic* assessment**). Beyond baseline biomarker assessment, the primary endpoint of the ADAPT HER2+ and TN or HER2+/HR+ protocols is the definition of molecular surrogate markers predictive for pCR and 5 year event-free survival. The ADAPT-principle of the trial is flexible enough to incorporate modifications based on new translational or clinical research data from HER2+ eBC. The trial will also establish and validate a model which allows rapid testing of various targeted and conventional (and combinations thereof) therapy approaches in a multicenter setting.
Rationale	Patients with HER2+/HR+ BC have a significantly better prognosis than patients with HER2+/HR- disease. Chemotherapy is regarded as a standard therapy for HER2 positive BC. Yet, it has never been compared to endocrine therapy in the subgroup of HER2+/HR+ BC, because responsiveness to endocrine treatment was questioned based on controversial data. Benefits from standard chemotherapy may not outweigh its toxicity and long-term morbidity in this subgroup. T-DM1 is a new compound composed of the following components: DM1, an anti-microtubule agent derived from maytansine; and succinimidyl 4-[N-maleimidomethyl] cyclohexane-1-carboxylate (SMCC), a thioether linker molecule used to conjugate DM1 to trastuzumab. It provided excellent tumor response and better preliminary PFS data compared to standard docetaxel + trastuzumab combination in a phase II study (Perez et al. ESMO 2010, Hurvitz et al ESMO 2011). The toxicity profile is excellent and significantly lower than for the chemotherapy standard. These data make T-DM1 an ideal candidate for treatment of the HER2+/HR+ subpopulation. Currently, the EMILIa study provided further excellent data on T-DM1 offering significant advantage in EFS and OS over standard capecitabine + lapatinib in the second-line treatment of BC with moderate toxicity profile[130]. In ADAPT HER2+/HR+, T-DM1 is compared vs. T-DM1 + endocrine therapy vs. Trastuzumab + endocrine therapy for 12 weeks. After surgery, patients receive standard chemotherapy (4 x EC → 12 x Pac). Patients achieving a pCR after 12 weeks may decide for a taxane-free chemotherapy (4x EC →Trastuzumab) in an informed consent process. After *static* baseline assessment of prognosis/breast MRI at study entry *dynamic* biomarker profile in HER2+ and HR+ (ER and/or PR) BC after a short duration of anti-HER2 therapy is evaluated by an early sequential jet needle biopsy and breast MRI. Biomarker/breast MRI changes correlating with pCR are identified.
Objectives	Run-in phase concept: <u>Primary objective</u> • Identification of molecular markers correlating with early response/pCR • Feasibility/reproducibility of assessment of these markers • Validation of statistical assumptions made for the whole sub-trial

	Run-in + Main phase concept: <u>Primary objectives</u> • Comparison of the pathological complete response rates in patients with HER2+/HR+ breast cancer (HER2+/HR+: HER2+/ER+ and/or PR+) treated by pre-surgical T-DM1 with or without standard endocrine therapy or trastuzumab with endocrine therapy given for a total of 12 weeks • Evaluation of dynamic testing (based on proliferation/apoptosis changes in serial biopsy and/or imaging by ultrasound/breast MRI) after three weeks of treatment as a surrogate parameter for response (pCR (residual cancer burden (RCB) 0-1) or resistance/low response (RCB II-III or progressive disease) <u>Secondary objectives</u> • Evaluation of dynamic test regarding prediction of 5-year event-free survival (EFS) • Overall survival • Relapse free survival • Local/regional relapse free survival • Toxicity/cardiac safety • Overall safety in the three treatment arms • Cost-effectiveness • <u>Exploratory analysis</u> • Survival of patients with pCR
Trial design	Prospective, multi-center, controlled, non-blinded, randomized phase II
Treatment	**Neoadjuvant Treatment:** Patients with HER2+/HR+ (HER2+ and ER+ and/or PR+) tumor will receive single agent T-DM1 for 12 weeks (3,6 mg/kg q3w) with or without standard endocrine therapy (tamoxifen in premenopausal women and an aromatase inhibitor in postmenopausal women, if no contraindications are present, in a standard daily dosage). The control group will receive trastuzumab in 3-weekly schedule (8 mg/kg as loading dose and then 6 mg/kg q3w) in combination with the same standard endocrine therapy, if no contraindications are existent. In patients with HER2 positive or triple negative tumors and significant tumor burden after 12 weeks of neoadjuvant therapy the neoadjuvant therapy may be prolonged as **<u>post-study treatment</u>**. The remaining tumor burden must be proven histologically, i.e. the tumor sample will be sent to the central pathology. **Breast Surgery:** After completion of 12 weeks (or prolonged) neoadjuvant treatment for all patients, surgery is planned. In case of disease progression treatment will be stopped prematurely and surgery will be performed immediately. (SLN see ADAPT Umbrella). **Adjuvant Treatment:** Patients should receive standard adjuvant treatment with EC (4 cycles) and paclitaxel weekly (12 cycles) and should complete for 52 weeks of trastuzumab. Further postoperative adjuvant therapy should be administered according to current guidelines at physician's/patient's decision. Particularly in T-DM1 containing arms, use of taxanes should be individually indicated depending on degree of pathological tumor response. In case of clinical tumor burden (non-pCR) after 12 weeks, neoadjuvant therapy may be prolonged as stated above.

Chemotherapy may be applied as stated for adjuvant therapy. Total duration of anti-HER2 therapy (neoadjuvant and adjuvant) should be one year.



Response Assessment:
Primary efficacy (i.e. pCR) is defined at time of surgery according to NCCN guidelines (no invasive cancer in both breast and lymph nodes) and based on provided data regarding residual tumor size, proportion of vital cells within invasive carcinoma, number of positive lymph nodes and size of the largest lymph node metastasis and ductal carcinoma in situ.
Based on these criteria residual cancer burden (and other pCR classifications) will be defined for further analysis (Symmans et al, JCO 2007). Further chemotherapy may be omitted only in tumors with no invasive and DCIS patterns.

Safety:
Safety of T-DM1 with or without concurrent endocrine therapy and trastuzumab with concurrent endocrine therapy will be measured by the incidence and severity of adverse events (AE) and serious adverse events (SAE). Frequency and reasons for discontinuation of therapy, modification and interruption will be evaluated in a prospective manner.

Dynamic test:
Drop of proliferation is considered as the key factor for efficacy of the combination therapy. During the run-in phase of the study, immunohistochemical measurement of Ki-67, mRNA-based proliferation (e.g. Ki-67, STK15, Survivin, MYBL2, CCNB1) and apoptosis genes (e.g. Bcl-2, SCUBE2, CASP3) will be performed on all samples from diagnostic and sequential biopsy.
All tumors will undergo central pathology assessment (ER, PR, HER2) for randomization to the study (analysis by Prof. H. Kreipe, Hannover).
PI3k mutation status, PTEN, IGF, p95 stem cell features and reverse phase protein arrays (RPPA) analysis for e.g. ERK/AKT, pS6K/p4EBP6, STAT5 are considered as candidate markers for further analysis for early discrimination of responders and low responders.
Study Examinations:

For timing of baseline examinations and examinations during neoadjuvant treatment please refer to table 1.

Table 1: Study Evaluations for ADAPT HER2+/HR+ Breast Cancer Patients

ASSESSMENT	BL	Cycle 1[4]	Cycle 2[4]	Cycle 3[4]	Cycle 4[4]	EOT	Surgery
week	-3 to 0	1	4	7	10	13	14
Medical history (incl. concomitant medications)	x						
Central pathology review of diagnostic core biopsy	x						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x[2]	x	x	x	x	x	
Serum sample (biomarker analysis)	x[2]		x			x	
Radiology: • Chest X-ray • Bone scan • Liver imaging • Mammography	x[3]						
Breast MRI (optional)	x		x				x prior to surgery
Ultrasound	x		x	x		x	
Clinical assessment	x[2]		x	x		x	
Pregnancy test	x						
ECG and LVEF	x[5]			x			x prior to surgery
Laboratory: • Hematology • Biochemistry	x	x	x	x	x	x	
Surgery							x
(Serious) Adverse Event		continuously					
Concomitant medication	x	continuously					

[1] prior to 2nd administration of study drug
[2] within ≤ 7 days prior to randomization
[3] within 3 months prior to randomization
[4] +/-3 days
[5] within 42 days prior to randomization
LVEF assessment after cycle 3 and then before surgery

Selection of patients

General Inclusion Criteria for ADAPT:

- Female patients, age at diagnosis 18 years and above Histologically confirmed unilateral primary invasive carcinoma of the breast
- Clinical T1 - T4 (except inflammatory breast cancer)
- All clinical N (cN)
- No clinical evidence for distant metastasis (M0)
- Known HR status and HER2 status (local pathology)
- Tumor block available for central pathology review
- Performance Status ECOG ≤ 1 or KI ≥ 80%
- Negative pregnancy test (urine or serum) within 7 days prior to registration in premenopausal patients
- Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements
- The patient must be accessible for treatment and follow-up

	Additional Inclusion criteria for participation in the HER2+/HR+ sub-protocol:
	• Confirmed ER and/or PR positive and HER2+ by central pathology
	• Patients must qualify for neoadjuvant treatment:
	  ○ Clinical cT1c - T4a-c (participation of patients with tumors >cT2 if cN0 is strongly recommended)
	  ○ All clinical N (participation of patients with cN+, irrespective of tumor size is strongly recommended)
	• LVEF ≥ 50%; LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization)
	
	General Exclusion Criteria:
	• Known hypersensitivity reaction to the compounds or incorporated substances
	• Prior malignancy with a disease-free survival of < 10 years, except curatively treated basalioma of the skin, pTis of the cervix uteri
	• Non-operable breast cancer including inflammatory breast cancer
	• Previous or concurrent treatment with cytotoxic agents for any reason after consultation with the sponsor
	• Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry (concurrent participation in non-interventional post authorization safety studies not influencing the primary study endpoints is allowed, e.g. WSG PROTROCA for evaluation of primary/secondary G-CSF prophylaxis)
	• Male breast cancer
	• Concurrent pregnancy; patients of childbearing potential must implement a highly effective (less than 1% failure rate) non-hormonal contraceptive measures during the study treatment
	• Breast feeding woman
	• Sequential breast cancer
	• Reasons indicating risk of poor compliance
	• Patient not able to consent
	
	Additional Exclusion Criteria for participation in the HER2+/HR+ sub-protocol:
	• Known polyneuropathy ≥ grade 2
	• Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study
	• Inadequate organ function (e.g. hepatic impairment, pulmonary disease, etc.)
	• Uncompensated cardiac function (current unstable ventricular arrhythmia requiring treatment, history of symptomatic CHF NYHA classes II-IV), history of myocardial infarction or unstable angina pectoris within 6 months of enrollment, history of severe hypertension, CAD – coronary artery disease)
	• Severe dyspnea
	• Pneumonitis
	• Abnormal blood values:
	  ○ Thrombocytopenia > CTCAE grade 1
	  ○ Increases in ALT/AST > CTCAE grade 1
	  ○ Hypokalaemia > CTCAE grade 1
	  ○ Neutropenia > CTCAE grade 1
	  ○ Anaemia > CTCAE grade 1

Efficacy evaluation	An intention to treat (ITT) analysis will be conducted for all patients. An additional analysis will be conducted among the eligible patients (per protocol)
Statistical considerations	The study comprises a **Run-in phase** (n=130) and a **Main phase** (n=250). Primary endpoint: • **The primary endpoint of the ADAPT HR+/HER2+ study is pCR after 12 weeks of pre-surgical therapy.** Assuming a drop-out rate of 5%, an ITT test collectiveof more than 300 patients is expected. The patients will be randomized to two T-DM1 arms and a trastuzumab + endocrine therapy arm. We expect a 10% rate of pCR in the trastuzumab + endocrine therapy arm. The study aims to test the hypothesis of higher pCR separately in each of the T-DM1 arms. In each case, 25% pCR is assumed. Assuming α= 2.5% (one-sided for each T-DM1 arm), we can detect an improvement of this magnitude with at least 80% power in each of the T-DM1 containing arms compared to the trastuzumab + endocrine therapy arm. Interim analysis on correlation between changes in the sequential biopsy and pCR rates in the first 130 patients (Run-In phase) is planned during ongoing recruitment of patients
Patient number/ Enrolment period	Run-in phase: 130 patients Main phase: 250 patients In total: 380 patients Number of sites: 30 Enrolment start: Q3 2012 Enrolment stop: Q1 2015 Total patient number has been achieved in Q1 2015, enrolment will not start again Follow-up period: 60 months, may be prolonged half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study.

2 Introduction and Background ADAPT HER2+/HR+ Breast Cancer

HER2 over-expressing breast cancer with its aggressive biology remains a major clinical challenge. Over-expression of the HER2 gene is reported in about 10-20% of breast cancers. It is associated with poor prognosis[108], with good response to neoadjuvant chemotherapy[109,110], decreased sensitivity to endocrine therapy[85] and response to targeted therapy such as trastuzumab[33,111]. In about half of the cases there is a co-expression of hormone receptors (ER and/or PR) and HER2 receptor (so called HER2+/HR+ (HER2+/HR+) cases).

Trastuzumab is a monoclonal antibody against the HER2 receptor. Its use leads to activation of antibody-dependent cellular cytotoxicity, inhibition of extracellular domain cleavage, abrogation of intracellular signaling, reduction of angiogenesis, and decreased DNA repair. These effects are increased by combination with a wide range of anti-cancer agents.
The use of trastuzumab changed the perception of HER2+ metastatic breast cancer as it rendered prognosis of HER2+ patients treated with trastuzumab-based chemotherapy comparable to that of patients with HER2- disease[112]. In the adjuvant setting, the use of trastuzumab (for one year[34] or shorter[113]) sequentially[34] or simultaneously[35] to an adjuvant chemotherapy backbone is associated with a reduction of the relapse risk by about 50%.
In HER2+ early breast cancer (eBC), adjuvant trastuzumab (T) therapy for 52 weeks in combination with chemotherapy is considered gold-standard.

Up to now HER2+/HR+ BC and HER2+/HR- disease have not been looked at separately. There is a large body of evidence for poor prognosis of HER2+/HR+ BC compared to HER2 negative cases[114]. Nevertheless, prognosis of HER2+/HR+ BC is essentially better than that of HER2+/HR- controls[45,46].

Relative endocrine resistance/chemotherapy responsiveness of HER2+/HR+ BC
Several studies reported reduced response of HER2+/HR+ tumors to endocrine therapy particularly in the metastatic setting[115]. These reports are supported by preclinical evidence for ER independent growth pathways triggered by HER2/HER1 receptors[116].
However, these data are conflicting and not fully supported by data from adjuvant and neoadjuvant studies. Ellis et al. reported substantial response to letrozole, but reduced response to tamoxifen in HER2+/HR+ tumors[117]. Other adjuvant trials revealed poor outcome for both tamoxifen- and aromatase inhibitors treated HER2+/HR+ tumors[114,118] and similar response of aromatase inhibitors in both HER2+ and HER2- tumors[118].
With respect to chemotherapy responsiveness, the large adjuvant trastuzumab trials reported similar risk reduction ratios for both HR positive and negative disease[46], even though in the neoadjuvant setting pCR rates seem to be lower in HER2+/HR+ than in HER2+/HR- tumors[44].

Role of pCR in HER2 over-expressing BC (HR+/HR-)
Similar to triple negative (ER/PR/HER2 negative) BC, achievement of pathological complete response (pCR) in patients with a HER2+ subtype is associated with significantly better long-term survival as compared to those patients without pCR[30].
Trastuzumab (T)-containing neoadjuvant chemotherapy has been reported to increase the probability of pathological complete response (pCR) in HER2+ disease up to 67%[36,110,119].
In the NOAH trial, the neoadjuvant use of trastuzumab was associated with improved disease-free survival[36].
The TECHNO trial is the first trial reporting a significant association between pCR after neoadjuvant anti-HER2 therapy (together with chemotherapy) and improved survival in HER2+ disease[31].
Thus, pCR in HER2 over-expressing BC is a validated surrogate parameter for patient outcome and survival.
For **HER2+/HR+ breast cancer,** these data have to be confirmed. A recent meta-analysis presented by von Minckwitz et al. revealed a differential prognostic impact of pCR in HER2+/HR- and HER2+/HR+ tumors. pCR was prognostically significant in HR- tumors, but not in HR+ tumors[120]. These data are not supported by other reports[121].

Dynamic measurement (breast MRI/tumor cell proliferation) as an early surrogate marker for pCR

Recently, neoadjuvant cytotoxic and/or tailored therapies have been suggested as an important tool for evaluation of response to a given systemic therapy *in vivo*. Clinical response measured by sequential evaluation of different proliferation markers (such as Ki-67) following a course of neoadjuvant chemotherapy has been demonstrated to correlate significantly with an increased risk of relapse in patients not achieving pCR[122]. Summing up divergent effects of several anti-HER2 therapies on proliferation, it would be clinically relevant to evaluate such proliferation tools for early prediction of combination therapy efficacy (chemotherapy and HER2 targeted therapy). So far, it remains unclear which method of proliferation measurement is the optimal marker for response evaluation regarding combined chemo-anti-HER2 therapy. However, measurement of proliferation and apoptosis as well as assessment of changes in PI3K/AKT, IGF and stem cell signaling after a short course of therapy could provide a unique signature for *dynamic* response evaluation and selecting patients for mono vs. combined targeted treatment.

Another way to assess early response could be **molecular imaging** by breast MRI (or other functional dynamic imaging), given the strong evidence, particularly in HER2+ and triple negative breast cancer[52,53]

Changes in contrast medium kinetics in contrast-enhanced MRI (DCE-MRI) or of the ADC (apparent diffusion coefficient) in the diffusion-weighted MRI or drop of the cholin peak in the ^{1}H-MR-Spektroskopy already after short induction therapy are possible measurement instruments for an imaging approach as an alternative non-invasive and complimentary method for dynamic patient stratification within the trial. A further advantage of breast MRI is an analysis of whole tumor (and not only a single biopsy area) and better evaluation of tumor heterogeneity.

Blockade of HER2 pathway in HER2+/HR+ and HER2+/HR- disease

Combination of trastuzumab with other HER2-targeted therapies (e.g. HER2/HER1 tyrosine kinase inhibitor lapatinib or HER2/HER3 dimerization inhibitor pertuzumab) is reported to improve significantly efficacy of therapy in both HER2+/HR- and HER2+/HR+ disease.

For a 12 weeks dual anti-HER2 therapy (Pertuzumab + Trastuzumab) without chemotherapy, the NEOSPHERE trial reports a pCR rate of 6% (in HER2+/HR+) and 29% in HER2+/HR-[43].

Blockade of HER2 pathway + chemotherapy in HER2+/HR+ and HER2+/HR- disease

Pathological CR rates up to 74% are reported for combination of standard chemotherapy and dual blockade by trastuzumab and lapatinib[123]. Comparable pCR rates of 39%[43] and 47%[38] are reported for even shorter taxane monochemotherapy duration in combination with dual blockade by T + lapatinib or pertuzumab.

Pathological CR rates in HER2+/HR+ tumors are generally lower compared to HR negative tumors. They vary from 15-25% for trastuzumab or lapatinib in combination with (ECx4→Docx4) [31] or 12-week taxane therapy[38,43]. For dual blockade (trastuzumab + pertuzumab or lapatinib) pCR rates from 25[43]-40%[38,124] have been reported.

Interestingly, Bianchini et al. reported different pathways responsible for achieving pCR in combination of chemotherapy with trastuzumab in HR+ and HR- tumors[125].

Due to short follow-up of the studies, no data on a survival impact of increased pCR rates from combination therapy are available so far.

Blockade of HER2 pathway + endocrine therapy (ET) in HER2+/HR+ tumors

Combinations of anti-HER2 targeted therapies with endocrine therapies have mainly been reported for metastatic breast cancer. The combination of anastrozole with trastuzumab has been reported to prolong progression free survival from 3.8 to 5.6 months[126] . The same is true for the combination of lapatinib + letrozole, which increases PFS from 3.0 to 8.3 vs. letrozole alone[127]. The combinations are generally well tolerated, while toxicity is significantly lower than reported for the corresponding combinations with chemotherapy.

Recently presented neoadjuvant trials provide further evidence for the subgroup of HER2+/HR+ patients. Combination of trastuzumab and lapatinib with endocrine therapy seems

to add further significant activity to targeted therapy and to produce pCR rate after 14 weeks of 21% in HR+ and 46% in HR- disease using an anti-HER2 combination alone[128].

T-DM1 in HER2+ BC
A combination approach of trastuzumab (T) with a linker to the cytotoxic drug DM1 **(**T-DM1) (trastuzumab emtansine) provided excellent tumor response and preliminary better PFS data (compared to standard docetaxel + trastuzumab combination) in a phase II study with excellent toxicity profile[129]. Currently, the EMILIa study provided further excellent data on T-DM1 offering significant advantage in EFS and OS over standard capecitabine + lapatinib in the second-line treatment of BC with moderate toxicity profile[130].

In summary, HER2+/HR+ tumors remain a not well-defined subgroup of BC, where numerous questions have to be answered to guide the next generation of adjuvant trials:
- direct comparison of standard (T + taxane) vs. T + endocrine therapy
- direct comparison of standard (T + taxane) vs. dual blockade/optimal anti-HER2 therapy + endocrine therapy
- direct comparison of standard (T + taxane) vs. new compounds like T-DM1
- direct comparison of standard (T + taxane) vs. T + endocrine therapy
- direct comparison of standard (T + taxane) vs. new compounds like T-DM1+/- P

The ADAPT philosophy – A combined static and dynamic model
Early response assessment in eBC may be essential to separate subpopulations with large or marginal benefit from therapy.
Drop of proliferative activity after a short course of endocrine therapy (2 weeks to 4 months) as measured by proliferation marker Ki-67 is an excellent predictor for local as well as systemic outcome in HR+ disease. It allows to identify groups of patients with excellent outcome in both low and higher risk groups independently from chemotherapy application[25-27]. ADAPT applies this dynamic model to all early breast cancer subtypes. First step is a broad baseline assessment (conventional central pathology, RS, biomarker) of prognosis. Sequential tissue sampling is realized (3 week interval, core biopsies and surgery) after a short induction anti-HER2/cht/endocrine- treatment. Thus, besides baseline prognosis estimation (***static* assessment**), therapy efficacy is evaluated at an early time of treatment (***dynamic* assessment**).
Beyond baseline biomarker assessment, the primary endpoint of the ADAPT HER2+ and TN protocols is the definition of molecular surrogate markers predictive for pCR and 5 year event-free survival.
The ADAPT-principle of the trial is flexible enough to incorporate modifications based on new translational or clinical research data from HER2+ eBC. The trial will also establish and validate a model which allows rapid testing of various targeted and conventional (and combinations thereof) therapy approaches in a multicenter setting.

3 Rationale ADAPT HER2+/HR+ Breast Cancer

Patients with HER2+/HR+ BC have a significantly better prognosis than patients with HER2+/HR- disease. Chemotherapy is regarded as a standard therapy for HER2 positive BC. Yet, it has never been compared to endocrine therapy in the subgroup of HER2+/HR+ BC, because responsiveness to endocrine treatment was questioned based on controversial data. Benefits from standard chemotherapy may not outweigh its toxicity and long-term morbidity in this subgroup.
T-DM1 is a new compound combining trastuzumab with a linker to the cytotoxic drug DM1 providing excellent tumor response and better preliminary PFS data compared to standard docetaxel + trastuzumab combination in a phase II study (Perez et al. ESMO 2010, Hurvitz et al. 2011). The toxicity profile is excellent and significantly lower than for the chemotherapy standard. These data make T-DM1 an ideal candidate for treatment of the HER2+/HR+ subpopulation. Currently, the EMILIa study provided further excellent data on T-DM1 offering

significant advantage in EFS and OS over standard capecitabine+lapatinib in the second-line treatment of BC with moderate toxicity profile[130].
In ADAPT HER2+/HR+, T-DM1 is compared vs. T-DM1 + endocrine therapy vs. Trastuzumab + endocrine therapy for 12 weeks. After surgery, patients receive standard 4 x EC → 12 x Pac). Patients achieving a pCR after 12 weeks of neoadjuvant treatment within this protocol may decide for a taxane-free chemotherapy in an informed consent process.
After *static* baseline assessment of prognosis/breast MRI at study entry *dynamic* biomarker profile in HER2+ and HR+ (ER and/or PR) BC after a short duration of anti-HER2 therapy is evaluated by an early sequential jet needle biopsy and breast MRI.
Biomarker/breast MRI changes correlating with pCR are identified.

4 Study Objectives ADAPT HER2+/HR+ Breast Cancer

Primary objectives
Run-in Phase:

- Identification of molecular markers correlating with early response/pCR
- Feasibility/reproducibility of assessment of these markers
- Validation of statistical assumptions made for the whole sub-trial

Run-in phase + main phase

- Comparison of the pathological complete response rates in patients with HER2+/HR+ breast cancer (HER2+/HR+: HER2+/ER+ and/or PR+) treated by pre-surgical T-DM1 with or without standard endocrine therapy or trastuzumab with endocrine therapy given for a total of 12 weeks
- Evaluation of dynamic testing (based on proliferation/apoptosis changes in serial biopsy and/or imaging by ultrasound or breast MRI) after three weeks of treatment as a surrogate parameter for response (pCR or residual cancer burden (RCB) 0-1) or resistance/low response (RCB II-III or progressive disease)

Secondary objectives

- Evaluation of dynamic test regarding prediction of 5-year event-free survival (EFS)
- Overall survival
- Relapse free survival
- Local/regional relapse free survival
- Toxicity/cardiac safety
- Overall safety in the three treatment arms
- Cost-effectiveness

Tertiary objectives

- Evaluation of all molecular, pathological and clinical markers and their combinations in terms of predictive and prognostic value

Additional translational research questions occurring during the trial will be defined in sub-protocols.

Exploratory analysis

- Survival of patients with pCR with and without further chemotherapy

5 Study Design ADAPT HER2+/HR+ Breast Cancer

The ADAPT HER2+/HR+ breast cancer sub-trial is a modern biomarker-based adjuvant, prospective, multi-center, controlled, non-blinded, randomized phase II trial.

Following the diagnostic core biopsy and identification of a HER2+/HR+ tumor, the patients meeting the inclusion/exclusion criteria will be registered for the trial, after informed consent was obtained. The patient will be randomized right from the beginning to either T-DM1 monotherapy, T-DM1 + endocrine therapy or Trastuzumab + endocrine therapy. Patients will be treated for three weeks with the respective regimen for induction treatment and will then undergo the second core biopsy for efficacy estimation and response assessment. After completion of 12 weeks of targeted therapy with either of the three treatment arms the patients will undergo surgery and pCR will be assessed.
Patients achieving a pCR after 12 weeks of neoadjuvant treatment as defined in this protocol may decide for a taxane-free chemotherapy in an informed consent process.
Patients without pCR will be treated with a standard of care post-study adjuvant chemotherapy regimen (EC followed by any taxane) following the surgery and will receive treatment with trastuzumab for 40 weeks to complete 52 weeks of trastuzumab treatment. Further postoperative adjuvant therapy should be administered according to current guidelines at physician's/patient's decision. Particularly in T-DM1 containing arms, use of taxanes should be individually indicated depending on degree of pathological tumor response. The HER2+/HR+ study design is depicted in figure 1 below.

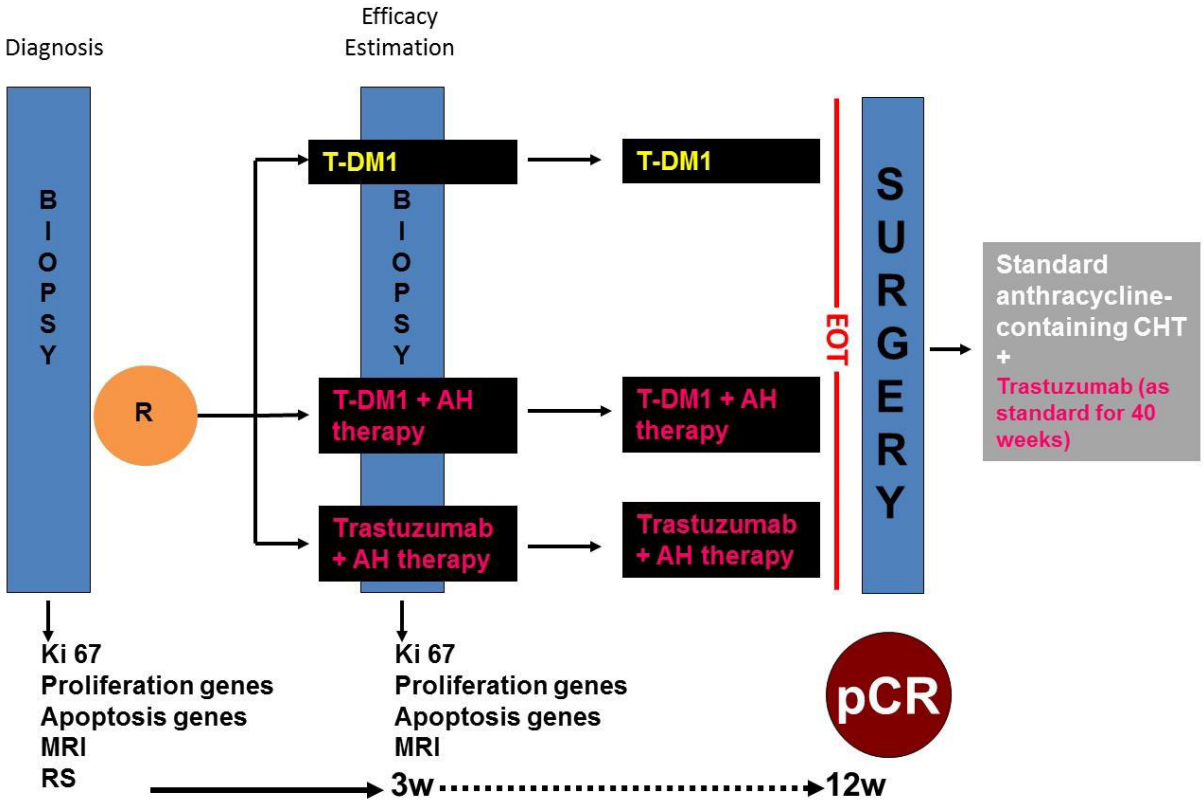


Figure 1: *Study Design for ADAPT HER2+/HR+ Breast Cancer*

5.1 Run-in Phase and Main Phase

For further information please refer to the ADAPT umbrella protocol, chapter 5.1. The run in phase of the HER2+/HR+ protocol will include 130 patients and the main phase 250 patients.

5.2 Timing of Surgery

The surgery is to be done after 12 weeks (or prolonged) neoadjuvant therapy, i.e. following end of therapy.

6 Patient Enrollment

Following the diagnostic core biopsy and local pathology assessment, the patients meeting the inclusion/exclusion criteria will be informed about the ADAPT trial and HER2+/HR+ sub-trial. After signing the informed consent patients will be registered and subsequently randomized to one of the three treatment arms.

The following examinations are mandatory prior to randomization:

Table 1: *Study Evaluations for Participation in ADAPT HER2+/HR+ Breast Cancer Trial*

	INVESTIGATIONS	TIMING
Positive ER and/or PR status **according to local pathology**	✔	Prior to registration (standard of care)
Positive HER2 status **according to local pathology**	✔	Prior to registration (standard of care)
Nodal status	Participation of patients with cN+ is strongly recommended, if cT1c	Prior to registration (standard of care)
Grading		Prior to registration (standard of care)
Ultrasound	✔	Prior to registration (standard of care)
History[1] and physical exam for patients receiving chemotherapy	Physical examination including: • Height • Weight • Karnofsky index for performance status/vital signs	≤ 7 days prior to randomization
LVEF ≥ 50%	Echocardiography	Within 42 days prior to randomization

[1]Within 3 weeks prior to registration

6.1 Additional Inclusion Criteria ADAPT HER2+/HR+ Breast Cancer

In order to be eligible for the participation in the ADAPT HER2+/HR+ breast cancer trial, patients, who meet the general inclusion criteria of the ADAPT trial also have to meet the following additional inclusion criteria:

- Confirmed ER and/or PR positive and HER2+ by central pathology
- Patients must qualify for neoadjuvant treatment:
  - Clinical cT1c - T4a-c (participation of patients with tumors >cT2 if cN0 is strongly recommended)
  - All clinical N (participation of patients with cN+, irrespective of tumor size is strongly recommended)
- LVEF ≥ 50%; LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization)

6.2 Additional Exclusion Criteria ADAPT HER2+/HR+ Breast Cancer

In order to be eligible for the participation in the ADAPT HER2+/HR+ breast cancer trial, patients, who meet the general exclusion criteria of the ADAPT trial **must** also **not** meet any of the following additional exclusion criteria:

- Known polyneuropathy ≥ grade 2
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study
- Inadequate organ function (e.g. hepatic impairment, pulmonary disease, etc.)
- Uncompensated cardiac function (current unstable ventricular arrhythmia requiring treatment, history of symptomatic CHF NYHA classes II-IV), history of myocardial infarction or unstable angina pectoris within 6 months of enrollment, history of severe hypertension, CAD – coronary artery disease)
- Severe dyspnea
- Pneumonitis
- Abnormal blood values:
  - Thrombocytopenia > CTCAE grade 1
  - Increases in ALT/AST > CTCAE grade 1
  - Hypokalaemia > CTCAE grade 1
  - Neutropenia > CTCAE grade 1
  - Anaemia > CTCAE grade 1

6.3 Randomization to ADAPT HER2+/HR+ Breast Cancer

Each eligible patient will be registered and subsequently randomized after informed consent was obtained, to receive either:

Arm A: T-DM1 monotherapy
- Trastuzumab Emtansine (T-DM1) (3.6 mg/kg) q3w for 12 weeks

or

Arm B: T-DM1 + endocrine therapy
- Trastuzumab Emtansine (T-DM1) (3.6 mg/kg) q3w for 12 weeks + daily Tamoxifen (20 mg) (premenopausal women) or Aromatase inhibitors (letrozole (2.5 mg), anastrozole (1 mg) or exemestane (25mg) for postmenopausal women) for 12 weeks

or

Arm C: Trastuzumab + endocrine therapy
- Trastuzumab (8 mg/kg initial dose, 6 mg/kg q3w for 12 weeks) + daily Tamoxifen (20 mg) (premenopausal women) or Aromatase inhibitors (letrozole (2.5 mg), anastrozole (1 mg) or exemestane (25mg) for postmenopausal women) for 12 weeks

The randomization forms have to be filled in online in the e-CRF. After completion it has to be printed, signed by an investigator and faxed to the coordinator of the study:

Fax: +49 (0)611 160248 - 29

The following information will be requested:

- Institution name
- Investigator's name
- Patient's identifiers (site number, patient code)
- Patient's birth date (day/month/year)
- Type of tumor (HR+/HER2-, HER2+/HR-, HER2+/HR+ or TN)

A patient who was not randomized prior to the first treatment administration will not be accepted for the study at a later date.

The patient randomization result will be available in the e-CRF within 24 hours after the randomization request fax was obtained.

6.3.1 **Arm A: T-DM1 Monotherapy**

T-DM1

Dose:	3.6 mg/kg bodyweight, day 1
Route:	90 minutes (± 10 minutes) intravenous infusion for first administration; 30 minutes (± 10 minutes) for subsequent administrations, if prior infusions were well tolerated
Schedule:	Every 3 weeks

This is called a cycle of treatment and is to be given four times.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

6.3.2 **Arm B: T-DM1 + endocrine therapy**

T-DM1

Dose:	3.6 mg/kg bodyweight, day 1
Route:	90 minutes (± 10 minutes) intravenous infusion for first administration 30 minutes (± 10 minutes) for subsequent administrations, if prior infusions were well tolerated
Schedule:	Every 3 weeks

This is called a cycle of treatment and is to be given four times.

Endocrine therapy

Tamoxifen (in premenopausal women)

Dose:	20 mg
Route:	Per os
Schedule:	Daily

Letrozole (in postmenopausal women)

Dose:	2.5 mg
Route:	Per os
Schedule:	Daily

or

Anastrozole (in postmenopausal women)

Dose:	1 mg
Route:	Per os
Schedule:	Daily

or

Exemestane (in postmenopausal women)

Dose:	25 mg
Route:	Per os
Schedule:	Daily

21 days of endocrine treatment are considered as a cycle of treatment and is to be given four times.

6.3.3 **Arm C: Trastuzumab + endocrine therapy**

Trastuzumab
Initial dose: 8 mg/kg bodyweight, day 1 of initial administration
Preservation dose: 6 mg/kg bodyweight, day 1 of subsequent administrations
Route: Intravenous infusion
Schedule: Every 3 weeks

This is called a cycle of treatment and is to be given four times.

Endocrine therapy

Tamoxifen (in premenopausal women)
Dose: 20 mg
Route: Per os
Schedule: Daily

Letrozole (in postmenopausal women)
Dose: 2.5 mg
Route: Per os
Schedule: Daily

or

Anastrozole (in postmenopausal women)
Dose: 1 mg
Route: Per os
Schedule: Daily

or

Exemestane (in postmenopausal women)
Dose: 25 mg
Route: Per os
Schedule: Daily

21 days of endocrine treatment are considered as a cycle of treatment and is to be given four times.

7 Study Plan ADAPT HER2+/HR+ Breast Cancer

7.1 Definition of Study Medication ADAPT HER2+/HR+ Breast Cancer

For the purpose of this sub-trial trastuzumab emtansine (T-DM1) and trastuzumab for neoadjuvant treatment will be labeled study-specific and is considered study medication. Trastuzumab after surgical treatment as well as endocrine therapy will be commercial ware and will not be labeled study-specific. The Investigational Medicinal Product (IMP) status of trastuzumab within the ADAPT HER2+/HR+ sub-trial will expire with completion of neoadjuvant treatment, i.e. with end of treatment prior to surgery.
Documentation of preparation and distribution of the study medication has to be documented in accordance with the Investigator's Brochure.

7.2 Study Treatment ADAPT HER2+/HR+ Breast Cancer

For induction treatment patients will receive either T-DM1 monotherapy, T-DM1 + endocrine therapy (tamoxifen in premenopausal and aromatase inhibitors in postmenopausal women) or trastuzumab + endocrine therapy (tamoxifen in premenopausal and aromatase inhibitors in postmenopausal women) for 3 weeks.
After completion of induction treatment, patients will get a second core biopsy for efficacy estimation. The treatment regimen from induction treatment will be continued for three further cycles until end of treatment and surgery.
Study treatment should be discontinued in case of disease progression and the patient should undergo surgery.
In case of clinical tumor burden (non-pCR) after 12 weeks, neoadjuvant therapy may be prolonged as stated below. Chemotherapy may be applied as stated for adjuvant therapy. Total duration of anti-HER2 therapy (neoadjuvant and adjuvant) should be one year.
Further postoperative adjuvant therapy should be administered according to current guidelines at physician's/patient's decision. Particularly in T-DM1 containing arms, use of taxanes should be individually indicated depending on degree of pathological tumor response.

7.2.1 T-DM1 Formulation, Preparation and Storage

Trastuzumab emtansine (T-DM1) is provided as a single-use lyophilized formulation in a colorless 20-mL Type I glass vial closed by means of a FluroTec-coated stopper and an overseal with flip-off cap. Upon receipt of T-DM1, vials should be refrigerated at 2°C–8°C (36°F−46°F) until use.

VIAL MUST NOT BE FROZEN OR SHAKEN. T-DM1 must be stored in the original carton to protect from light. Do not use beyond the expiration date provided by the manufacturer. The reconstituted product contains no preservative and is intended for single use only. Any remaining medication should be discarded.
All vials of T-DM1 should be handled by appropriately trained site staff wearing gloves and using appropriate procedures in place at the clinical site for preparation of chemotherapeutic drugs. Vials should be visually inspected upon receipt to ensure that they are intact without exterior contamination. Discard any cracked vials and report vials with surface contamination to the clinical site manager for assessment.
The lyophilized product should be reconstituted using Sterile Water for Injection (SWFI). Using a new syringe, 8 mL SWFI should be added to the vial and the vial swirled gently until the product is completely dissolved. The vial should not be shaken. The resulting product contains 20 mg/mL T-DM1, 10 mM sodium succinate, pH 5.0, 60 mg/mL sucrose, and 0.02% (w/v) polysorbate 20. Each 20 mL vial contains enough T-DM1 to allow delivery of 160 mg T-DM1. The reconstituted product contains no preservative and is intended for single use only.
The vial should be inspected to ensure the reconstituted product is a clear colorless solution, and is free of particulates before proceeding. Drug from any vial that appears abnormal upon inspection should not be administered to patients. Using a new syringe, the indicated volume

of T-DM1 solution should be removed from the vial(s) and added to the IV bag containing at least 250 mL of 0.45% sodium chloride (preferred) or 0.9% sodium chloride injection and gently inverted to mix the solution. A 0.22 micron non-protein adsorptive polyethersulfone (PES) in-line filter is recommended when using 0.45% sodium chloride and required when using 0.9% sodium chloride injection. The solution of T-DM1 should not be shaken.
The solution of T-DM1 for infusion should be used immediately. If not used immediately, storage times should not be longer than 24 hours at 2°C−8°C (36°F−46°F) for solutions of T-DM1 diluted in polyvinyl chloride (PVC) or latex-free PVC-free polyolefin, polypropylene, or polyethylene bags containing 0.45% or 0.9% Sodium Chloride Injection, USP.
For additional details, please refer to the current version of the T-DM1 Investigator Brochure.

7.2.2 **Dosing and Administration – T-DM1**

T-DM1 will be administered on day 1 of a 3-week cycle every 3 weeks at a dose of 3.6 mg/kg bodyweight as intravenous infusion. The total dose will be calculated based on the patient's weight on day 1 of (or up to 3 days before) each cycle with no upper limit.
T-DM1 doses may be reduced to as low as 2.4 mg/kg, according to the dose-modification guidelines in chapter 9.1.1 of the HER2+/HR+ sub-protocol. Dose delays of up to 42 days from last administered dose are permitted.
If the timing of a protocol-mandated procedure such as administration of T-DM1 coincides with a holiday that precludes the procedure, the procedure should be performed within 3 business days of the scheduled date and, when possible, on the earliest following date, with subsequent protocol-specified procedures rescheduled accordingly.
The first infusion of T-DM1 will be administered over 90 minutes (± 10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs must be assessed before and after dose administration. Following the initial dose, patients will be observed for at least 60 minutes for fever, chills, or other infusion-associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions) subsequent doses of T-DM1 may be administered over 30 minutes (± 10 minutes), with a minimum 30-minute observation period after infusion.
Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable.
Premedication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, anti-histamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.

7.2.3 **Dosing and Administration – Trastuzumab**

IV trastuzumab will be administered as described in the Herceptin® SmPC/local prescribing information and Investigator Brochure. Weight should be recorded at screening and prior to subsequent IV trastuzumab infusions. An initial loading dose of 8 mg/kg should be given for the first cycle (induction therapy). All other doses are 6 mg/kg trastuzumab every 3 weeks for another 3 cycles.
The first infusion of IV trastuzumab should be given over approximately 90 minutes. If the initial dose of IV trastuzumab was well tolerated, subsequent doses can be administered as a 30-minute infusion. It is recommended to observe patients at the start of infusion for fever, chills and other infusion-related symptoms. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. All infusion-related symptoms must have resolved before the patient is discharged, unless deemed clinically not significant by the investigator. Patients, who experience infusion-related symptoms may be pre-medicated with paracetamol and antihistamines for subsequent infusions at the discretion of the investigator.

7.2.4 End of Treatment (EOT) Definition ADAPT HER2+/HR+ Breast Cancer

End of treatment is defined as 21 days after the last application of study drug and prior to surgery. pCR will be the target endpoint of the study. Further postoperative adjuvant therapy should be administered according to current guidelines at physician's/patient's decision. Particularly in T-DM1 containing arms, use of taxanes should be individually indicated depending on degree of pathological tumor response.

7.2.5 End of Study

End of study is defined as database closure.

7.2.6 Prophylactic Premedication Regimen

Premedication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, anti-histamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.

7.2.7 Concomitant Treatment during Targeted Treatment

For permitted prophylactic premedication please refer to the previous chapter.
Ancillary treatments will be given as medically indicated. Any concomitant medication must be documented in the Case Report Form.

7.3 Post-Study Treatment – Adjuvant Chemotherapy

In case of clinical tumor burden (non-pCR) after 12 weeks, neoadjuvant therapy may be prolonged as stated below. Chemotherapy may be applied as stated for adjuvant therapy. Total duration of anti-HER2 therapy (neoadjuvant and adjuvant) should be one year.
After completion of 12 weeks of neoadjuvant targeted study treatment and surgery, post-study treatment by adjuvant chemotherapy is at the discretion of the investigator. Standard anthracycline-containing adjuvant chemotherapy is highly recommended. Further postoperative adjuvant therapy should be administered according to current guidelines at physician's/patient's decision. Particularly in T-DM1 containing arms, use of taxanes should be individually indicated depending on degree of pathological tumor response.
If the patients are treated by post-study standard adjuvant chemotherapy, the patients should be treated by trastuzumab for 40 weeks to complete 52 weeks of trastuzumab treatment.

7.4 Follow-up

For the follow-up please refer to the ADAPT protocol, chapter 7.10.

7.4.1 Therapy after Protocol Treatment is discontinued

Except for study targeted therapy and radiotherapy as per protocol, no further antitumor therapy is allowed (surgery, chemotherapy, immunotherapy, etc.) before tumor relapse is documented.
If patients are removed from the study because of disease relapse, further treatment is at the discretion of the investigator. The metastatic regimen(s) used will be documented in the Case Report Form.

8 Study Evaluations ADAPT HER2+/HR+ Breast Cancer

8.1 Evaluation during Targeted Treatment

While under targeted treatment, all patients must be examined according to the schedule outlined below until they come off therapy.

Table 2: *Study Evaluations before each Cycle of Treatment*

ASSESSMENT	BL	Cycle 1[4]	Cycle 2[4]	Cycle 3[4]	Cycle 4[4]	EOT	Surgery
week	-3 to 0	1	4	7	10	13	14
Medical history (incl. concomitant medications)	x						
Central pathology review of diagnostic core biopsy	x						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x[2]	x	x	x	x	x	
Serum sample (biomarker analysis)	x[26]		x[6]			x[6]	
Radiology: • Chest X-ray • Bone scan • Liver imaging • Mammography	x[3]						
Breast MRI (inclusion of patients without MRI is allowed)	x[6]		x[6]				x[6] prior to surgery
Ultrasound	x		x	x		x	
Clinical assessment	x[2]		x	x		x	
Pregnancy test	x						
ECG and LVEF	x[5]			x			x prior to surgery
Laboratory: • Hematology • Biochemistry	x	x	x	x	x	x	
Surgery or confirmation of non-pCR							x
(Serious) Adverse Event		continuously					
Concomitant medication	x	continuously					

[1] prior to 2nd administration of study drug
[2] within ≤ 7 days prior to randomization
[3] within 3 months prior to randomization
[4] +/-3 days
[5] within 42 days prior to randomization
[6] optionally

Physical examination will include:

- Weight
- ECOG or Karnofski index for performance status
- Clinical tumor assessment

Laboratory work-up will include:
Hematology:

- Hemoglobin
- WBC
- Neutrophils
- Platelets count

Biochemistry:

- Alkaline phosphatase
- ASAT (SGOT)
- ALAT (SGPT)
- Bilirubin
- Serum creatinine
- Creatinine clearance
- Electrolytes: Na^+, K^+, Cl^-

8.2 Evaluation at End of Induction Treatment

Please refer to chapter 7.8 of the ADAPT protocol for further information.

8.3 Evaluation at End of Treatment (EOT)

To be performed at latest 21 days after the last treatment and/or prior to surgery. Work-up will include:

- Physical examination with Karnofsky Index or ECOG
- Hematology, biochemistry
- Documentation of toxicity

8.4 Evaluation in Follow-up after End of Treatment

Patients will be followed every 6 months for two years after registration and every 12 months thereafter until year 5 (corresponding to German aftercare plan) or until relapse to document:

- Event-free survival
- Overall survival
- Further therapy (and/or endocrine treatment/treatment with Herceptin)
- Relapse (local relapse)
- 2nd primary malignancy
- First treatment for metastatic breast cancer or 2nd primary malignancy
- Results for biopsy of distant metastases
- Yearly evaluation of lifestyle parameter (optional)

Timing of follow-up visits is based on the date of registration. Follow-up visits will be scheduled at month 6, 12, 18, 24, 36, 48, and 60 after registration.
Patients who relapse or suffer from 2nd primary malignancy will only be followed for survival. For any distant metastasis occurring, if biopsied, IHC should be reported in the CRF.

Patients completing follow-up month 60 may be followed half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study, provided that an additional informed consent regarding prolongation of the follow-up was signed.

8.5 Response Assessment

Please refer to the ADAPT Umbrella protocol chapter 8.6.

9 Dose Delays and Reduction/Modification ADAPT HER2+/HR+ Breast Cancer

9.1 Treatment Dose Adjustments and Treatment Delays

Toxicities will be graded using the NCI Common Toxicity Criteria (NCI CTC), version 4.0.

Dose reduction is planned for each treatment arm in case of severe hematological and/or non-hematological toxicities. Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. In case of several toxicities in one patient and conflicting recommendations, the most conservative dose adjustment has to be followed.
Doses which have been reduced for toxicity must not be re-escalated.

9.1.1 Dose Adjustments and Treatment Delays – T-DM1

Treatment with T-DM1 may be delayed no more than 42 days to allow recovery from acute toxicity.

Patients should be assessed for toxicity prior to each dose. Dosing will occur only, if the clinical assessment and laboratory test values are acceptable.
Dose delays and reductions are designed to maximize treatment for those who derive clinical benefit from treatment, while ensuring patient safety.
Dose delays for T-DM1-related toxicity are specified in Appendix 1 – Treatment Dose Adjustments and Treatment Delays for ADAPT HER2+/HR+ Breast Cancer.

The following dose-reduction levels are applicable for treatment with T-DM1:
Dose level: − **0** 3.6 mg/kg (initial dose level)
− **1** 3.0 mg/kg
− **2** 2.4 mg/kg
Indication for further dose reduction → withdrawal from study treatment

9.1.2 Dose Adjustments and Treatment Delays – Trastuzumab

For Trastuzumab no dose adjustments are applicable. The patient will either receive full dose or will be withdrawn from further treatment.

9.1.3 Dose Adjustments and Treatment Delays – Endocrine Therapy

In case of non-tolerability of endocrine therapy any dose adjustment, switch of endocrine medication or treatment delay is at the discretion of the investigator. Any delay, switch or dose reduction must be documented in both the patient's file and the e-CRF.

9.2 Toxicity Related Guidelines for Dose Reduction and Dose Modification of T-DM1, Trastuzumab and endocrine therapy

Please refer to the ADAPT protocol, Appendix 1 – Treatment Dose Adjustments and Treatment Delays for further information.

10 Safety Monitoring

10.1 Safety Plan

Overall safety will be assessed on an ongoing basis during the conduct of the study. The DSMB (IDMSC) will monitor cumulative safety data at least once every 6 months during the course of

the study. In addition, data on serious adverse events and deaths will be monitored by the DSMB (IDMSC) at least once every 3 months.

10.2 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording of protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drugs.
The Sponsor or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, Roche and participating investigators, in accordance with ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.
The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Roche will be notified within 1 business day.
The Sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification. Roche will be notified within 1 business day.

10.3 Adverse Event Reporting

The investigator is responsible for ensuring that all AEs and SAEs (as defined in chapter 12 of the ADAPT umbrella protocol) are recorded in the e-CRF and reported to the sponsor in accordance with protocol instructions. Additional reference document for AE reporting is the respective IB in its current version. For patient safety, all AEs must be documented in the e-CRF**, irrespective of the CTC Grade in the ADAPT HER2+/HR+ sub-trial**. Coding of AEs will be done according to mEDRA.
Investigators should use correct medical terminology/concepts when recording AEs or SAEs in the e-CRF. Avoid colloquialisms and abbreviations. There is one e-CRF page for recording AEs and a hardcopy printout page for recording SAEs. Only one medical concept should be recorded in the event field on the (Serious) Adverse Event report.

10.3.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as blood draws or no treatment run-in).
After initiation of study treatment (the Genentech/Roche product(s) or other investigational medicinal product), all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see chapter 12.3 of the ADAPT umbrella protocol).

10.3.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:
“How have you felt since your last clinic visit?”
“Have you had any new or changed health problems since you were last here?”

10.3.3 **Type and Duration of Follow-up of Patients after Adverse Events**

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost-to-follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event e-CRF and in the patient's medical record to facilitate source data verification (SDV).
For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

10.3.4 **Post-Study Adverse Events**

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient's personal physician believes could be related to prior study treatment.
The investigator should notify the sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation, if deemed to be related to prior study treatment. The sponsor should also be notified, if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to the sponsor on the study e-CRF. If the study e-CRF is no longer available, the investigator should report the event directly to the sponsor via telephone.

10.3.5 **Adverse Events Occurring Secondary to Other Events**

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the e-CRF.
However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the e-CRF.
For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the e-CRF.

10.3.6 **Persistent or Recurrent Adverse Events**

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the e-CRF. The persistent AE will be only documented once with the highest CTC Grade occurring.
A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event e-CRF.

10.3.7 **Abnormal Laboratory Values**

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the e-CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).
If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event e-CRF.
If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the e-CRF.

If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."
Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the e-CRF, unless the seriousness, or etiology changes.

10.3.8 **Deaths**

Deaths that occur during the protocol-specified AE reporting period (see chapter 10.3.1 of the ADAPT HER2+/HR+ sub-protocol) that are attributed by the investigator solely to progression of breast cancer will be recorded only on the Death Report Form (DRF) in the e-CRF. All other on-study deaths, regardless of attribution, will be recorded on an e-CRF and expeditiously reported to the Sponsor. An independent monitoring committee will monitor the frequency of deaths from all causes.
When recording a death on the e-CRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the e-CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" on the DRF in the e-CRF.
During post-study survival follow-up, deaths attributed to progression of breast cancer will be recorded only on the Survival e-CRF.

10.3.9 **Relevant Medical History**

Relevant medical history includes any preexisting medical condition that is present at the start of the study. Such conditions should be recorded on the Baseline 1 e-CRF page.
A preexisting medical condition should be only recorded as an AE or SAE if the frequency, severity, or character of the condition worsens during the study.
When recording such events on an Adverse Event, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.3.10 **Worsening of Breast Cancer**

Worsening and/or progression of breast cancer should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

10.3.11 **Hospitalization, Prolonged Hospitalization or Surgery**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

10.3.12 **Pregnancy**

If a female patient becomes pregnant while receiving investigational therapy (T-DM1 or comparative treatment) or within 6 months after the last dose of investigational product, a Pregnancy Report Form should be completed and expeditiously submitted to the sponsor within

24 hours of learning of the pregnancy, to facilitate outcome follow-up. The Pregnancy Report Form will be available for printout from the e-CRF, but should be available as hardcopy at each study site from the Investigator Site File. The Pregnancy Report Form has to be faxed along with the Pregnancy Fax Cover Page to the Sponsor.

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The pregnancy should not be recorded on the Adverse Event e-CRF.
Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the sponsor considers these medically significant), recorded on an e-CRF, and expeditiously reported to the Sponsor.
Any congenital anomaly/birth defect in a child born to a female patient should be recorded and reported as an SAE.

10.4 T-DM1 Arms

The safety plan for patients in the T-DM1 treatment arms is based on non-clinical toxicities of T-DM1, the clinical experience with this molecule in completed and ongoing studies, and clinical toxicities related to its components (trastuzumab and maytansine, the parent drug of DM1). The potential safety issues anticipated in these treatment arms as well as measures intended to avoid or minimize such toxicities are outlined below. Please refer to the T-DM1 Investigator Brochure in its actual version for the most recent information.
Because exposure in humans to T-DM1 has been limited, all patients will be monitored closely for toxicity. T-DM1 dose modifications are described in Appendix 1 – Treatment Dose Adjustments and Treatment Delays of the ADAPT umbrella protocol.**Cardiotoxicity**

Patients without significant cardiac history and with an LVEF ≥ 50% determined by echocardiogram (Echo) are eligible for study participation. LVEF will be monitored at screening and regularly throughout the study until the assessment at the end of treatment. Patients with symptomatic cardiac dysfunction will be discontinued from study treatment. Asymptomatic declines in LVEF will be handled as per the algorithm shown in figure 2 below.
Treatment with trastuzumab, a component of trastuzumab emtansine, has resulted in subclinical and clinical cardiac failure manifesting as congestive heart failure (CHF), decreased left ventricular ejection fraction (LVEF), and cardiac death. Although significant cardiotoxicity has been infrequently seen in clinical trials with trastuzumab emtansine to date, severe cardiotoxicity remains an important potential risk. Standard cardiac function test (echocardiogram or MUGA) should be assessed at regular intervals in patients receiving trastuzumab emtansine. Specific guidelines regarding dosing if toxicities are observed are provided in the clinical trial protocol.

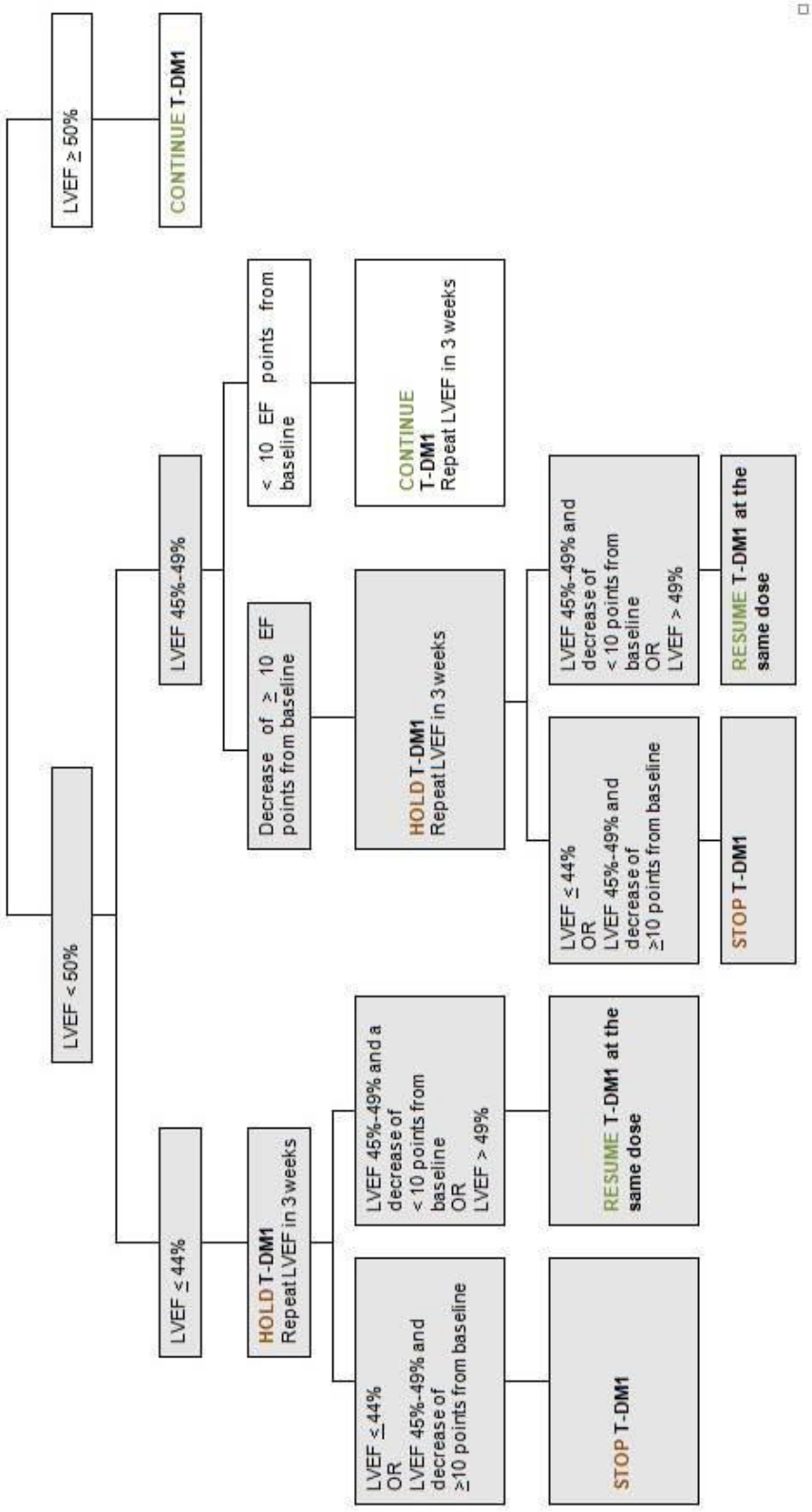

Figure 2 - Algorithm for Continuation and Discontinuation of T-DM1 Based on Left Ventricular Ejection Fraction Assessments in Patients
CHF = congestive heart failure;
LVEF = left ventricular ejection fraction;
T-DM1 = Trastuzumab-MCC-DM1;
Note: LVEF assessment results must be reviewed before the next scheduled T-DM1 infusion.

a. LVEF can be repeated within 21 days, and T-DM1should be discontinued if LVEF ≤ 44% is confirmed. T-DM1 should be held while the repeat LVEF is obtained. **b.** After a second consecutive confirmatory result, T-DM1 should be discontinued if the LVEF is confirmed to be ≥ 10% points below baseline or if medical management was required to correct the LVEF.

Figure 2 *– Algorithm for Continuation and Discontinuation of Study Medication T-DM1 Based on LVEF Assessment in Asymptomatic Patients*

10.5 Hematologic Toxicity

Thrombocytopenia is an identified risk with T-DM1. Patients must have adequate bone marrow function, as manifested by measurements of blood granulocytes, hemoglobin, and platelets, for initial and continued dosing. Evaluations of blood granulocytes, hemoglobin, and platelets will be performed regularly.

Use of erythropoiesis-stimulating agents will be allowed as consistent with prescribing guidelines. Transfusion of red blood cells and/or platelets will be allowed according to and at the discretion of the investigator.

Thrombocytopenia is the dose limiting toxicity seen in the phase 1 trials with trastuzumab emtansine. There was no clear association between thrombocytopenia and hemorrhagic events; however, severe Grade 4 thrombocytopenia, some requiring platelet transfusion, associated with trastuzumab emtansine has been uncommonly reported. Monitoring with a complete blood count (CBC) for hematologic toxicity should occur at least every week in the first cycle and in subsequent cycles as described per protocol. Dose reductions for severe thrombocytopenia are described in each individual protocol.

10.6 Hepatotoxicity

Transient and reversible elevations of liver enzymes (Grade 1-4 transamininitis) have been observed following treatment with trastuzumab emtansine. Although significant hepatotoxicity has rarely been seen in clinical trials with trastuzumab emtansine to date, and when observed, the relationship to trastuzumab emtansine has not been clear, severe liver injury remains an important potential risk. Liver function should be monitored at least prior to every cycle. Dose reductions for severe liver enzyme elevations are described in each individual protocol.

10.7 Infusion Reactions

Infusion-related reactions may occur with the administration of monoclonal antibodies and have been reported with T-DM1. Administration of T-DM1 will be performed in a setting with access to emergency facilities and staff who are trained to monitor and respond to medical emergencies. Patients will be monitored during and after each T-DM1 infusion for a minimum of 90 minutes after the first infusion and for a minimum of 30 minutes after subsequent infusions in the absence of infusion-related adverse events.

Consistent with the Herceptin package insert/national prescribing information, patients should be made aware of the possibility of severe delayed infusion reactions associated with T-DM1, because of its trastuzumab component.

Patients should be instructed to contact the investigator with any concerns after dosing.

In case of severe infusion reaction, the patient is to be withdrawn from study treatment.

10.8 Neurotoxicity

DM1, an anti-microtubule agent, can potentially cause peripheral neuropathy. Patients must have Grade ≤ 2 peripheral neuropathy to be eligible for study participation. Patients should be examined for signs of peripheral neuropathy prior to each dose of T-DM1. Patients who experience Grade ≥ 3 neurotoxicity in the form of peripheral neuropathy that does not resolve to Grade ≤ 2 within 42 days after last dose was received will be discontinued from study treatment.

10.9 Identified Risks

Thrombocytopenia, elevated liver enzymes, infusion /hypersensitivity reaction, and pneumonitis have been identified as risks with trastuzumab emtansine use.

10.9.1 **Pneumonitis**

Severe pulmonary events including interstitial lung disease, dyspnea, pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency, hypoxia, and acute respiratory distress syndrome have been reported with the use of trastuzumab, a component of trastuzumab emtansine. These events may or may not occur as sequelae of infusion reactions and occasionally resulted in fatal outcome. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs may be at greater risk of severe reactions. Pneumonitis has been rarely reported with trastuzumab emtansine (four cases as of April 2011). Signs, symptoms, and clinical findings include dyspnea, cough, fatigue, and pulmonary infiltrates. There were no fatalities among the four cases of pneumonitis reported with trastuzumab emtansine; however, in some patients with multiple lung metastases, ventilatory support (mechanical ventilation) was required. Treatment included administration of steroids, oxygen, and study drug discontinuation.
Two cases of interstitial lung disease (ILD) and three cases of acute respiratory distress syndrome (ARDS) have also been reported in trastuzumab emtansine clinical trials to date. However, a causal relationship between these events and trastuzumab emtansine has not been established.

10.10 Potential Risks

10.10.1 **Nodular Regenerative Hyperplasia**

Nodular regenerative hyperplasia has been identified from liver biopsies of two subjects treated with trastuzumab emtansine (as of May 2011). In the first case, a patient who was receiving trastuzumab emtansine plus pertuzumab for 14 months developed abdominal pain and distension with radiologic findings of portal hypertension, including small-volume ascites and esophageal varices. Laboratory data were notable for a progressive increase in serum alkaline phosphatase while serum transaminase and total bilirubin concentrations remained relatively stable. Signs of portal hypertension improved following the discontinuation of study treatment and medical management of the portal hypertension. In the second case, a patient who was receiving single-agent trastuzumab emtansine for 26 months developed progressive disease including brain metastases and developed increased serum transaminases, bilirubin, alkaline phosphatase and ascites following the last dose of trastuzumab emtansine. The patient subsequently died. The cause of death was attributed to liver failure by the investigator. No autopsy was performed. Evaluation of the case suggests the patient died following documented disease progression leading to multi-organ failure.

10.10.2 **Immunogenicity**

Anti-therapeutic antibodies (ATA) may affect efficacy through neutralization of T-DM1, but also safety (hypersensitivity reactions). Development of anti-T-DM1 antibodies has been observed in clinical trials, with preliminary assessment showing a low immunogenicity rate of 3.2%. To date, no associated adverse events have been observed associated with ATA.

10.10.3 **Pregnancy Risks**

To date, no pregnancies have been reported in patients treated with T-DM1, and no studies of T-DM1 have been conducted in pregnant women. No reproductive and developmental toxicology studies have been conducted with T-DM1. Trastuzumab, a component of T-DM1, can cause fetal harm or death when administered to a pregnant woman. In the post-marketing setting, cases of oligohydramnios, some associated with fatal pulmonary hypoplasia, have been reported in pregnant women receiving trastuzumab. Animal studies of maytansine, a closely related chemical entity of the same maytansinoid class as DM1, suggest that DM1, the microtubule inhibiting cytotoxic drug component of T-DM1, is expected to be teratogenic and potentially embryotoxic. In summary blockade of the HER2 receptor and inhibition of tubulin

polymerization have been shown independently to result in serious detrimental effects on fetal development and viability. Based on these data, it is expected T-DM1 to exhibit an unacceptable developmental and genotoxic profile and the use of T-DM1 during pregnancy should, therefore, be contraindicated.
Patients should be advised to use effective contraception during treatment with T-DM1 and for at least 6 months after treatment has concluded. Women who become pregnant should be advised of the possibility of harm to the fetus. If a pregnant woman is treated with T-DM1, close monitoring by a multidisciplinary team is recommended.

10.10.4 **Nursing Mothers**

It is not known whether T-DM1 or any of its metabolites or breakdown products is excreted in human breast milk. Therefore, T-DM1 should not be administered to nursing mothers. Breastfeeding should be discontinued during T-DM1 therapy and for at least 6 months after the last dose.

10.11 Warnings and Precautions

10.11.1 **Extravasation**

Cellulitis or phlebitis was described after paravenous injection of maytansine (weekly i.v. bolus or 24 hour infusions) in a series of 71 patients with leukemia, lymphoma or carcinoma [1]. Cellulitis at the site of extravasation was described in one subject in a series of 29 patients with squamous cell carcinoma of the cervix treated with maytansine every 3 weeks. In trastuzumab emtansine clinical studies one case of extravasation was reported in a 29 year-old subject who developed Grade 2 cellulitis of the right arm due to extravasation of 20-30mL trastuzumab emtansine infusion on study day 113.
Treatment included analgesics and antibiotics. The event resolved with no sequelae after approximately 3 weeks. Trastuzumab emtansine treatment was
resumed at a later date.
Another case of skin exposure to trastuzumab emtansine occurred in a 39-year-old nurse who experienced accidental exposure to trastuzumab emtansine to the internal part of the auricle of her ear while preparing the drug for a patient. The nurse reported local skin irritation, redness, burning sensation and pain. Treatment consisted of saline solution compresses and hyaluronan cream. The event resolved with no sequelae on the following day. In trastuzumab emtansine clinical studies, injection site reactions, including reactions secondary to extravasation, have usually been mild and comprised erythema, tenderness, skin discoloration, or swelling at the injection site. These reactions have been observed more frequently within 24 hours of infusion/extravasation. Rare reports of more severe events such as cellulitis, pain (tenderness and burning sensation), and skin irritation have been received as part of the continuing surveillance of trastuzumab emtansine safety. Specific treatment for trastuzumab emtansine extravasation is unknown at this time. It is advisable to closely monitor the infusion site for possible subcutaneous infiltration during drug administration.

11 Data Analysis and Statistical Considerations

The study comprises a **Run-in phase** (n=130) and a **Main phase** (n=250).

11.1 Run-in phase

The Run-in phase will determine the cut-off for a dynamic test (performed after 3 weeks of therapy) result to predict pathological complete response (pCR) probability. This cut-off will be used during the main phase of the trial to define responders (and non-responders) from the dynamic test result.

Additionally, the Run-in phase will pursue the following objectives:

- Identification of molecular markers correlating with early response/pCR
- Feasibility/reproducibility of assessment of these markers
- Validation of statistical assumptions made for the whole sub-trial

11.2 Primary endpoints and hypothesis testing

The primary endpoint of the ADAPT HR+/HER2+ study is pCR after 12 weeks of pre-surgical therapy.

Intention-to-treat (ITT) analysis will be conducted for all randomized hypothesis tests (the ITT3 population is defined below).
Assuming a drop-out rate of 5%, an ITT test collective of more than 300 patients is expected. The primary hypotheses are tested in this test collective.
The study will test the hypothesis of higher pCR proportion separately in each of the T-DM1 arms. We expect a 10% rate of pCR in the trastuzumab + endocrine therapy arm. In each T-DM1 arm, 25% pCR is assumed. Assuming total α= .05 (one-sided), i.e., α=0.025 for each hypothesis, the test has 80% power to detect superiority in each of the T-DM1 containing arms compared to the trastuzumab + endocrine therapy arm.
Other primary objectives:

- Evaluation of dynamic testing (based on proliferation/apoptosis changes in serial biopsy and/or imaging by ultrasound/breast MRI) after three weeks of treatment as a surrogate parameter for response in terms of residual cancer burden.

11.3 Interim analysis

Interim analysis on correlation between changes in the sequential biopsy and pCR rates in the first 130 patients (Run-In phase) is planned during ongoing recruitment of patients

11.4 Secondary objectives

Secondary objectives include extended pCR analysis, survival analysis, safety analysis, and cost-effectiveness. Analysis of secondary objectives is descriptive and exploratory.

Extended pCR analysis (descriptive):

Pathological complete response rates (pCR) and RCB rates will be computed in the three pre-surgical therapy subgroups defined above for those without proliferation response and for all patients.

Survival analysis:

Event-free survival (EFS) and overall survival (OS) were defined in Chapter 11.1 of the ADAPT umbrella protocol.

As stated above, although achievement of pCR in patients with a HER2+ disease has been associated with long-term survival, this association has not been specifically confirmed in the HER2+/HR+ subtype. Subgroup analysis of EFS and OS by pCR and by RCB will be carried out.

The dynamic test will also be evaluated regarding prediction of 5-year event-free survival (EFS) and overall survival (OS) including subgroup analysis.

Further survival analysis is defined in the ADAPT Umbrella Protocol.

Safety:

- Toxicity/cardiac safety
- Overall and specific safety in the three treatment arms

Cost-effectiveness

Cost-effectiveness will be evaluated based on the data of the trial and the availability of price information, particularly for T-DM1.

11.5 Further (tertiary) objectives

Analysis of further objectives is descriptive and exploratory. Further planned analyses include:

- Assessment of impact of lifestyle factors (body mass index/change of weight), sport activity, alcohol and smoking on prognosis in a subset of patients
- Evaluation of all molecular, pathological and clinical markers and their combinations in terms of predictive and prognostic value
- Further survival analysis (EFS, OS) by pCR (and by RCB) and by chemotherapy.

Further exploratory analysis
Additional translational research questions occurring during the trial will be defined in sub-protocols.

11.6 Ethical Considerations ADAPT HER2+/HR+

All participants will give written informed consent for participation in the trial. All participants will be protected by the insurance cover as standard in the clinical trials. Possible under-treatment should be excluded by the data from several trials. Donating of tumor block to the central tumor bank is planned for further research purposes.

11.7 Randomization

For **HER2+/HR+ patients** randomization is applicable right from the beginning of study participation. Eligible patients will be randomized to either arm A (T-DM1 monotherapy), arm

B (T-DM1 + endocrine therapy) or arm C (trastuzumab + endocrine therapy) in the ratio 1:1:1; randomization will be performed centrally according to a permuted block design.

11.8 Efficacy Evaluation

11.8.1 Primary efficacy parameters and populations

As stated above, the primary efficacy parameter for HER2+/HR+ disease will be pCR, defined as no invasive patterns in the breast and lymph nodes at the time of surgery. The primary efficacy analysis will be based on the ITT3 population, defined as the eligible study population of recruited patients.

11.8.2 Further efficacy parameters and populations

In addition to pCR, secondary and exploratory analyses will include RCB rates.

Exploratory analyses will also be conducted in per-protocol populations.

11.9 Further statistical details

For further information please refer to the ADAPT umbrella protocol chapter 11.

11.10 Safety Evaluations

All patients who receive at least one dose of T-DM1 or trastuzumab will be included in the safety analysis.

11.10.1 Interim Safety Analysis

For further information please refer to the umbrella protocol chapter 11.4.3.

12 Translational Research

Please refer to the ADAPT protocol, chapter 10 for further information.

13 Adverse Events

Please refer to the ADAPT protocol, chapter 12 for further information.

13.1 Protocol-Defined Events of Special Interest/Non-Serious Expedited Adverse Events

Any potential case of STIAMP (Suspected transmission of an infectious agent by the study drug).
Any potential case of Drug Induced Liver Injury (DILI) as assessed by laboratory criteria for Hy's Law should be reported to the sponsor expeditiously (see chapter 13.2 of the ADAPT HER2+/HR+ sub-protocol for reporting instructions), irrespective of regulatory seriousness criteria or causality. Hy's law is a prognostic indicator that a pure drug-induced liver injury leading to jaundice, without a hepatic transplant, has a case fatality rate of 10% to 50%.

The following laboratory abnormalities define potential Hy's Law cases:

- AST or ALT elevations that are ≥ 3 × ULN with concurrent elevation (within 21 days of AST and/or ALT elevations) of total bilirubin > 2 × ULN except in patients with documented Gilbert syndrome.

13.2 Expedited Reporting for Adverse Events of Special Interest

Any Adverse Event of special interest is subject to expedited reporting, i.e. CIOMS I reporting within 15 working days is mandatory. The investigator is obliged to report any AE of special interest as an SAE **within 24 hours** to the sponsor.

14 Definition of Study Medication

14.1 Study Medication

For the purpose of this sub-trial, T-DM1 is the investigational medicinal product. The combination of T-DM1 with endocrine therapy, as well as the combination of trastuzumab and endocrine therapy will be regarded as investigational. Trastuzumab for induction treatment is regarded as study medication and will be labeled study-specific. Only commercial ware will be used for endocrine therapy, thus it will not be labeled study-specific.

15 Administrative Aspects

Please refer to the ADAPT umbrella protocol, chapter 14 for further information.

The planned patient numbers were reached Q1 2015 and the recruitment was ended..

ADAPT HER2 Positive/Hormone Receptor Negative Breast Cancer Sub-trial

(Recruitment for the substudy prematurely stopped)

A prospective, randomized multicenter, open-label comparison of pre-surgical combination of Trastuzumab and Pertuzumab with or without concurrent taxan chemotherapy given for twelve weeks in patients with operable HER2+/HR- breast cancer within the ADAPT protocol.

SPONSOR: WSG – Westdeutsche Studiengruppe GmbH

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Coordinating Investigator: Prof. Dr. med. Nadia Harbeck

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Final Version 5.0, 11 November 2021

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Protocol Title: ADAPT HER2 positive/Hormone Receptor negative Breast Cancer Sub-trial

A prospective, randomized multicenter, open-label comparison of pre-surgical combination of Trastuzumab and Pertuzumab with or without concurrent taxan chemotherapy given for twelve weeks in patients with operable HER2+/HR- breast cancer within the ADAPT protocol.

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A prospective, randomized multicenter, open-label comparison of pre-surgical combination of Trastuzumab and Pertuzumab with or without concurrent taxan chemotherapy given for twelve weeks in patients with operable HER2+/HR- breast cancer within the ADAPT protocol.

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A prospective, randomized multicenter, open-label comparison of pre-surgical combination of Trastuzumab and Pertuzumab with or without concurrent taxan chemotherapy given for twelve weeks in patients with operable HER2+/HR- breast cancer within the ADAPT protocol.

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A prospective, randomized multicenter, open-label comparison of pre-surgical combination of Trastuzumab and Pertuzumab with or without concurrent taxan chemotherapy given for twelve weeks in patients with operable HER2+/HR- breast cancer within the ADAPT protocol.

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Signature Page ADAPT HER2+/HR- Biostatistics

Protocol Title: ADAPT HER2 positive/Hormone Receptor negative Breast Cancer Sub-trial

A prospective, randomized multicenter, open-label comparison of pre-surgical combination of Trastuzumab and Pertuzumab with or without concurrent taxan chemotherapy given for twelve weeks in patients with operable HER2+/HR- breast cancer within the ADAPT protocol.

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1 Study Summary ADAPT HER2+/HR- Breast Cancer

ADAPT HER2+/HR-	A prospective, randomized multicenter, open-label comparison of pre-surgical combination of Trastuzumab and Pertuzumab with or without concurrent taxane chemotherapy given for twelve weeks in patients with operable HER2+/HR- breast cancer within the ADAPT protocol.
Study Overview	HER2 over-expressing breast cancer with its aggressive biology remains a major clinical challenge. Over-expression of the HER2 gene is reported in about 10-20% of breast cancers. It is associated with poor prognosis[108], with good response to neoadjuvant chemotherapy[109,110], decreased sensitivity to endocrine therapy[85] and response to targeted therapy such as trastuzumab[33,111]. In about half of the cases HER2 positive tumors do not co-express hormone receptors (ER and/or PR). Up to now HER2+/HR+ BC and HER2+/HR- disease have not been looked upon separately. There is a large body of evidence for poor prognosis of HER2+/HR+ BC compared to HER2 negative cases[114]. Nevertheless, prognosis of HER2+/HR+ BC is essentially better than that of HER2+/HR- controls[45,46] **Standard treatment of HER2 + breast cancer** Trastuzumab is a monoclonal antibody against the HER2 receptor. Its use leads to activation of antibody-dependent cellular cytotoxicity, inhibition of extracellular domain cleavage, abrogation of intracellular signaling, reduction of angiogenesis, and decreased DNA repair. These effects are increased by combination with a wide range of anti-cancer agents. The use of trastuzumab changed the perception of HER2+ metastatic breast cancer as it rendered prognosis of HER2+ patients treated with trastuzumab-based chemotherapy comparable to that of patients with HER2- disease[112]. In the adjuvant setting, the use of trastuzumab (for one year[34] or shorter[113]) sequentially[34] or simultaneously[35] to an adjuvant chemotherapy backbone is associated with a reduction of the relapse risk by about 50%. In HER2+ early breast cancer (eBC), adjuvant trastuzumab (T) therapy for 52 weeks in combination with chemotherapy is considered gold-standard. **Response evaluation in HER+ breast cancer** **Role of pCR in HER2 over-expressing BC (HR+/HR-)** Similar to triple negative (ER and PR and HER2 negative) BC, achievement of pathological complete response (pCR) in patients with a HER2+ subtype is associated with significantly better long-term survival as compared to those patients without pCR[30]. Trastuzumab (T)-containing neoadjuvant chemotherapy has been reported to increase the probability of pathological complete response (pCR) in HER2+ disease up to 67%[36,110,119]. In the NOAH trial, the neoadjuvant use of trastuzumab was associated with improved disease-free survival[36]. The TECHNO trial is the first trial reporting a significant association between pCR after neoadjuvant anti-HER2 therapy (together with chemotherapy) and improved survival in HER2+ disease[31]. Thus, pCR in HER2 over-expressing BC is a validated surrogate parameter for patient outcome and survival. A recent meta-analysis presented by von Minckwitz et al. revealed a differential prognostic impact of pCR in HER2+/HR- and HER2+/HR+ tumors. pCR was prognostically significant in HR- tumors, but not in HR+ tumors[120]. These data are not supported by other reports[121]. Loibl et al. could further demonstrate that the survival of HER2+/HR- breast cancer patients, who had a pCR after treatment with trastuzumab was even better than that of patients with pCR in HER2- disease[131]. Interestingly, Bianchini et al. reported different pathways

responsible for achieving pCR in combination of chemotherapy with trastuzumab in HR+ and HR- tumors.[104]

Dynamic measurement (breast MRI/tumor cell proliferation) as an early surrogate marker for pCR

Recently, neoadjuvant cytotoxic and/or tailored therapies have been suggested as an important tool for evaluation of response to a given systemic therapy *in vivo*. Clinical response measured by sequential evaluation of different proliferation markers (such as Ki-67) following a course of neoadjuvant chemotherapy has been demonstrated to correlate significantly with an increased risk of relapse in patients not achieving pCR[122]. Summing up divergent effects of several anti-HER2 therapies on proliferation, it would be clinically relevant to evaluate such proliferation tools for early prediction of combination therapy efficacy (chemotherapy and HER2 targeted therapy). So far, it remains unclear which method of proliferation measurement is the optimal marker for response evaluation regarding combined chemo-anti-HER2 therapy.

However, measurement of proliferation and apoptosis as well as assessment of changes in PI3K/AKT, IGF and stem cell signaling after a short course of therapy could provide a unique signature for *dynamic* response evaluation and selecting patients for mono vs. combined targeted treatment.

Another way to assess early response could be **molecular imaging** by breast MRI (or other functional dynamic imaging), given the strong evidence, particularly in HER2+ and triple negative breast cancer[52,53]

Changes in contrast medium kinetics in contrast-enhanced MRI (DCE-MRI) or of the ADC (apparent diffusion coefficient) in the diffusion-weighted MRI or drop of the cholin peak in the ^{1}H-MR-Spektroskopy already after short induction therapy are possible measurement instruments for an imaging approach as an alternative non-invasive and complimentary method for dynamic patient stratification within the trial. A further advantage of breast MRI is an analysis of whole tumor (and not only a single biopsy area) and better evaluation of tumor heterogeneity.

Future perspectives in anti-HER2 therapy - dual blockade of HER2 pathway in HER2+/HR+ and HER2+/HR- disease

Combination of trastuzumab with other HER2-targeted therapies (e.g. HER2/HER1 tyrosine kinase inhibitor lapatinib or HER2/HER3 dimerization inhibitor pertuzumab) is reported to improve significantly pCR rates in both HER2+/HR- and HER2+/HR+ disease.

Trastuzumab + lapatinib

Neo ALTTO was the first trial to report on dual blockade with trastuzumab and lapatinib vs. lapatinib or trastuzumab monotherapy. 455 patients received the anti-HER therapy for 18 weeks + 12 weeks of concurrent weekly paclitaxel. Treatment could not be completed as previewed in 34% (L) , 8% (T) and 39% (T + L) patients due to toxicity mainly diarrhea, hepatic and skin disorders. Pathologic complete remission rates were reported to be 24.7% (L), 29.5% (T) and 51.3% (T+L). In HER2+/HR+ disease the corresponding pCR rates were 16.2%, 22.7% and 41.6%. The benefit in the HER2+/HR- population was higher with pCR rates of 33.8%, 36.5% and 61.3%[38].

Holmes reported data about 100 patients with stage III disease receiving T, L or T+ L for 26 weeks with concurrent FE75C x 4 → Paclitaxel q1w x 12 for 24 weeks. Pathological complete remission was reported in 54% (T), 52% (H) and 74% (T + L)[123].

Chang reported on 66 patients only receiving anti-HER2 dual therapy (L+H) for 12 weeks together with endocrine therapy in ER positive disease. Pathological

complete remission rates were 28% for the overall population and 21% in ER positive and 40% in ER negative disease[128].
The Cherlob trial randomized patients to neoadjuvant T, L or L+T with concurrent weekly paclitaxel q1w x 12 → FEC x 4 q3w. Pathological complete response rates were reported to be 25.7% for T, 27.8% for L, and 43.1% for T+L. For HR positive disease pCR rates were 25%, 22.7% and 36.7%. For HR negative disease pCR rates of 26.6%, 35.7% and 56.2%[124].

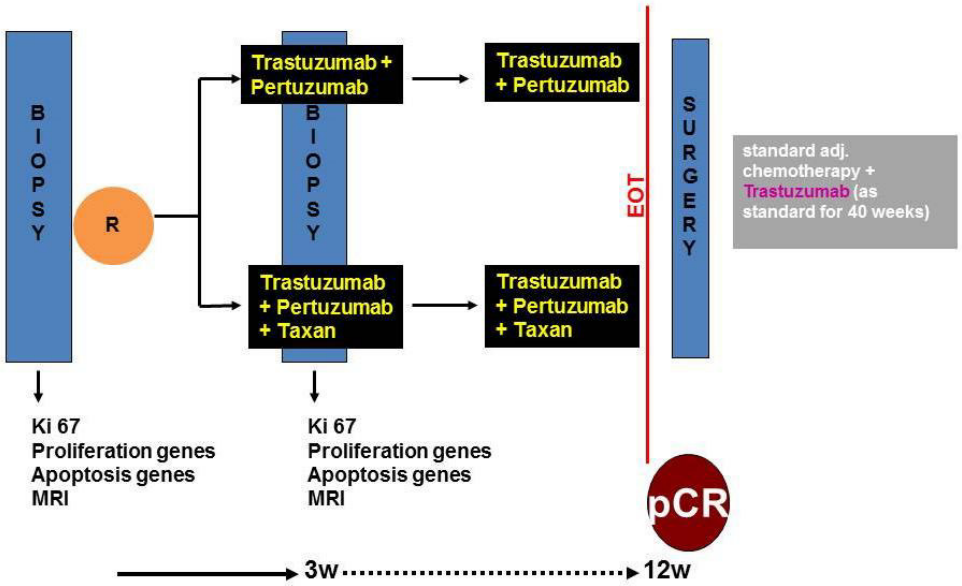
Trastuzumab + pertuzumab
NEOSPHERE is a neoadjuvant trial in 417 patients with operable, locally advanced or inflammatory breast cancer. Patients received either 12 weeks of standard therapy with docetaxel and trastuzumab or standard + pertuzumab or docetaxel + pertuzumab or dual blockade with pertuzumab and trastuzumab without a chemotherapy backbone. The primary endpoint was the comparison of pCR rates, one secondary endpoint was toxicity. The dual blockade did not significantly increase the toxicity compared to standard treatment and especially no increased rates of cardiotoxicity were reported. Within the four arms pCR rates were: 29 % for standard treatment, 45 % if pertuzumab was added, 24 % for docetaxel + pertuzumab and 16.8% for dual blockade without chemotherapy. In this latter treatment arm the NEOSPHERE trial reports a pCR rate of 6% (in HER2+/HR+) and 29% in HER2+/HR-[43]. CLEOPATRA tested and trastuzumab + docetaxel ± pertuzumab in first line therapy of 808 patients with metastatic breast cancer. 10.1% in the standard arm and 11.7% of patients in the experimental arm were pretreated with trastuzumab. Overall response rate was 69.3 vs. 80%, median PFS increased by 6.1 months from 12.4 to 18.5 months and overall survival was significantly improved by dual HER2 blockade with trastuzumab and pertuzumab (HR 0.64, p=0.0053). The combination of pertuzumab and trastuzumab plus docetaxel increased rates of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. These adverse events were primarily grades 1–2, manageable, and occurred during docetaxel therapy. Cardiac adverse events or LVSD were not increased[132]. TRYPHANEA is a randomized phase II neoadjuvant trial comparing the same dual blockade plus anthracycline-taxane-based (FEC→ Doc concurrent or sequential) or carboplatin-taxane-based standard chemotherapy (Doc/Carbo) regimens. Primary endpoint was cardiac safety, secondary endpoints were toxicity and efficacy parameters. Incidence of cardiac events was low irrespective of treatment arms. Pathologic complete response rates were 57.3 – 66.2% in the overall population and 65% to 83.8% in the HER2+ hormone insensitive tumors[133].. In September of 2013, neoadjuvant trastuzumab and pertuzumab has received FDA approval.

Role of chemotherapy in HER2 + breast cancer treated with dual blockade with T + P
The only available data come from the neoadjuvant NEOSPHERE trial, which compared docetaxel + trastuzumab vs. docetaxel + trastuzumab + pertuzumab vs. trastuzumab + pertuzumab vs. docetaxel + pertuzumab in 417 patients. The pCR rate is 45.8 vs. 16.8% for docetaxel + trastuzumab and pertuzumab vs. trastuzumab and pertuzumab. For HR- disease the corresponding rates were 63.2% vs. 29.1%[43]. TRYPHAENA study revealed pCR (ypT0/N0) rates of about 50% for the combination chemotherapy of FEC→Docetaxel or TCarbo+ double blockade of trastuzumab+pertuzumab in 225 patients with HER2 positive disease[134]

Due to short follow-up of the studies, only little data on a survival impact of increased pCR rates from combination therapy are available so far. First survival

	data from NeoALTTO showed an EFS advantage for dual blockade only for HER2+ HR- tumors (Piccart et al, SABCS 2013). **The ADAPT philosophy – A combined static and dynamic model** Early response assessment in eBC may be essential to separate sub-populations with large or marginal benefit from therapy. Drop of proliferative activity after a short course of endocrine therapy (2 weeks to 4 months) as measured by proliferation marker Ki-67 is an excellent predictor for local as well as systemic outcome in HR+ disease. It allows to identify groups of patients with excellent outcome in both low and higher risk groups independently from chemotherapy application[25-27]. ADAPT applies this dynamic model to all early breast cancer subtypes. First step is a broad baseline assessment (conventional central pathology, RS, biomarker) of prognosis. Sequential tissue sampling is realized (3 week interval, core biopsies and surgery) after a short subtype specific treatment. Thus, besides baseline prognosis estimation (***static* assessment**), therapy efficacy is evaluated at an early time of treatment (***dynamic* assessment**). Beyond baseline biomarker assessment, the primary endpoint of the ADAPT HER2+ and TN protocols is the definition of molecular surrogate markers predictive for pCR and 5 year event-free survival.
Rationale	ADAPT is designed to assess early response to therapy in all breast cancer subtypes. After a short subtype-specific 3 week "induction" treatment therapy response is assessed by dynamic biomarker assessment in tumor tissue derived from a second core biopsy. Patients with HER2+ breast cancer are conventionally candidates for adjuvant chemotherapy. Early data for dual anti-HER2 blockade suggest substantial improvement of pCR rates as compared to trastuzumab monotherapy. Pertuzumab and lapatinib are the best evaluated partners for dual blockade. Pertuzumab is a humanized monoclonal antibody blocking the pairing of the most potent signaling HER dimer, HER2:HER3 thus affecting the key signaling pathways which mediate cancer cell proliferation and survival in breast cancer. Neosphere, Cleopatra and Tryphanea document high activity of the dual blockade with trastuzumab and pertuzumab in HER2+ early and metastatic breast cancer. The role of chemotherapy in this context has to be re-evaluated since we learned that HER2+ disease is a heterogeneous subgroup[131] with patients achieving pCR have excellent outcome. In HER2+/HR- patients - according to the data presented by Loibl et al. - the effect of anti-HER2 therapy is even more important than in HER2+/HR+ disease. The hypothesis that a large subgroup of HER2+ patients responds to this targeted treatment has been confirmed. Nevertheless, we learned from the first generation of anti-HER2 trials such as HERA and from metastatic disease that primary resistance to anti-HER2 therapy with trastuzumab exists. ADAPT HER2+/HR- will test 12 week dual blockade with trastuzumab + pertuzumab vs. identical dual blockade with 12 weeks of taxane chemotherapy backbone. After 12 weeks of treatment surgery will be performed with assessment of pCR rates. After surgery patients will receive standard treatment. ADAPT HER2+/HR- tries to identify an early biomarker (profile) for response to anti-HER2 dual blockade ± taxane backbone. The trial primarily aims at the identification of good responders to dual HER2 blockade, who do not need chemotherapy. It will also allow for exploratory biomarker analyses in non-responders, who according to the recently published data from GEPARTRIO trial might benefit from non- cross-resistant further therapy.
Objectives	Run-in phase concept: <u>Primary objective</u> • Identification of molecular markers correlating with early response/pCR

	• Feasibility/reproducibility of assessment of these markers • Validation of statistical assumptions made for the whole sub-trial Run-in + Main phase concept: <u>Primary objective</u> • Definition of a biomarker (profile) characterizing "good responders" to dual blockade T and P anti-HER2 blockade that have similar pCR rates as patients treated with identical dual anti-HER2 blockade + taxane backbone <u>Secondary objectives</u> • Evaluation of dynamic test regarding prediction of 5-year event-free survival (EFS) • Overall survival • Relapse free survival • Local and regional relapse free survival • Toxicity/cardiac safety • Evaluation of predictive value of molecular imaging with breast MRI for pCR • Health-related quality of life (HRQL) (optional) • Cost-effectiveness (to be defined) <u>Exploratory analysis:</u> • Translational research • Survival of patients with pCR (as part of the phase III umbrella protocol)
Trial design	Prospective, multi-center, controlled, non-blinded, randomized phase II
Treatment	**Neoadjuvant Treatment:** Patients with HER2+ / HR- tumor will receive a combination therapy with trastuzumab and pertuzumab in 3-weekly schedule (trastuzumab: 8 mg/kg as loading dose and then 6 mg/kg q3w; pertuzumab 840 mg as loading dose and then 420 mg q3w). The control group will receive trastuzumab and pertuzumab in 3-weekly schedule (trastuzumab: 8 mg/kg as loading dose and then 6 mg/kg q3w; pertuzumab 840 mg as loading dose and then 420 mg q3w) in combination with taxane (weekly paclitaxel) chemotherapy. In patients with HER2 positive or triple negative tumors and significant tumor burden after 12 weeks of neoadjuvant therapy the neoadjuvant therapy may be prolonged as **post-study treatment**. The remaining tumor burden must be proven histologically, i.e. the tumor sample will be sent to the central pathology. **Surgery:** After completion of 12 weeks (or prolonged) neoadjuvant treatment for all patients, surgery is planned. In case of disease progression systemic treatment will be stopped prematurely and surgery will be performed immediately. **Adjuvant Treatment:** Patients should receive complete standard adjuvant chemotherapy treatment (preferentially taxane → EC x 4 or EC x 4 → taxane), if randomized to the dual blockade alone arm or anthracycline-based chemotherapy (EC x4) if randomized to the taxane-containing arm: They should complete a total of 52 weeks of trastuzumab. In case of clinical tumor burden (non-pCR) after 12 weeks, neoadjuvant therapy may be prolonged as stated above. Chemotherapy may be applied as stated for adjuvant therapy. Total duration of anti-HER2 therapy (neoadjuvant and adjuvant) should be one year.



Response Assessment:
Primary efficacy (i.e. pCR) is defined at time of surgery according to NCCN guidelines (no invasive cancer in both breast and lymph nodes) and based on provided data regarding residual tumor size, proportion of vital cells within invasive carcinoma, number of positive lymph nodes and size of the largest lymph node metastasis and ductal carcinoma in situ.
Based on these criteria residual cancer burden (and other pCR classifications) will be defined for further analysis. Further chemotherapy may be omitted only in tumors with no invasive and DCIS patterns.

Safety:
Safety of pertuzumab with concurrent trastuzumab and pertuzumab with concurrent trastuzumab and taxane therapy will be measured by the incidence and severity of adverse events (AE) and serious adverse events (SAE). Frequency and reasons for discontinuation of therapy, modification and interruption will be evaluated in a prospective manner.

Dynamic test:
Drop of proliferation is considered as the key factor for efficacy of the combination therapy. During the run-in phase of the study, immunohistochemical measurement of Ki-67 and proliferation and apoptosis genes will be performed on all samples from diagnostic and sequential biopsy.
All tumors will undergo central pathology assessment (ER, PR, HER2) for randomization to the study (analysis by Prof. H. Kreipe, Hannover).

Study Examinations:

For timing of baseline examinations and examinations during neoadjuvant treatment please refer to table 1.

Table 1: Study Evaluations for ADAPT HER2+/HR- Breast Cancer Patients

ASSESSMENT	BL	Cycle 1[4]	Cycle 2[4]	Cycle 3[4]	Cycle 4[4]	EOT	Surgery
week	-3 to 0	1	4	7	10	13	14
Medical history (incl. concomitant medications)	x						
Central pathology review of diagnostic core biopsy	x						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x[2]	x	x	x	x	x	
Serum sample (biomarker analysis)	x[26]		x[6]			x[6]	
Radiology: • Chest X-ray • Bone scan • Liver imaging • Mammography	x[3]						
Breast MRI (inclusion of patients without MRI is allowed)	x[6]		x[6]				x[6] prior to surgery
Ultrasound	x		x	x		x	
Clinical assessment	x[2]		x	x		x	
Pregnancy test	x						
ECG and LVEF	x[5]			x			x prior to surgery
Laboratory: • Hematology • Biochemistry	x	x	x	x	x	x	
Surgery							x
(Serious) Adverse Event		continuously					
Concomitant medication	x	continuously					

[1] prior to 2nd administration of study drug
[2] within ≤ 7 days prior to randomization
[3] within 3 months prior to randomization
[4] +/-3 days
[5] within 42 days prior to randomization
[6] optionally

LVEF assessment after cycle 3 and then before surgery

Selection of patients

General Inclusion Criteria for ADAPT:

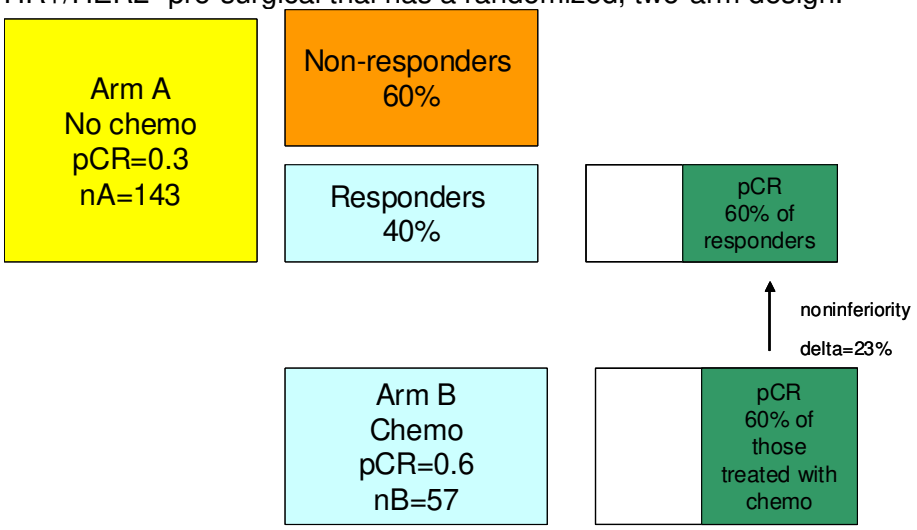
- Female patients, age at diagnosis 18 years and above Histologically confirmed unilateral primary invasive carcinoma of the breast
- Clinical T1 - T4 (except inflammatory breast cancer)
- All clinical N (cN)
- No clinical evidence for distant metastasis (M0)
- Known HR status and HER2 status (local pathology)
- Tumor block available for central pathology review
- Performance Status ECOG ≤ 1 or KI ≥ 80%
- Negative pregnancy test (urine or serum) within 7 days prior to registration in premenopausal patients
- Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and

follow-up, must be obtained and documented according to the local regulatory requirements
- The patient must be accessible for treatment and follow-up

Additional Inclusion criteria for participation in the HR-/HER2+ sub-protocol:
- Confirmed ER and PR negative and HER2+ by central pathology
- Patients must qualify for neoadjuvant treatment:
  - Clinical cT1c - T4a-c (participation of patients with tumors >cT2 if cN0 is strongly recommended)
  - All clinical N (participation of patients with cN+, irrespective of tumor size is strongly recommended)
- LVEF $\geq$ 50%; LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization)

General Exclusion Criteria:
- Known hypersensitivity reaction to the compounds or incorporated substances
- Prior malignancy with a disease-free survival of < 10 years, except curatively treated basalioma of the skin, pTis of the cervix uteri
- Non-operable breast cancer including inflammatory breast cancer
- Previous or concurrent treatment with cytotoxic agents for any reason after consultation with the sponsor
- Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry (concurrent participation in non-interventional post authorization safety studies not influencing the primary study endpoints is allowed, e.g. WSG PROTROCA for evaluation of primary/secondary G-CSF prophylaxis)
- Male breast cancer
- Concurrent pregnancy; patients of childbearing potential must implement a highly effective (less than 1% failure rate) non-hormonal contraceptive measures during the study treatment
- Breast feeding woman
- Sequential breast cancer
- Reasons indicating risk of poor compliance

Additional Exclusion Criteria for participation in the HER2+/HR- sub-protocol:
- Known polyneuropathy ≥ grade 2
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study
- Inadequate organ function (e.g. hepatic impairment, pulmonary disease, etc.)
- Uncompensated cardiac function (current unstable ventricular arrhythmia requiring treatment, history of symptomatic CHF NYHA classes II-IV), history of myocardial infarction or unstable angina pectoris within 6 months of enrollment, history of severe hypertension, CAD – coronary artery disease)
- Severe dyspnea
- Abnormal blood values:
  - Thrombocytopenia > CTCAE grade 1
  - Increases in ALT/AST > CTCAE grade 1
  - Hypokalaemia > CTCAE grade 1
  - Neutropenia > CTCAE grade 1
  - Anaemia > CTCAE grade 1

Efficacy evaluation	An intention to treat (ITT) analysis will be conducted for all patients. An additional analysis will be conducted among the eligible patients (per protocol).
Statistical considerations	**Summary of basic objectives** Design: To address the issue of a subgroup with favorable pCR rate, the ADAPT HR+/HER2- pre-surgical trial has a randomized, two-arm design.  Patients randomized to Arm A ("no-chemotherapy arm") receive P+H; patients randomized to Arm B ("chemotherapy arm") receive P+H+T. The primary endpoint of the study is pCR after 12 weeks of presurgical therapy. Primary hypothesis: The issue of a pCR rate "sufficiently favorable such that chemotherapy could be omitted" is defined in terms of a non-inferiority test. The trial will test a primary hypothesis of non-inferiority in "early responding" patients who receive no pre-surgical chemotherapy (Arm A) compared to all patients of a group receiving pre-surgical chemotherapy (Arm B). **Specifically, pCR of "early responders" of Arm A is compared with pCR of Arm B as a whole.** Assumptions Arm A: Sample size computations for this primary hypothesis take into account the probability of response in Arm A, the expected overall pCR rate in HER2+/HR- breast cancer under this therapy, and the expected enhanced pCR rate in the responder subset of Arm A: • Assumed overall pCR in arm A (no chemo): 30% • Assumed fraction of arm A with biomarker positive: 40% • Desired "enhanced" pCR in responder subset of Arm A: 60% Assumption Arm B: The computations also take into account an assumed pCR in Arm B (chemo) of 60%. (Possible distinctions between responders and non-responders of Arm B are the subject of secondary endpoints only.) Noninferiority hypothesis:

The primary hypothesis of non-inferiority is defined as pCR difference (delta) no worse than 23%. The following sample sizes will allow this trial to demonstrate the primary hypothesis under the above assumptions with 80% power:

- **n_A=total subjects in Arm A: 143**
- **n_B=total subjects in Arm B: 57**
- **total subjects in both arms: 200 + dropouts**
- **Estimated testing collective: 57 Arm A responders vs. 57 Arm B**

Design ratio:

The trial has a design ratio n_A/n_B=2.5, i.e., **five patients are randomized to Arm A for every two patients in Arm B.**

The design ratio n_A/n_B=2.5 allows the study to keep as many patients as possible in Arm A to test possible secondary endpoints within that group while also satisfying the requirements on overall power for the primary endpoint. The study power will still remain reasonably stable even if there are small deviations, particularly if more patients are admitted to the chemo arm.

Secondary analyses

Estimation of pCR in subgroups:

If the primary hypothesis is confirmed (i.e., the null hypothesis for the primary endpoint is rejected), a secondary analysis will be performed in which pCR will be estimated in three subgroups defined via the combination of treatment and biomarker status.

In these three subgroups, the PCR-rates with confidence intervals adjusted for multiple testing by the Sidak correction (α=0.017) to achieve a family-wise error rate no larger than α=0.05 will have expected precision as follows (Table 1):

Table 6: Estimation of pCR

Treatment arm	Biomarker status	Expected PCR-rate	Expected number of patients	Confidence interval precision*
A: P+H (no chemo)	Positive	60%	57	±14.8%
	Negative	10%	86	±7.9%
B: P+H+T (chemo)	Positive and negative	60%	57	±14.8%

* 98.3% confidence intervals due to Sidak correction

P-values for these comparisons will be adjusted accordingly. From a clinical perspective, a confidence interval precision better than +/-20% would be of potential clinical relevance pending confirmation; for the patient numbers listed in the table, the conditional probability to arrive at the pre-specified precision (i.e., power) exceeds 80% for all three groups.

Predictive quality of the early-response biomarker in Arm A:

Table 2 shows a sample two-factorial frequency distribution (responders / pCR) in 143 patients satisfying the assumptions of Arm A.

Table 7: Arm A

	pCR	no pCR		
test positive	34	23	57	(responders)
test negative	9	77	86	(non-responders)
Total	43	100	143	

The predictive quality of the early-response biomarker in Arm A (pertuzumab and trastuzumab without chemotherapy) will also be reported in terms of characteristics including OR, sensitivity and specificity with respect to the endpoint pCR, together with formal (uncorrected) 95% confidence intervals.

Predictive quality of the early-response biomarker in Arm B:

The same characteristics will also be reported for the early-response biomarker in the chemotherapy arm (Arm B) and in the HER2 positive, HR- study as a whole; this analysis is considered exploratory because there is no prior evidence suggesting a predictive hypothesis (higher pCR in early responders) under chemotherapy.

Exploratory supervised search for pCR classifier:

In exploratory analysis, searches for an optimal biomarker-based pCR classifier by a supervised learning algorithm are planned, including an optimal cutpoint search involving Ki-67 drop and classifier algorithms based on the additional biomarker measurements. An exploratory quality analysis adjusting for the large number of tests will be performed. The adjustments for these tests will be computed by the methods of Lausen et al., Hilsenbek et al., and / or by bootstrap or simulation methods as appropriate depending on the classifier algorithm.

Patient number/ Enrolment period	Run-in phase: 75 patients Main phase: 145 patients In total: 220 patients Number of sites: 30 Enrolment start: Q2 2013 Enrolment stop: Q4 2015 Recruitment for the Substudy was prematurely stopped after analysis of first 120 enroled patients; low propability, that primary objective could be reached Follow-up period: 60 months, may be prolonged half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study

2 Introduction and Background ADAPT HER2+/HR- Breast Cancer

HER2 over-expressing breast cancer with its aggressive biology remains a major clinical challenge. Over-expression of the HER2 gene is reported in about 10-20% of breast cancers. It is associated with poor prognosis[108], with good response to neoadjuvant chemotherapy[109,110], decreased sensitivity to endocrine therapy[85] and response to targeted therapy such as trastuzumab[33,111]. In about half of the cases HER2 positive tumors do not co-express hormone receptors (ER and/or PR). Up to now HER2+/HR+ BC and HER2+/HR- disease have not been looked upon separately. There is a large body of evidence for poor prognosis of HER2+/HR+ BC compared to HER2 negative cases[114]. Nevertheless, prognosis of HER2+/HR+ BC is essentially better than that of HER2+/HR- controls[45,46]

Standard treatment of HER2 + breast cancer

Trastuzumab is a monoclonal antibody against the HER2 receptor. Its use leads to activation of antibody-dependent cellular cytotoxicity, inhibition of extracellular domain cleavage, abrogation of intracellular signaling, reduction of angiogenesis, and decreased DNA repair. These effects are increased by combination with a wide range of anti-cancer agents.

The use of trastuzumab changed the perception of HER2+ metastatic breast cancer as it rendered prognosis of HER2+ patients treated with trastuzumab-based chemotherapy comparable to that of patients with HER2- disease[112]. In the adjuvant setting, the use of trastuzumab (for one year[34] or shorter[113]) sequentially[34] or simultaneously[35] to an adjuvant chemotherapy backbone is associated with a reduction of the relapse risk by about 50%.

In HER2+ early breast cancer (eBC), adjuvant trastuzumab (T) therapy for 52 weeks in combination with chemotherapy is considered gold-standard.

Response evaluation in HER+ breast cancer

Role of pCR in HER2 over-expressing BC (HR+/HR-)

Similar to triple negative (ER and PR and HER2 negative) BC, achievement of pathological complete response (pCR) in patients with a HER2+ subtype is associated with significantly better long-term survival as compared to those patients without pCR[30].

Trastuzumab (T)-containing neoadjuvant chemotherapy has been reported to increase the probability of pathological complete response (pCR) in HER2+ disease up to 67%[36,110,119].

In the NOAH trial, the neoadjuvant use of trastuzumab was associated with improved disease-free survival[36].

The TECHNO trial is the first trial reporting a significant association between pCR after neoadjuvant anti-HER2 therapy (together with chemotherapy) and improved survival in HER2+ disease[31].

Thus, pCR in HER2 over-expressing BC is a validated surrogate parameter for patient outcome and survival.

A recent meta-analysis presented by von Minckwitz et al. revealed a differential prognostic impact of pCR in HER2+/HR- and HER2+/HR+ tumors. pCR was prognostically significant in HR- tumors, but not in HR+ tumors[120]. These data are not supported by other reports[121]. Loibl et al. could further demonstrate that the survival of HER2+/HR- breast cancer patients, who had a pCR after treatment with trastuzumab was even better than that of patients with pCR in HER2- disease[131]. Interestingly, Bianchini et al. reported different pathways responsible for achieving pCR in combination of chemotherapy with trastuzumab in HR+ and HR- tumors.[104]

Dynamic measurement (breast MRI/tumor cell proliferation) as an early surrogate marker for pCR

Recently, neoadjuvant cytotoxic and/or tailored therapies have been suggested as an important tool for evaluation of response to a given systemic therapy *in vivo*. Clinical response measured by sequential evaluation of different proliferation markers (such as Ki-67) following a course of neoadjuvant chemotherapy has been demonstrated to correlate significantly with an increased risk of relapse in patients not achieving pCR[122]. Summing up divergent effects of several anti-HER2 therapies on proliferation, it would be clinically relevant to evaluate such proliferation tools for early prediction of combination therapy efficacy (chemotherapy and

HER2 targeted therapy). So far, it remains unclear which method of proliferation measurement is the optimal marker for response evaluation regarding combined chemo-anti-HER2 therapy. However, measurement of proliferation and apoptosis as well as assessment of changes in PI3K/AKT, IGF and stem cell signaling after a short course of therapy could provide a unique signature for *dynamic* response evaluation and selecting patients for mono vs. combined targeted treatment.
Another way to assess early response could be **molecular imaging** by breast MRI (or other functional dynamic imaging), given the strong evidence, particularly in HER2+ and triple negative breast cancer[52,53]
Changes in contrast medium kinetics in contrast-enhanced MRI (DCE-MRI) or of the ADC (apparent diffusion coefficient) in the diffusion-weighted MRI or drop of the cholin peak in the ^{1}H-MR-Spektroskopy already after short induction therapy are possible measurement instruments for an imaging approach as an alternative non-invasive and complimentary method for dynamic patient stratification within the trial. A further advantage of breast MRI is an analysis of whole tumor (and not only a single biopsy area) and better evaluation of tumor heterogeneity.

New compounds in anti HER2 therapy
Lapatinib
Lapatinib (L) is a small molecule reversible tyrosine kinase inhibitor directed against HER2 and HER1 by binding to the ATP binding site, which prevents receptor phosphorylation and thereby abrogates activation of downstream signaling. Lapatinib demonstrated in vitro-activity in trastuzumab-resistant cells [135], indicating that these agents are non-cross-resistant. In vivo, lapatinib in combination with capecitabine improved progression-free survival in patients resistant to trastuzumab-based therapy compared to capecitabine alone as second-line systemic therapy in metastatic breast cancer [136]. Furthermore, lapatinib is active in combination with both paclitaxel [137] as well as letrozole in HER2 and HR positive metastatic breast cancer [138]. Interestingly, the combination of trastuzumab and lapatinib was reported to have increased efficacy in in-vitro[139,140] and in metastatic setting[141] in patients who were mostly resistant to both individual therapies in their prior course of disease.

Pertuzumab
The HER2–HER3 heterodimer is considered a potent HER dimer pair with respect to strength of interaction, ligand-induced tyrosine phosphorylation and downstream signaling
Pertuzumab is a HER2 dimerisation inhibitor. It is a humanized monoclonal antibody that binds to the dimerization domain of HER2 – an extracellular region essential for HER activation and signaling. Blocking the pairing of the potent signaling HER dimer, HER2:HER3, pertuzumab affects key signaling pathways – including phosphoinositide 3-kinase (PI3K) and AKT – which mediate cancer cell proliferation and survival in cancers such as breast cancer[142-144 145].
As pertuzumab binds to HER2 at the extracellular level, it also activates immune effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC).[146]
In preclinical experiments, small molecule tyrosine kinase inhibitors (TKIs) directed at the HER family fail to fully inhibit HER3-mediated signaling. Blocking HER1 and HER2 activity with tyrosine kinase inhibitors results in upregulation of HER3 activity, leading to survival of tumor cells[144,147]
Preclinical data in a breast cancer xenograft model (KPL-4) single-agent tumor growth inhibition was 38% for pertuzumab and 45% for trastuzumab.
The combination of pertuzumab + trastuzumab was more than additive, with tumor growth inhibition of >100% and complete tumor remission in 6/10 animals[146].

Future perspectives in anti-HER2 therapy - dual blockade of HER2 pathway in HER2+/HR+ and HER2+/HR- disease

Combination of trastuzumab with other HER2-targeted therapies (e.g. HER2/HER1 tyrosine kinase inhibitor lapatinib or HER2/HER3 dimerization inhibitor pertuzumab) is reported to improve significantly pCR rates in both HER2+/HR- and HER2+/HR+ disease.

Trastuzumab + lapatinib

Neo ALTTO was the first trial to report on dual blockade with trastuzumab and lapatinib vs. lapatinib or trastuzumab monotherapy. 455 patients received the anti-HER therapy for 18 weeks + 12 weeks of concurrent weekly paclitaxel. Treatment could not be completed as previewed in 34% (L) , 8% (T) and 39% (T + L) patients due to toxicity mainly diarrhea, hepatic and skin disorders. Pathologic complete remission rates were reported to be 24.7% (L), 29.5% (T) and 51.3% (T+L). In HER2+/HR+ disease the corresponding pCR rates were 16.2%, 22.7% and 41.6%. The benefit in the HER2+/HR- population was higher with pCR rates of 33.8%, 36.5% and 61.3%[38].

Holmes reported data about 100 patients with stage III disease receiving T, L or T+ L for 26 weeks with concurrent FE75C x 4 → Paclitaxel q1w x 12 for 24 weeks. Pathological complete remission was reported in 54% (T), 52% (H) and 74% (T + L)[123].

Chang reported on 66 patients only receiving anti-HER2 dual therapy (L+H) for 12 weeks together with endocrine therapy in ER positive disease. Pathological complete remission rates were 28% for the overall population and 21% in ER positive and 40% in ER negative disease[128].

The Cherlob trial randomized patients to neoadjuvant T, L or L+T with concurrent weekly paclitaxel q1w x 12 → FEC x 4 q3w. Pathological complete response rates were reported to be 25.7% for T, 27.8% for L, and 43.1% for T+L. For HR positive disease pCR rates were 25%, 22.7% and 36.7%. For HR negative disease pCR rates of 26.6%, 35.7% and 56.2%[124].

Trastuzumab + pertuzumab

NEOSPHERE is a neoadjuvant trial in 417 patients with operable, locally advanced or inflammatory breast cancer. Patients received either 12 weeks of standard therapy with docetaxel and trastuzumab or standard + pertuzumab or docetaxel + pertuzumab or dual blockade with pertuzumab and trastuzumab without a chemotherapy backbone. The primary endpoint was the comparison of pCR rates, one secondary endpoint was toxicity. The dual blockade did not significantly increase the toxicity compared to standard treatment and especially no increased rates of cardiotoxicity were reported. Within the four arms pCR rates were: 29 % for standard treatment, 45 % if pertuzumab was added, 24 % for docetaxel + pertuzumab and 16.8% for dual blockade without chemotherapy. In this latter treatment arm (12 weeks pertuzumab + trastuzumab) the NEOSPHERE trial reports a pCR rate of 6% (in HER2+/HR+) and 29% in HER2+/HR-[43].. CLEOPATRA tested and trastuzumab + docetaxel ± pertuzumab in first line therapy of 808 patients with metastatic breast cancer. 10.1% in the standard arm and 11.7% of patients in the experimental arm were pretreated with trastuzumab. Overall response rate was 69.3 vs. 80%, median PFS increased by 6.1 months from 12.4 to 18.5 months and overall survival was significantly improved by dual HER2 blockade with trastuzumab and pertuzumab (HR 0.64, p=0.0053). The combination of pertuzumab and trastuzumab plus docetaxel increased rates of diarrhea, rash, mucosal inflammation, febrile neutropenia, and dry skin. These adverse events were primarily grades 1–2, manageable, and occurred during docetaxel therapy. Cardiac adverse events or LVSD were not increased[132].

TRYPHANEA is a randomized phase II neoadjuvant trial comparing the same dual blockade plus anthracycline-taxane-based (FEC→ Doc concurrent or sequential) or carboplatin-taxane-based standard chemotherapy (Doc/Carbo) regimens. Primary endpoint was cardiac safety, secondary endpoints were toxicity and efficacy parameters. Incidence of cardiac events was low irrespective of treatment arms. Pathologic complete response rates were 57.3 – 66.2% in the overall population and 65% to 83.8% in the HER2+ hormone insensitive tumors[133]. In September o f2013, neoadjuvant trastuzumab and pertuzumab has received FDA approval.

Role of chemotherapy in HER2 + breast cancer treated with dual blockade with T + P

The only available data come from the neoadjuvant Neosphere trial, which compared docetaxel + trastuzumab vs. docetaxel + trastuzumab + pertuzumab vs. trastuzumab + pertuzumab vs. docetaxel + pertuzumab in 417 patients. The pCR rate is 45.8 vs. 16.8% for docetaxel + trastuzumab and pertuzumab vs. trastuzumab and pertuzumab. For HR- disease the corresponding rates were 63.2% vs. 29.1%.

Due to short follow-up of the studies, only little data on a survival impact of increased pCR rates from combination therapy are available so far. First survival data from NeoALTTO showed an EFS advantage for dual blockade only for HER2+ HR- tumors (Piccart et al, SABCS 2013).

The ADAPT philosophy – A combined static and dynamic model

Early response assessment in eBC may be essential to separate sub-populations with large or marginal benefit from therapy.

Drop of proliferative activity after a short course of endocrine therapy (2 weeks to 4 months) as measured by proliferation marker Ki-67 is an excellent predictor for local as well as systemic outcome in HR+ disease. It allows to identify groups of patients with excellent outcome in both low and higher risk groups independently from chemotherapy application[25-27]. ADAPT applies this dynamic model to all early breast cancer subtypes. First step is a broad baseline assessment (conventional central pathology, RS, biomarker) of prognosis. Sequential tissue sampling is realized (3 week interval, core biopsies and surgery) after a short induction anti-HER2/cht/endocrine- treatment. Thus, besides baseline prognosis estimation (***static* assessment**), therapy efficacy is evaluated at an early time of treatment (***dynamic* assessment**).

Beyond baseline biomarker assessment, the primary endpoint of the ADAPT HER2+ and TN protocols is the definition of molecular surrogate markers predictive for pCR and 5 year event-free survival.

The ADAPT-principle of the trial is flexible enough to incorporate modifications based on new translational or clinical research data from HER2+ eBC. The trial will also establish and validate a model which allows rapid testing of various targeted and conventional (and combinations thereof) therapy approaches in a multicenter setting.

3 Rationale ADAPT HER2+/HR- Breast Cancer

ADAPT is designed to assess early response to therapy in all breast cancer subtypes. After a short subtype-specific 3 week “induction” treatment therapy response is assessed by dynamic biomarker assessment in tumor tissue derived from a second core biopsy.

Patients with HER2+ breast cancer are conventionally candidates for adjuvant chemotherapy. Early data for dual anti-HER2 blockade suggest substantial improvement of pCR rates as compared to trastuzumab monotherapy.

Pertuzumab and lapatinib are the best evaluated partners for dual blockade.

Pertuzumab is a humanized monoclonal antibody blocking the pairing of the most potent signaling HER dimer, HER2:HER3 thus affecting the key signaling pathways which mediate cancer cell proliferation and survival in breast cancer. Neosphere, Cleopatra and Tryphanea document high activity of the dual blockade with trastuzumab and pertuzumab in HER2+ early and metastatic breast cancer.

The role of chemotherapy in this context has to be re-evaluated since we learned that HER2+ disease is a heterogeneous subgroup[131]. HER2+/HR+ patients have better outcome, but pCR rates reported from the neoadjuvant trials are substantially lower than those for HER2+/HR- patients. ADAPT HER2+/HR+ will explore the potential role of T-DM1 and endocrine therapy as substitute for chemotherapy in these patients.

In HER2+/HR- patients - according to the data presented by Loibl et al. - the effect of anti-HER2 therapy is even more important than in HER2+/HR+ disease[131]. The hypothesis that a large subgroup of HER2+ patients responds to this targeted treatment has been confirmed.

Nevertheless, we learned from the first generation of anti-HER2 trials such as HERA[34] and from metastatic disease that primary resistance to anti-HER2 therapy with trastuzumab exists. ADAPT HER2+/HR- will test 12 week dual blockade with trastuzumab + pertuzumab vs. identical dual blockade with 12 weeks of taxane chemotherapy backbone. After 12 weeks of treatment surgery will be performed with assessment of pCR rates. After surgery patients will receive standard treatment.
ADAPT HER2+/HR- tries to identify an early biomarker (profile) for response to anti-HER2 dual blockade ± taxane backbone. The trial primarily aims at the identification of good responders to dual HER2 blockade, who do not need chemotherapy. It will also allow for exploratory biomarker analyses in non-responders, who according to the recently published data from GEPARTRIO trial might benefit from non-cross-resistant further therapy[68].

4 Study Objectives ADAPT HER2+/HR- Breast Cancer

Run-in phase concept:
Primary objective

- Identification of molecular markers correlating with early response/pCR
- Feasibility/reproducibility of assessment of these markers
- Validation of statistical assumptions made for the whole sub-trial

Run-in + Main phase concept:
Primary objective

- Definition of a biomarker (profile) characterizing “good responders” to dual blockade T and P anti-HER2 blockade that have similar pCR rates as patients treated with identical dual anti-HER2 Blockade + taxane backbone

Secondary objectives

- Evaluation of dynamic test regarding prediction of 5-year event-free survival (EFS)
- Overall survival
- Relapse free survival
- Local and regional relapse free survival
- Toxicity/cardiac safety
- Evaluation of predictive value of molecular imaging with breast MRI for pCR
- Health-related quality of life (HRQL) (optional)
- Cost-effectiveness (to be defined)

Exploratory analysis:

- Translational research
- Survival of patients with pCR (as part of the phase III umbrella protocol)

5 Study Design ADAPT HER2+/HR- Breast Cancer

The ADAPT HER2+/HR- breast cancer sub-trial is a modern biomarker-based adjuvant, prospective, multi-center, controlled, non-blinded, randomized phase II trial.

Following the diagnostic core biopsy and identification of a HER2+/HR- tumor, the patients meeting the inclusion/exclusion criteria will be registered for the trial, after informed consent was obtained. The patient will be randomized right from the beginning to either trastuzumab + pertuzumab or trastuzumab + pertuzumab + taxane-based chemotherapy. Patients will be treated for three weeks with the respective regimen for induction treatment and will then

undergo the second core biopsy for efficacy estimation and response assessment. After completion of 12 weeks of targeted therapy within either of the two treatment arms the patients will undergo surgery and pCR will be assessed.
Further standard adjuvant chemotherapy is strongly recommended after completion of study treatment.
Patients without pCR will be treated with a standard of care post-study adjuvant chemotherapy regimen following the surgery and will receive treatment with trastuzumab for 40 weeks to complete 52 weeks of trastuzumab treatment. For patients with pCR the adjuvant chemotherapy regimen can be optionally omitted at the discretion of the investigator and the patient's informed consent (in the taxan-containing arm, only).
The HER2+/HR- study design is depicted in figure 1 below.

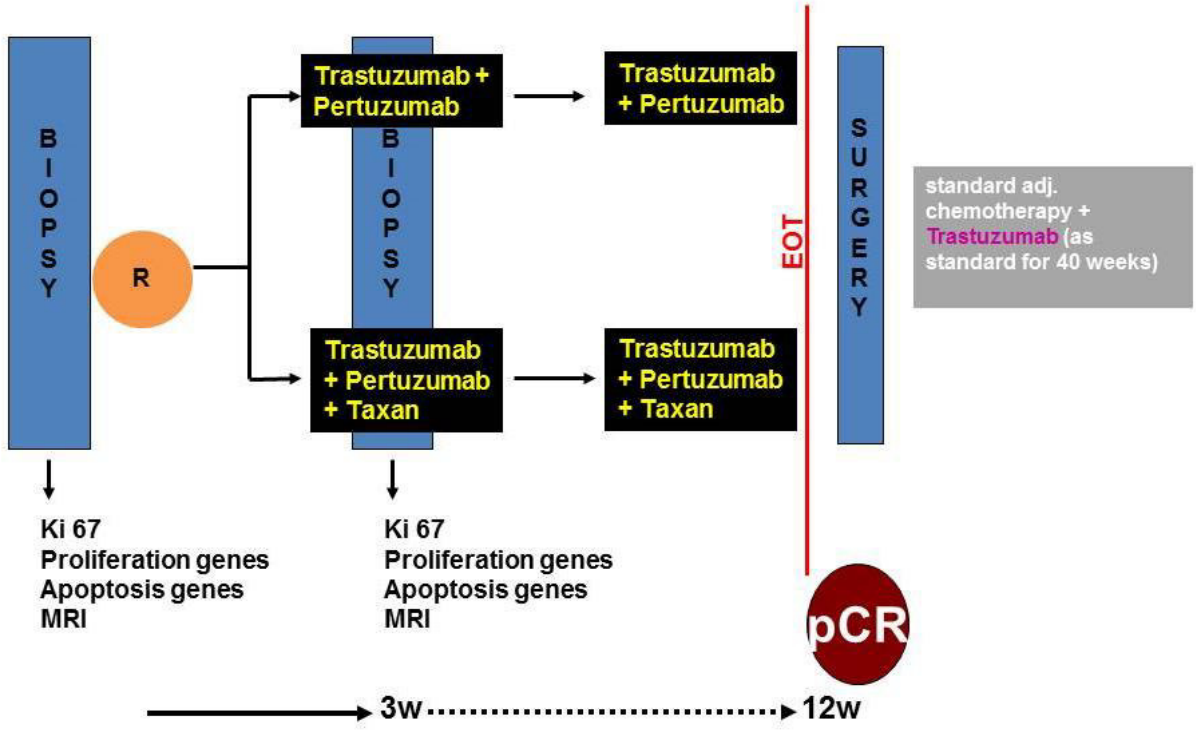


Figure 1: *Study Design for ADAPT HER2+/HR- Breast Cancer*

5.1 Run-in Phase and Main Phase

For further information please refer to the ADAPT umbrella protocol, chapter 5.1. The run in phase of the HER2+/HR+ protocol will include 150 patients and the main phase 292 patients.

5.2 Timing of Surgery

The surgery is to be done after 12 weeks (or prolonged) neoadjuvant therapy, i.e. following end of therapy. SLN see ADAPT Umbrella.

6 Patient Enrollment HER2+/HR-

Following the diagnostic core biopsy and local pathology assessment, the patients meeting the inclusion/exclusion criteria will be informed about the ADAPT trial and HER2+/HR- sub-trial. After signing the informed consent patients will be registered and subsequently randomized to one of the two treatment arms.

The following examinations are mandatory prior to randomization:

Table 1: *Study Evaluations for Participation in ADAPT HER2+/HR- Breast Cancer Trial*

	INVESTIGATIONS	TIMING
Negative ER and PR status **according to local pathology**	✔	Prior to registration (standard of care)
Positive HER2 status **according to local pathology**	✔	Prior to registration (standard of care)
Clinical or pathological nodal status	Participation of patients with cN+ is strongly recommended, if cT1c	Prior to registration (standard of care)
Grading		Prior to registration (standard of care)
Ultrasound		Prior to registration (standard of care)
History[1] and physical exam for patients receiving chemotherapy	Physical examination including: • Height • Weight • Karnofsky index for performance status/vital signs	≤ 7 days prior to randomization
LVEF ≥ 50%	Echocardiography	Within 42 days prior to randomization

[1]Within 3 weeks prior to registration

6.1 Additional Inclusion Criteria ADAPT HER2+/HR- Breast Cancer

In order to be eligible for the participation in the ADAPT HER2+/HR- breast cancer trial, patients, who meet the general inclusion criteria of the ADAPT trial also have to meet the following additional inclusion criteria:

- Confirmed ER and PR negative and HER2+ by central pathology
- Patients must qualify for neoadjuvant treatment:
    - Clinical cT1c - T4a-c (participation of patients with tumors >cT2 if cN0 is strongly recommended)
    - All clinical N (participation of patients with cN+, irrespective of tumor size is strongly recommended)
- LVEF ≥ 50%; LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization)

6.2 Additional Exclusion Criteria ADAPT HER2+/HR- Breast Cancer

In order to be eligible for the participation in the ADAPT HER2+/HR- breast cancer trial, patients, who meet the general exclusion criteria of the ADAPT trial **must** also **not** meet any of the following additional exclusion criteria:

- Known polyneuropathy ≥ grade 2
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study
- Inadequate organ function (e.g. hepatic impairment, pulmonary disease, etc.)
- Uncompensated cardiac function (current unstable ventricular arrhythmia requiring treatment, history of symptomatic CHF NYHA classes II-IV), history of myocardial infarction or unstable angina pectoris within 6 months of enrollment, history of severe hypertension, CAD – coronary artery disease)
- Severe dyspnea
- Abnormal blood values:
    - Thrombocytopenia > CTCAE grade 1

- Increases in ALT/AST > CTCAE grade 1
- Hypokalaemia > CTCAE grade 1
- Neutropenia > CTCAE grade 1
- Anaemia > CTCAE grade 1

6.3 Randomization to ADAPT HER2+/HR- Breast Cancer

Each eligible patient will be registered and subsequently randomized after informed consent was obtained, to receive either:

Arm A: Trastuzumab + Pertuzumab

- Trastuzumab (8 mg/kg initial dose, 6 mg/kg q3w for 12 weeks) + Pertuzumab (840 mg initial dose, 420 mg for 12 weeks)

Arm B: Trastuzumab + Pertuzumab + paclitaxel weekly

- Trastuzumab (8 mg/kg initial dose, 6 mg/kg q3w for 12 weeks) + Pertuzumab (840 mg initial dose, 420 mg for 12 weeks) + paclitaxel weekly 80 mg/m^2 x 12

The randomization forms have to be filled in online in the e-CRF. After completion it has to be printed, signed by an investigator and faxed to the coordinator of the study:

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The following information will be requested:

- Institution name
- Investigator's name
- Patient's identifiers (site number, patient code)
- Patient's birth date (day/month/year)
- Type of tumor (HR+/HER2-, HER2+/HR-, HER2+/HR+ or TN)

A patient who was not randomized prior to the first treatment administration will not be accepted for the study at a later date.
The patient randomization result will be available in the e-CRF within 24 hours after the randomization request fax was obtained.

6.3.1 Arm A: Trastuzumab + Pertuzumab

Trastuzumab

Initial dose:	8 mg/kg bodyweight, day 1 of initial administration
Preservation dose:	6 mg/kg bodyweight, day 1 of subsequent administrations
Route:	Intravenous infusion
Schedule:	Every 3 weeks

Pertuzumab

Initial dose:	840 mg, day 1 of initial administration
Preservation dose:	420 mg, day 1 of subsequent administrations
Route:	Intravenous infusion
Schedule:	Every 3 weeks

This is called a cycle of treatment and is to be given four times.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

6.3.2 **Arm B: Trastuzumab + Pertuzumab + Paclitaxel**

Trastuzumab

Initial dose:	8 mg/kg bodyweight, day 1 of initial administration
Preservation dose:	6 mg/kg bodyweight, day 1 of subsequent administrations
Route:	Intravenous infusion
Schedule:	Every 3 weeks

Pertuzumab

Initial dose:	840 mg, day 1 of initial administration
Preservation dose:	420 mg, day 1 of subsequent administrations
Route:	Intravenous infusion
Schedule:	Every 3 weeks

This is called a cycle of treatment and is to be given four times.

Paclitaxel

Dose:	80 mg/m², day 1
Route:	1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule:	Every week

This is called a cycle of treatment and is to be given 12 times. Following completion of 12 cycles with paclitaxel, the patient will either enter the anthracycline segment for this arm of treatment or undergo surgery, if neoadjuvant treatment is intended.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

7 Study Plan ADAPT HER2+/HR- Breast Cancer

7.1 Definition of Study Medication ADAPT HER2+/HR- Breast Cancer

For the purpose of this sub-trial pertuzumab will be labeled study-specific and is considered study medication.
Documentation of preparation and distribution of the study medication has to be documented in accordance with the Investigator's Brochure.

7.2 Study Treatment ADAPT HER2+/HR- Breast Cancer

For induction treatment patients will receive either trastuzumab + pertuzumab or trastuzumab + pertuzumab + taxane-based chemotherapy for 3 weeks.
After completion of induction treatment, patients will obtain the second core biopsy for efficacy estimation. The treatment regimen from induction treatment will be continued for three further cycles until end of treatment and surgery.
Study treatment should be discontinued in case of disease progression and the patient should undergo surgery.
In case of clinical tumor burden (non-pCR) after 12 weeks, neoadjuvant therapy may be prolonged as stated below. Chemotherapy may be applied as stated for adjuvant therapy. Total duration of anti-HER2 therapy (neoadjuvant and adjuvant) should be one year.
Post-study treatment with adjuvant chemotherapy is planned as standard of care at the discretion of investigator.

7.2.1 Pertuzumab Formulation, Preparation and Storage

For additional details, please refer to the current version of the pertuzumab Investigator Brochure.

7.2.2 Dosing and Administration – Trastuzumab

IV trastuzumab will be administered as described in the Herceptin® SmPC/local prescribing information and Investigator Brochure. Weight should be recorded at screening and prior to subsequent IV trastuzumab infusions. An initial loading dose of 8 mg/kg should be given for the first cycle (induction therapy). All other doses are 6 mg/kg trastuzumab every 3 weeks for another 3 cycles.
The first infusion of IV trastuzumab should be given over approximately 90 minutes. If the initial dose of IV trastuzumab was well tolerated, subsequent doses can be administered as a 30-minute infusion. It is recommended to observe patients at the start of infusion for fever, chills and other infusion-related symptoms. Interruption or slowing of the infusion may help control such symptoms and may be resumed when symptoms abate. All infusion-related symptoms must have resolved before the patient is discharged, unless deemed clinically not significant by the investigator. Patients, who experience infusion-related symptoms may be pre-medicated with paracetamol and antihistamines for subsequent infusions at the discretion of the investigator.

7.2.3 Dosing and Administration – Pertuzumab

Pertuzumab will be administered on day 1 of a 3-week cycle every 3 weeks at an initial loading dose of 840 mg (induction therapy). All other doses are 420 mg every 3 weeks for another 3 cycles.
The first infusion of pertuzumab will be administered over 60 minutes (± 10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs must be assessed before and after dose administration.

Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable.
Premedication with paracetamol and/or antihistamines may be given at the investigator's discretion.
Trastuzumab and pertuzumab may be delayed due to toxicities. If trastuzumab or pertuzumab are withheld for more than 6 weeks the patient will be withdrawn from all study treatment and will be treated at the discretion of the investigator. Dose modifications are not allowed. If trastuzumab or pertuzumab are withheld for more than 6 weeks a (re)loading dose is required.

7.2.4 End of Treatment (EOT) Definition ADAPT HER2+/HR- Breast Cancer

End of treatment is defined as 21 days after the last application of study drug and prior to surgery. pCR will be the target endpoint of the study. Any further treatment after surgery is at the discretion of the investigator, but it is highly recommended to treat patients with standard therapy Patients should receive complete standard adjuvant chemotherapy treatment (preferentially taxane → EC x 4 or EC x 4 → taxane), if randomized to the dual blockade alone arm or anthracyclines alone (EC x4) if randomized to the taxane-containing arm: They should complete a total of 52 weeks of trastuzumab.

7.2.5 End of Study

End of study is defined as database closure.

7.2.6 Prophylactic Premedication Regimen

Premedication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, anti-histamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.

7.2.7 Concomitant Treatment during Targeted Treatment

For permitted prophylactic premedication please refer to the previous chapter.
Ancillary treatments will be given as medically indicated. Any concomitant medication must be documented in the Case Report Form.

7.3 Post-Study Treatment – Adjuvant Chemotherapy

In case of clinical tumor burden (non-pCR) after 12 weeks, neoadjuvant therapy may be prolonged as stated below. Chemotherapy may be applied as stated for adjuvant therapy. Total duration of anti-HER2 therapy (neoadjuvant and adjuvant) should be one year.
After completion of 12 weeks of neoadjuvant targeted study treatment and surgery, post-study treatment by adjuvant chemotherapy is at the discretion of the investigator. Standard adjuvant chemotherapy is highly recommended.
If the patients are treated by post-study standard adjuvant chemotherapy, the patients should be treated by trastuzumab for 40 weeks to complete 52 weeks of trastuzumab treatment.

7.4 Follow-up

For the follow-up please refer to the ADAPT protocol, chapter 7.10.

7.4.1 **Therapy after Protocol Treatment is discontinued**

Except for study targeted therapy and radiotherapy as per protocol, no further antitumor therapy is allowed (surgery, chemotherapy, immunotherapy, etc.) before tumor relapse is documented.
If patients are removed from the study because of disease relapse, further treatment is at the discretion of the investigator. The metastatic regimen(s) used will be documented in the Case Report Form.

8 Study Evaluations ADAPT HER2+/HR- Breast Cancer

8.1 Evaluation during Targeted Treatment

While under targeted treatment, all patients must be examined according to the schedule outlined below until they come off therapy.

Table 2: *Study Evaluations before each Cycle of anti- HER2-Treatment*

ASSESSMENT	BL	Cycle 1[4]	Cycle 2[4]	Cycle 3[4]	Cycle 4[4]	EOT	Surgery
week	-3 to 0	1	4	7	10	13	14
Medical history (incl. concomitant medications)	x						
Central pathology review of diagnostic core biopsy	x						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x[2]	x	x	x	x	x	
Serum sample (biomarker analysis)	x[26]		x[6]			x[6]	
Radiology: • Chest X-ray • Bone scan • Liver imaging • Mammography	x[3]						
Breast MRI (inclusion of patients without MRI is allowed)	x[6]		x[6]				x[6] prior to surgery
Ultrasound	x		x	x		x	
Clinical assessment	x[2]		x	x	x	x	
Pregnancy test	x						
ECG and LVEF	x[5]			x			x prior to surgery
Laboratory: • Hematology • Biochemistry	x	x	x	x	x	x	
Surgery or confirmation of non-pCR							x
(Serious) Adverse Event		continuously					
Concomitant medication	x	continuously					

[1] prior to 2nd administration of study drug
[2] within ≤ 7 days prior to randomization
[3] within 3 months prior to randomization
[4] +/-3 days

[5] within 42 days prior to randomization
[6] optionally

Physical examination will include:

- Weight
- ECOG or Karnofski index for performance status
- Clinical tumor assessment

Laboratory work-up will include:
Hematology:

- Hemoglobin
- WBC
- Neutrophils
- Platelets count

Biochemistry:

- Alkaline phosphatase
- ASAT (SGOT)
- ALAT (SGPT)
- Bilirubin
- Serum creatinine
- Creatinine clearance
- Electrolytes: Na^+, K^+, Cl^-

8.2 Evaluation at End of Induction Treatment

Please refer to chapter 7.8 of the ADAPT protocol for further information.

8.3 Evaluation at End of Treatment (EOT)

To be performed latest 21 days after the last treatment and/or prior to surgery. Work-up will include:

- Physical examination with Karnofsky Index or ECOG
- Hematology, biochemistry
- Documentation of toxicity

8.4 Evaluation in Follow-up after End of Treatment

Patients will be followed every 6 months for two years starting from registration and every 12 months thereafter until year 5 (corresponding to German aftercare plan) or until relapse to document:

- Event-free survival
- Overall survival
- Further therapy
- Long term toxicities
- Relapse (local relapse)
- 2nd primary malignancy
- First treatment for metastatic breast cancer or 2nd primary malignancy
- Results for biopsy of distant metastases (if feasible)

Timing of follow-up visits is based on the date of registration. Follow-up visits will be scheduled at month 6, 12, 18, 24, 36, 48, and 60 after registration. Patients who relapse or suffer from 2nd primary malignancy will only be followed for survival. For any distant metastasis occurring, if biopsied, IHC should be reported in the CRF.

Patients completing follow-up month 60 may be followed half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study, provided that an additional informed consent regarding prolongation of the follow-up was signed.

8.5 Response Assessment

Please refer to the ADAPT Umbrella protocol chapter 8.6.

9 Dose Delays and Reduction/Modification ADAPT HER2+/HR- Breast Cancer

9.1 Treatment Dose Adjustments and Treatment Delays

Toxicities will be graded using the NCI Common Toxicity Criteria (NCI CTC), version 4.0.

Dose reduction is planned for the chemotherapy containing treatment arm in case of severe hematological and/or non-hematological toxicities. Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. In case of several toxicities in one patient and conflicting recommendations, the most conservative dose adjustment has to be followed.
Doses which have been reduced for toxicity must not be re-escalated with the exception of liver function tests that improve within ranges given.

9.1.1 Dose Adjustments and Treatment Delays – Trastuzumab

For trastuzumab no dose adjustments are applicable. Trastuzumab and pertuzumab may be delayed due to toxicities. If trastuzumab or pertuzumab are withheld for more than 6 weeks the patient will be withdrawn from all study treatment and will be treated at the discretion of the investigator. Dose modifications are not allowed. If trastuzumab or pertuzumab are withheld for 6 weeks a (re)loading dose is required.

9.1.2 Dose Adjustments and Treatment Delays – Pertuzumab

Treatment with pertuzumab may be delayed no more than 42 days to allow recovery from acute toxicity. Trastuzumab and pertuzumab may be delayed due to toxicities. If trastuzumab or pertuzumab are withheld for more than 6 weeks the patient will be withdrawn from all study treatment and will be treated at the discretion of the investigator. Dose modifications are not allowed. If trastuzumab or pertuzumab are withheld for 6 weeks a (re)loading dose is required.

Patients should be assessed for toxicity prior to each dose. Dosing will occur only, if the clinical assessment and laboratory test values are acceptable.
Dose delays are designed to maximize treatment for those who derive clinical benefit from treatment, while ensuring patient safety.
Dose delays for pertuzumab-related toxicity are specified in Appendix 1 – Treatment Dose Adjustments and Treatment Delays for ADAPT HER2+/HR- Breast Cancer.

9.1.3 Dose Adjustments and Treatment Delays – taxane-based chemotherapy

Treatment with paclitaxel may be delayed no more than 14 days to allow recovery from acute toxicity. The following dosing levels are applicable for paclitaxel:

- **Level 0** (initial dose): 80 mg/m² BSA
- **Level -1:** 60 mg/m²
- **Level -2:** 50 mg/m²

Dose adjustments for paclitaxel-related toxicity are specified in Appendix 1 – Treatment Dose Adjustments and Treatment Delays.

9.2 Toxicity Related Guidelines for Dose Reduction and Dose Modification of Trastuzumab + Pertuzumab + Taxane-Based Chemotherapy

Please refer to the ADAPT protocol, Appendix 1 – Treatment Dose Adjustments and Treatment Delays for further information.

10 Safety Monitoring

10.1 Safety Plan

Overall safety will be assessed on an ongoing basis during the conduct of the study. The DSMB (IDMSC) will monitor cumulative safety data at least once every 6 months during the course of the study. In addition, data on serious adverse events and deaths will be monitored by the DSMB (IDMSC) at least once every 3 months.

10.2 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording of protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urinalysis variables; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study drugs.

The Sponsor or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities, Roche and participating investigators, in accordance with ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

The Sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event. Roche will be notified within 1 business day.

The Sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification. Roche will be notified within 1 business day.

10.3 Adverse Event Reporting

The investigator is responsible for ensuring that all AEs and SAEs (as defined in chapter 12 of the ADAPT umbrella protocol) are recorded in the e-CRF and reported to the sponsor in accordance with protocol instructions. Additional reference document for AE reporting is the respective IB in its current version. For patient safety, all AEs must be documented in the e-CRF**, irrespective of the CTC Grade in the ADAPT HER2+/HR- sub-trial**. Coding of AEs will be done according to mEDRA.

Investigators should use correct medical terminology/concepts when recording AEs or SAEs in the e-CRF. Avoid colloquialisms and abbreviations. There is one e-CRF page for recording AEs and a hardcopy printout page for recording SAEs. Only one medical concept should be recorded in the event field on the (Serious) Adverse Event report.

10.3.1 Adverse Event Reporting Period

After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as blood draws or no treatment run-in).
After initiation of study treatment (the Genentech/Roche product(s) or other investigational medicinal product), all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see chapter 12).

10.3.2 Eliciting Adverse Events

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:
“How have you felt since your last clinic visit?”
“Have you had any new or changed health problems since you were last here?”

10.3.3 Type and Duration of Follow-up of Patients after Adverse Events

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost-to-follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event e-CRF and in the patient’s medical record to facilitate source data verification (SDV).
For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

10.3.4 Post-Study Adverse Events

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient’s personal physician believes could be related to prior study treatment.
The investigator should notify the sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation, if deemed to be related to prior study treatment. The sponsor should also be notified, if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to the sponsor on the study e-CRF. If the study e-CRF is no longer available, the investigator should report the event directly to the sponsor via telephone.

10.3.5 Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the e-CRF.
However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the e-CRF.
For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the e-CRF.

10.3.6 **Persistent or Recurrent Adverse Events**

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the e-CRF. The persistent AE will be only documented once with the highest CTC Grade occurring.
A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event e-CRF.

10.3.7 **Abnormal Laboratory Values**

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the e-CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).
If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event e-CRF.
If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the e-CRF.
If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as “hyperkalemia.”
Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the e-CRF, unless the seriousness, or etiology changes.

10.3.8 **Deaths**

Deaths that occur during the protocol-specified AE reporting period (see chapter 10.3.1 of the ADAPT HER2+/HR- sub-protocol) that are attributed by the investigator solely to progression of breast cancer will be recorded only on the Death Report Form (DRF) in the e-CRF. All other on-study deaths, regardless of attribution, will be recorded on an e-CRF and expeditiously reported to the Sponsor. An independent monitoring committee will monitor the frequency of deaths from all causes.
When recording a death on the e-CRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the e-CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record “Unexplained Death” on the DRF in the e-CRF.
During post-study survival follow-up, deaths attributed to progression of breast cancer will be recorded only on the Survival e-CRF.

10.3.9 **Relevant Medical History**

Relevant medical history includes any preexisting medical condition that is present at the start of the study. Such conditions should be recorded on the Baseline 1 e-CRF page.
A preexisting medical condition should be only recorded as an AE or SAE if the frequency, severity, or character of the condition worsens during the study.
When recording such events on an Adverse Event, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

10.3.10 **Worsening of Breast Cancer**

Worsening and/or progression of breast cancer should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

10.3.11 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed
- Receive scheduled therapy for the target disease of the study

10.3.12 Pregnancy

If a female patient becomes pregnant while receiving investigational therapy (Pertuzumab or comparative treatment) or within 6 months after the last dose of investigational product, a Pregnancy Report Form should be completed and expeditiously submitted to the sponsor within **24 hours** of learning of the pregnancy, to facilitate outcome follow-up. The Pregnancy Report Form will be available for printout from the e-CRF, but should be available as hardcopy at each study site from the Investigator Site File. The Pregnancy Report Form has to be faxed along with the Pregnancy Fax Cover Page to the Sponsor.

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The pregnancy should not be recorded on the Adverse Event e-CRF.
Abortion, whether therapeutic or spontaneous, should always be classified as serious (as the sponsor considers these medically significant), recorded on an e-CRF, and expeditiously reported to the Sponsor.
Any congenital anomaly/birth defect in a child born to a female patient should be recorded and reported as an SAE.

10.4 Cardiac Safety Monitoring

Since targeted anti-HER2 treatment has been implicated in cardiac toxicity there is a need to monitor cardiac safety, as both trastuzumab and pertuzumab are directed against HER2, although, there is currently no suggestion of increased cardiac toxicity with pertuzumab combinations.

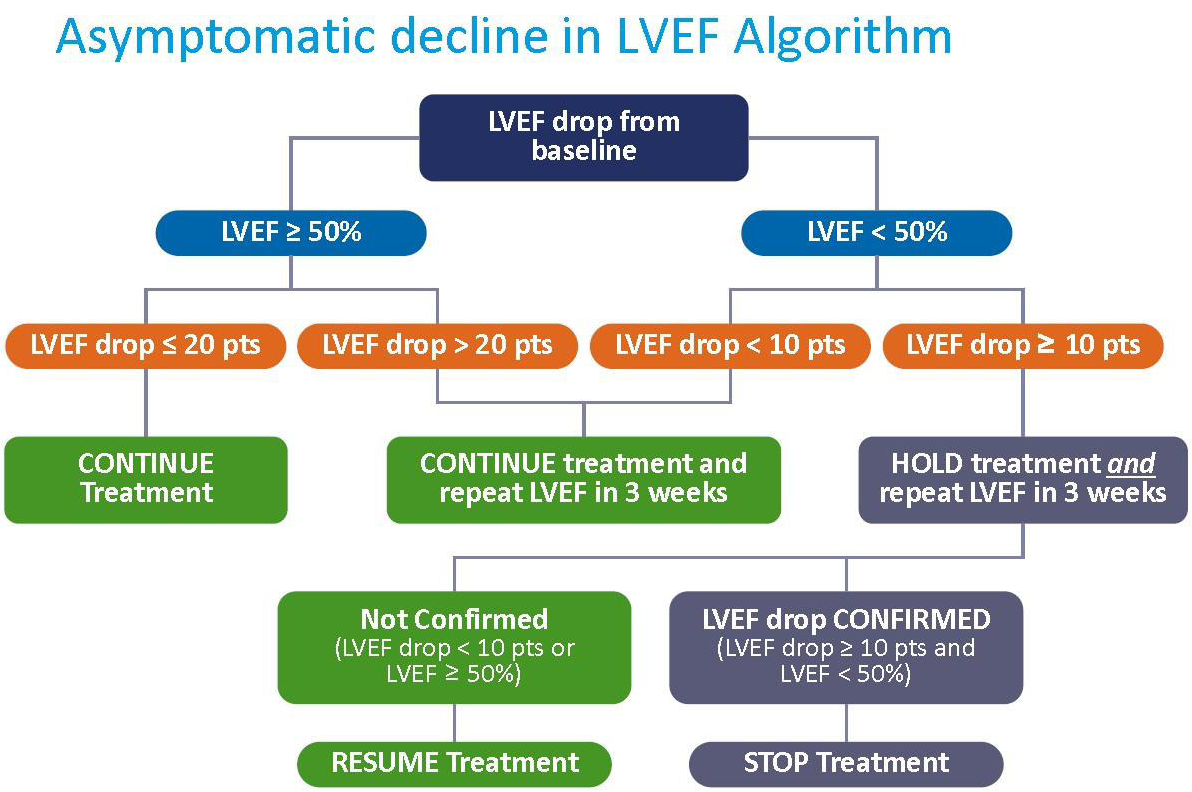

Figure 2: *Asymptomatic decline in LVEF Algorithm.*

11 Data Analysis and Statistical Considerations

The issue is whether an early-response biomarker can be found that defines a subgroup of patients ("early responders") with an "enhanced" rate of pCR, that is, their rate turns out to be sufficiently favorable such that chemotherapy could be omitted in a clinical context.

The study comprises a **Run-in phase** (n=75) and a **Main phase** (n=145), total: 220 patients.

11.1 Run-in phase

The Run-in phase has the following objectives:

- Validation of statistical assumptions made for the whole ADAPT HER2+/HER2- trial
- Identification of molecular markers correlating with early response/pCR
- Feasibility/reproducibility of assessment of these markers

"Early response" during the run-in phase is defined in terms of Ki-67 measurements after 3 weeks, as in the ADAPT study as a whole.

11.2 Primary endpoints and hypothesis testing

Design:

To address the issue of a subgroup with favorable pCR rate, the ADAPT HR+/HER2- pre-surgical trial has a randomized, two-arm design (Figure 23):

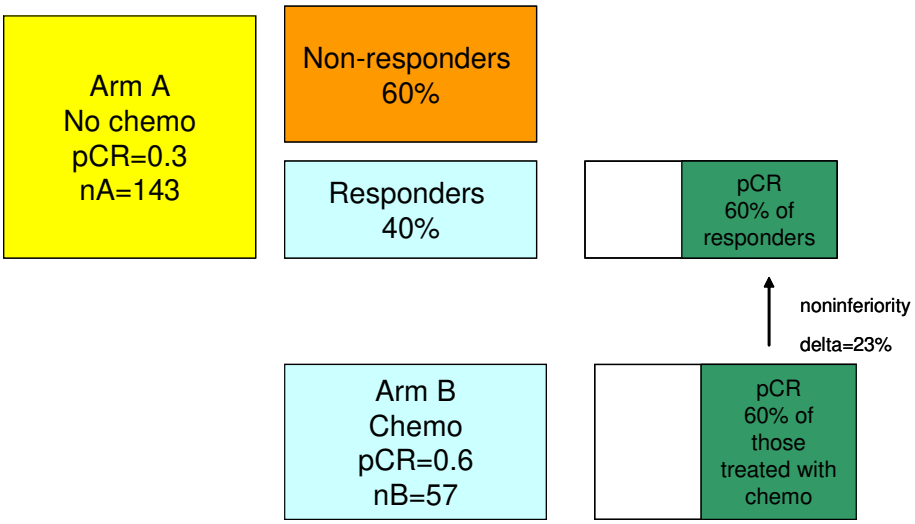

Figure 2: Design and primary hypothesis test.

Patients randomized to Arm A ("no-chemotherapy arm") receive P+H; patients randomized to Arm B ("chemotherapy arm") receive P+H+T. The primary endpoint of the study is pCR after 12 weeks of presurgical therapy.

Primary hypothesis:

The issue of a pCR rate "sufficiently favorable such that chemotherapy could be omitted" is defined in terms of a non-inferiority test. The trial will test a primary hypothesis of non-inferiority in "early responding" patients who receive no pre-surgical chemotherapy (Arm A) compared to all patients of a group receiving pre-surgical chemotherapy (Arm B). **Specifically, pCR of "early responders" of Arm A is compared with pCR of Arm B as a whole.**

Assumptions Arm A:

Sample size computations for this primary hypothesis take into account the probability of response in Arm A, the expected overall pCR rate in HER2+/HR- breast cancer under this therapy, and the expected enhanced pCR rate in the responder subset of Arm A:

- Assumed overall pCR in arm A (no chemo): 30%
- Assumed fraction of arm A with biomarker positive: 40%
- Desired “enhanced” pCR in responder subset of Arm A: 60%

Assumption Arm B:

The computations also take into account an assumed pCR in Arm B (chemo) of 60%. (Possible distinctions between responders and non-responders of Arm B are the subject of secondary endpoints only.)

Noninferiority hypothesis:

The primary hypothesis of non-inferiority is defined as pCR difference (delta) no worse than 23%. The following sample sizes will allow this trial to demonstrate the primary hypothesis under the above assumptions with 80% power:

- **n_A=total subjects in Arm A: 143**
- **n_B=total subjects in Arm B: 57**
- **total subjects in both arms: 200 + dropouts**

Estimated testing collective: 57 Arm A responders vs. 57 Arm B

Design ratio:

The trial has a design ratio n_A/n_B=2.5, i.e., **five patients are randomized to Arm A for every two patients in Arm B.**

The design ratio n_A/n_B=2.5 allows the study to keep as many patients as possible in Arm A to test possible secondary endpoints within that group while also satisfying the requirements on overall power for the primary endpoint. The study power will still remain reasonably stable even if there are small deviations, particularly if more patients are admitted to the chemo arm.

11.3 Unsupervised biomarker testing

A candidate for the definition of “early-response” is Ki-67 after 3 weeks of pre-surgical therapy. However, since one cannot be sure that this particular cut-off is optimal across subtypes, the study design allows for an “unsupervised” search for an optimal cutoff involving either Ki-67 or another marker or a combination of markers. (In this context, the term “unsupervised search” means that the search is blinded to pCR, i.e., it determines a cutoff according to the intrinsic properties of the statistical distribution of the biomarker.)

The primary hypothesis can then be tested without any multiple-testing correction. Supervised searches are the subject of exploratory analyses (see below).

11.4 Secondary analyses

Estimation of pCR in subgroups:

If the primary hypothesis is confirmed (i.e., the null hypothesis for the primary endpoint is rejected), a secondary analysis will be performed in which pCR will be estimated in three subgroups defined via the combination of treatment and biomarker status.

In these three subgroups, the PCR-rates with confidence intervals adjusted for multiple testing by the Sidak correction (α=0.017) to achieve a family-wise error rate no larger than α=0.05 will have expected precision as follows (Table 1):

Table 8: Estimation of pCR

Treatment arm	Biomarker status	Expected PCR-rate	Expected number of patients	Confidence interval precision*
A: P+H (no chemo)	Positive	60%	57	±14.8%
	Negative	10%	86	±7.9%
B: P+H+T (chemo)	Positive and negative	60%	57	±14.8%

* 98.3% confidence intervals due to Sidak correction

P-values for these comparisons will be adjusted accordingly. From a clinical perspective, a confidence interval precision better than +/-20% would be of potential clinical relevance pending confirmation; for the patient numbers listed in the table, the conditional probability to arrive at the pre-specified precision (i.e., power) exceeds 80% for all three groups.

Predictive quality of the early-response biomarker in Arm A:

Table 2 shows a sample two-factorial frequency distribution (responders / pCR) in 143 patients satisfying the assumptions of Arm A.

Table 9: Arm A

	pCR	no pCR		
test positive	34	23	57	(responders)
test negative	9	77	86	(non-responders)
Total	43	100	143	

The predictive quality of the early-response biomarker in Arm A (pertuzumab and trastuzumab without chemotherapy) will also be reported in terms of characteristics including OR, sensitivity and specificity with respect to the endpoint pCR, together with formal (uncorrected) 95% confidence intervals.

Predictive quality of the early-response biomarker in Arm B:

The same characteristics will also be reported for the early-response biomarker in the chemotherapy arm (Arm B) and in the HER2 positive, HR- study as a whole; this analysis is

considered exploratory because there is no prior evidence suggesting a predictive hypothesis (higher pCR in early responders) under chemotherapy.

Exploratory supervised search for pCR classifier:

In exploratory analysis, searches for an optimal biomarker-based pCR classifier by a supervised learning algorithm are planned, including an optimal cutpoint search involving Ki-67 drop and classifier algorithms based on the additional biomarker measurements. An exploratory quality analysis adjusting for the large number of tests will be performed. The adjustments for these tests will be computed by the methods of Lausen et al[1], Hilsenbek et al.[2], and / or by bootstrap or simulation methods as appropriate depending on the classifier algorithm.

Secondary objectives also include exploratory survival analysis and safety analysis.

11.5 Ethical Considerations ADAPT HER2+/HR-

All participants will give written informed consent for participation in the trial. All participants will be protected by the insurance cover as standard in the clinical trials. Possible under-treatment should be excluded by the data from several trials. Donating of tumor block to the central tumor bank is planned for further research purposes.

11.6 Randomization ADAPT HER2+/HR-

In the **HER2+/HR- trial,** randomization is applicable right from the beginning of study participation. Eligible patients will be randomized to either arm A (trastuzumab + pertuzumab) or arm B (trastuzumab + pertuzumab + taxane-based chemotherapy) by permuted blocks **in the ratio 5:2**.

11.7 Efficacy Evaluation

11.7.1 Primary efficacy parameters and ITT

The primary efficacy parameter will be pCR, defined as no invasive patterns in the breast and lymph nodes at the time of surgery. The primary efficacy analysis for HER2+/HR- disease will be based on the ITT4 population.

11.7.2 Further efficacy parameters and populations

In addition to pCR, exploratory analyses will include RCB rates. Exploratory analyses will also be conducted in per-protocol populations.

11.8 Further statistical details

For further information please refer to the ADAPT umbrella protocol chapter 11.5.

[1] Lausen B, Schumacher M. Maximally selected rank statistics. Biometrics 1992. 48:73–85;

[2] Hilsenbeck SG, Clark GM. Practical P-value adjustment for optimally selected cutpoints. Stat Med 1996; 15:103–112.

11.9 Safety Evaluations

All patients who receive at least one dose of trastuzumab, pertuzumab or chemotherapy will be included in the safety analysis. 95% confidence intervals will be reported for safety of each therapy.

11.9.1 Interim Safety Analysis

For further information please refer to the umbrella protocol chapter 11.4.3

12 Translational Research

Please refer to the ADAPT protocol, chapter 10 for further information.

13 Adverse Events

Please refer to the ADAPT protocol, chapter 12 for further information.

14 Definition of Study Medication

14.1 Study Medication

For the purpose of this sub-trial, pertuzumab is the only investigational medicinal product. The combination of pertuzumab with trastuzumab, as well as the combination of pertuzumab, trastuzumab and chemotherapy will be regarded as investigational. For trastuzumab and the taxane chemotherapy, only commercial ware will be used for both induction therapy and subsequent treatment, thus it will not be labeled study-specific.

15 Administrative Aspects

Please refer to the ADAPT umbrella protocol, chapter 14 for further information.

Due to a significant difference in pCR rates between responders of arm A and all patients of arm B after the interim analysis of only 120 patients, the recruitment of new patients for the elderly study was stopped prematurely in Q4 2015. There was only a low propability that the primary objective could be reached were the treatment to be continued. The recruitment for the substudy was prematurely stopped.
The follow-up for the patients who are already enrolled in the study will be continued as described in the ***ADAPT umbrella*** protocol, chapter 7.10.

ADAPT Triple Negative (HER2-/HR-) Breast Cancer Sub-trial

(Recruitment for substudy stopped)

Adjuvant **D**ynamic marker-**A**djusted **P**ersonalized **T**herapy trial optimizing risk assessment and therapy response prediction in early breast cancer – **T**riple **N**egative (**HER2 negative**/**H**ormone **R**eceptor **negative**) breast cancer

Protocol Number:	WSG-AM06
EUDRA-CT Number:	2011-001462-17
SPONSOR:	WSG – Westdeutsche Studiengruppe GmbH
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Coordinating Investigator:	Prof. Dr. med. Nadia Harbeck
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Final Version 5.0, 11 November 2021

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Protocol title: Adjuvant **D**ynamic marker-**A**djusted **P**ersonalized **T**herapy trial optimizing risk assessment and therapy response prediction in early breast cancer – **T**riple **N**egative (**HER2 negative**/**H**ormone **R**eceptor **negative**) breast cancer

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1 Study Summary ADAPT Triple Negative Breast Cancer

ADAPT TN	**A**djuvant **D**ynamic marker-**A**djusted **P**ersonalized **T**herapy trial optimizing risk assessment and therapy response prediction in early breast cancer – **T**riple **N**egative breast cancer
Study overview	About 15% percent of breast cancers lack expression of ER and PR as well as amplification/over-expression of HER2 and are thus described as triple negative breast cancers. Substantial molecular heterogeneity is reported for this subtype where most of basal like and hereditary breast cancers are included. In the neoadjuvant setting it has been shown that TNBC is sensitive to standard chemotherapy. Patients achieving pathological complete response (pCR) after standard chemotherapy have an excellent prognosis that is not significantly different from that observed in other breast cancer subtypes. However, patients with less responsive disease (i.e. with residual disease after completion of neoadjuvant chemotherapy) suffer from a significantly worse prognosis compared to non-TNBC[30]. The number of primarily resistant disease is high. Optimal subtype-specific chemotherapy remains to be defined. Retrospective data identify several potentially predictive factors such as BRCA1gene mutation status etc. Kriege et al. published response rates to first line therapy (CMF and anthracyclines) in BRCA mutated metastatic breast cancer with an even better response in BRCA2 mutation carriers and decreased response to different lines of taxane-based chemotherapy[4]. In contrast, Gonzales-Angulo et al. showed improved survival (OR 0.19) after anthracycline and taxane-based chemotherapy among BRCA1 or 2 mutation carriers with early BC compared to patients with sporadic TNBC[5]. In summary the body of evidence for optimal compounds in TN and/or hereditary BC is small. The most promising drugs are taxanes, platinum/alkylating compounds and gemcitabine. **Platinum compounds**: the association of TNBC with BRCA1 mutations as one mechanism of dysfunctional DNA repair may indicate an increased sensitivity towards DNA-damaging agents, such as platinum salts. One small study in BRCA1 carriers (mostly cT1, cN0) revealed excellent pCR rate for four cycles of cisplatin and lower response rates to other regimens[50]. Other trials in unselected patients with locally advanced TNBC showed significantly lower overall response rates but showed particular benefit from cisplatin among patients with BRCA1 dysfunction through lower BRCA1 mRNA expression and BRCA1 methylation[57]. However, a recent publication in 163 patients does not support the predictive value of BRCA1 dysfunction (methylation, mutation etc.) regarding efficacy of neoadjuvant anthracyclines and/or taxane-based treatment in TNBC. It showed a substantial predictive impact of a CGH classifier derived from *BRCA1*-mutated breast cancer in patients treated by high dose platinum-based chemotherapy[148]. A number of anthracycline-free combinations in small-size early phase studies of taxanes and platinum-compounds have been demonstrated to be highly effective in TNBC resulting in an excellent pCR rate. For instance, in a phase II trial, a pCR rate of 67 % was observed among patients with TNBC after 16 weeks paclitaxel weekly + carboplatin AUC6 q4w translating into excellent short-term survival[39]. A second phase II neoadjuvant study using 4 cycles of docetaxel and carboplatin showed a pCR-rate of 55 % associated with an improved survival[149]. In both studies, an increased response was observed in patients with TNBC and HER2 subtypes (the latter also receiving trastuzumab). To what extent these results reflect an increased overall chemo-sensitivity of TNBC or rather mirror a particular efficacy of platinum salts in these particular subtypes remains unclear. However, if carboplatin was added to the anthracyclines- and taxane-based combination chemotherapy (EC-Doc) no significant effect was shown (pCR fo

30 % vs. 35 %) in unselected TNBC patients[150]. Moreover, O'Shaugnessy used the combination of carboplatin and gemcitabine as a chemotherapy backbone for a targeted compound (iniparib) within two phase II and III studies in TNBC, so that this doublet is considered an evidence-based and widely used standard in treatment of TNBC[151].

Nab-paclitaxel: nab-paclitaxel has been shown to be a potent taxane in TNBC, although its optimal combination partner still needs to be defined[45]. Overexpression of SPARC and/or caveolin-1 which are discussed as possible predictive markers for efficacy of nab-paclitaxel, have been frequently observed in TNBC[56,152].

Combination of Carboplatin and nab-paclitaxel: studies in non-small cell lung carcinoma reported higher ORR for the combination of nab-paclitaxel with carboplatin vs. solvent paclitaxel and carboplatin and non-significantly better PFS and OS for the nab-paclitaxel combination[153]. Several small phase II studies evaluated the effect of nab-paclitaxel and carboplatin with/without bevacizumab/trastuzumab in the neoadjuvant and metastatic setting. So Hamilton et al. reported encouraging a Clinical Benefit Rate (CBR) of 88 % in 27 patients with TNBC in the first- and second-line setting for the combination of nab-paclitaxel 100 mg/m^2, carboplatin AUC2 (upper limit 300 mg) weekly for 3 weeks and bevacizumab with one week off[152].

Recently a small phase II study examined the effect of 12 weeks of nab-paclitaxel with carboplatin and bevacizumab – a pCR rate of 27 % in TNBC (with 55 % had residual cancer burden 0 or 1) was reported after this short course of therapy. Although it could be increased to 81 % by addition of four cycles of dose-dense AC, it remains a clinical important issue to identify those patients with excellent response to taxane/carboplatin without anthracyclines[154].

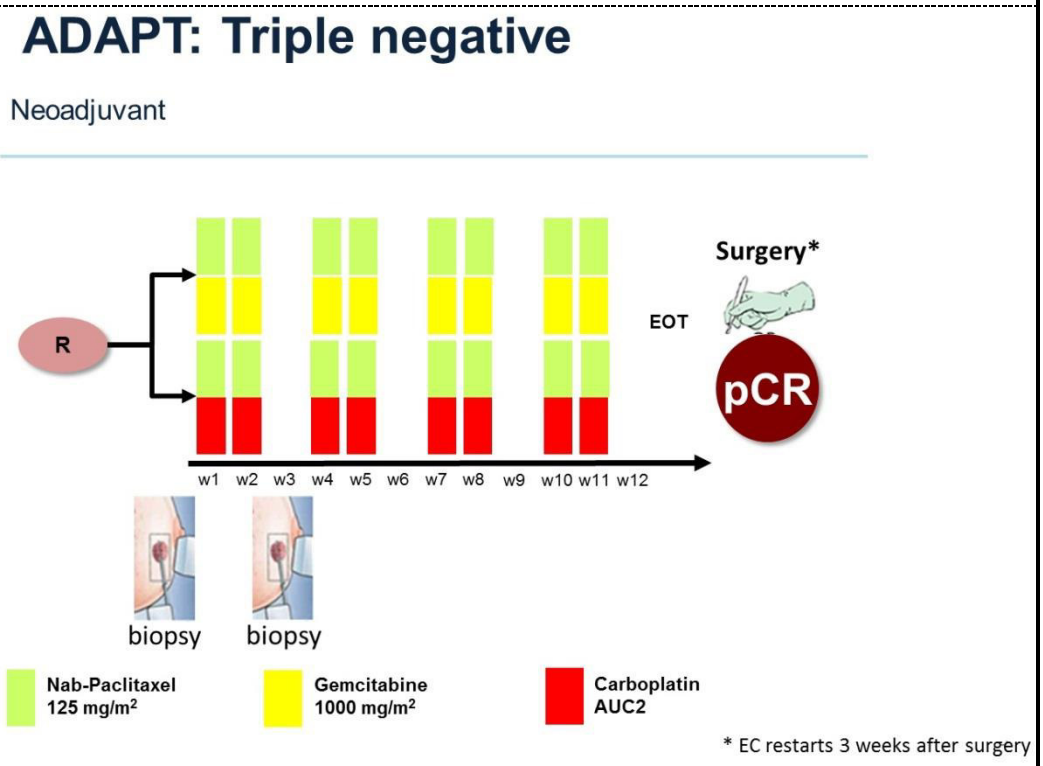
Gemcitabine: gemcitabine, in particular as combination agent, is considered as an active drug in the treatment of breast cancer. Although there is only limited efficacy of gemcitabine as a part of poly-chemotherapy used in the (neo)- or adjuvant setting[96], the combination of gemcitabine and taxanes (paclitaxel or docetaxel) is considered as a standard in the first line treatment of metastatic breast cancer. Nielsen et al. reported longer time to progression for the combination of gemcitabine with docetaxel vs. docetaxel alone (10.3 vs. 8.3 months) but similar RR of combination vs. taxane alone (34 - 36 %)[155]. Other phase III trials reported ORR of 40 % and median PFS of 7.9 months for the combination of docetaxel and gemcitabine[156] as well as borderline significant prolongation of time to treatment failure (TTF) compared to gemcitabine and capecitabine[156]. Albain et al. reported better TTF (6.1 months vs. 4 months), and better ORR (41 vs. 26 %) for the combination of gemcitabine and 3-weekly paclitaxel vs. paclitaxel alone. Both studies were conducted in the first line setting[157].

Roy et al. reported significant efficacy for combination of nab-paclitaxel 125 mg/m^2 combined with gemcitabine 1000 mg/m^2 on day 1 and 8 of 21 day cycle. Median PFS was 7.9 months and overall response of 50 % in 50 patients in the first-line setting[158]. Recently Lobo et al. reported encouraging ORR of 75.9 % in 30 patients with HER2 negative BC treated by the bi-weekly combination of nab-paclitaxel 150 mg/m^2 and gemcitabine 1500 mg/m^2. Clinical benefit rate was 93.1 % in the overall group and 86 % in the triple negative group[159].

Van Hoff reported encouraging results for the combination of nab-paclitaxel and gemcitabine in pancreatic carcinoma[160], SPARC expression in the stroma was predictive for response of the combination therapy. SPARC expression also seems to be associated with TNBC/basal-like tumors.

Thus, beside taxanes (nab-paclitaxel, docetaxel or solvent-based paclitaxel) as an important part of therapy in TNBC, there is an urgent need to evaluate the optimal combination therapy in TNBC (e.g. taxane +/- carboplatin/gemcitabine).

	Hence, for patients with TNBC it is particularly important to • identify early markers of response • optimize novel chemotherapy regimens/combinations • identify patient subgroups, with primary drug resistance who would potentially benefit from an early change to non cross-resistant drugs/ novel agents ADAPT-TN surrogate response markers may provide answers to these problems by showing a strong association between pCR and early response. To this end, the sub-trial is powered to detect a 17 % better pCR rate between responders and non-responders. The TN sub-trial will also be able to explore possible better response under nab-paclitaxel + carboplatin compared to nab-paclitaxel + gemcitabine irrespective of responder status.
Rationale	ADAPT is designed to assess early response to therapy in all breast cancer subtypes. After a short subtype-specific three-week "induction" treatment therapy response is assessed by dynamic biomarker assessment in tumor tissue derived from a second core biopsy. Patients with triple negative breast cancer (TNBC) are conventionally candidates for adjuvant taxane-anthracycline based poly-chemotherapy. However, there is a subgroup of patients with chemo-sensitive tumors achieving pathological complete response already after a short course of neoadjuvant chemotherapy. Additionally there is a group of patients without benefit from anthracyclines with a strong need for effective taxane-based combinations. At last but not at least the role of the optimal partner for modern taxane agents (e.g. nab-paclitaxel) as well as the role of platinum agents remain still unclear. The role of standard anthracycline-taxane based chemotherapy in all TNBC patients in this context has to be re-evaluated since we learned that TNBC is a heterogeneous subgroup of patients. ADAPT TN will test 12-week two-agent chemotherapy with nab-paclitaxel +/- carboplatin or gemcitabine. After 12 weeks of treatment surgery will be performed and pCR rates assessed. After surgery, patients are recommended to receive standard treatment. Furthermore ADAPT TN seeks to identify an early biomarker (profile) for response to the two different chemotherapy regimens in context of a taxane backbone. The trial primarily aims at the identification of good responders to carboplatin or gemcitabine with nab-paclitaxel. These patients would potentially need no further chemotherapy. It will also allow for exploratory biomarker analysis in non-responders and for early switch of patients to non-cross-resistant further therapy.

Objectives	Primary objectives • Comparison: pCR in nab-paclitaxel/carboplatin vs. nab-paclitaxel/gemcitabine, • Comparison: pCR in responders vs. non-responders. Secondary objectives • Comparison of nab-paclitaxel/carboplatin vs. nab-paclitaxel/gemcitabine with regard to pCR in both responders and non-responders, • Evaluation of proliferation/apoptosis changes as surrogate marker for 5 year EFS, • Overall survival • (local/regional) relapse free survival • Toxicity, • EFS in pCR patients defined as responders by dynamic testing with no further therapy vs. low-risk HR+/HER2- with no chemotherapy, • Definition of the molecular profile of non-responding patients, • Comparison of imaging (changes in dynamic breast MRI after 3 weeks of therapy or response by ultrasound vs. dynamics of Ki-67/further proliferation markers).
Trial design	A Prospective, multi-center, controlled non-blinded randomized phase II trial 

Treatment and dosing rationale	4 x nab-Paclitaxel 125mg/m² + Gemcitabine 1000mg/m² d1/8 q3w vs. 4 x nab-Paclitaxel 125mg/m² + Carboplation AUC2, upper limit 300 mg, d1/8 q3w Bisphosphonates according to current AGO guidelines (optional). In patients with HER2 positive or triple negative tumors and significant tumor burden after 12 weeks of neoadjuvant therapy, the neoadjuvant therapy may be prolonged as **post-study treatment**. The remaining tumor burden must be proven histologically, i.e. the tumor sample will be sent to the central pathology. **Dosing rationale:** TNBC is a chemosensitive subtype including a subgroup of patients experiencing pCR already after short course of therapy • Gemcitabine (1000 mg/m2 d1-8 q3w) - cis- or carboplatin (among others AUC2, upper limit 300 mg, d1+8 q3w) containing regimens are shown to be particularly effective in TNBC[68] and are widely used in the metastatic TNBC; • Nab-paclitaxel combinations with both gemcitabine and carboplatin are associated with promising activity in metastatic BC (all studies used dose-intensity of 75-84 mg/m² per week); • Based on data from the neoadjuvant setting suggesting particular efficacy of taxanes if combination therapies are used (e.g. carboplatin), nab-paclitaxel dose of 125 mg/m² is used in this trial; • Predictive markers (SPARC, BRCA-ness, caveolin-1 etc.) are urgently needed in the TNBC for targeting or individualizing therapy; • Undertreatment will be omitted by recommendation for all patients to be treated by dose-dense EC after surgery. **Surgery:** After completion of 12 weeks (or prolonged) neoadjuvant treatment for all patients, surgery is planned. In case of disease progression, systemic neo-adjuvant treatment will be stopped prematurely and surgery will be performed immediately. **Adjuvant Treatment:** After the 12-week neoadjuvant treatment, all patients will complete standard adjuvant treatment (4 cycles Epirubicin 90 mg/m² / Cyclophosphamide 600 mg/m²). In case of early pCR it will be at the investigator´s and patient´s discretion not to complete full chemotherapy treatment after surgery. **Response Assessment:** Primary efficacy (i.e. pCR) is defined at time of surgery according to NCCN guidelines (no invasive cancer in both breasts and lymph nodes) and based on provided data regarding residual tumor size, proportion of vital cells within invasive carcinoma, number of positive lymph nodes and size of the largest lymph node metastasis and ductal carcinoma in situ. Based on these criteria residual cancer burden (RCB) (and other pCR classifications) will be defined for further analysis[161]. Further chemotherapy may only be omitted in tumors with no invasive and DCIS patterns. **Safety:** Safety of nab-paclitaxel with concurrent carboplatin and gemcitabine will be assessed by incidence and severity of adverse events (AE) and serious adverse events (SAE). Frequency and reasons for discontinuation-, modification-, and interruption of the therapy will be evaluated in a prospective manner. **Dynamic test:** Drop of proliferation is considered as the key factor for efficacy of the combination therapy. Immuno-histochemical measurement of Ki-67 as

well as proliferation and apoptosis genes will be performed on samples of the diagnostic and sequential biopsy.
All tumors will undergo central pathology assessment (ER, PR, HER2) for randomization to the study (analysis by Prof. H. Kreipe, Hannover).

Study Examinations: For timing of baseline examinations and examinations during neoadjuvant treatment, please refer to table 1.

Table 1: Study Evaluations for ADAPT TNBC Patients

ASSESSMENT	BL	Cycle 1[4]	Cycle 2[4]	Cycle 3[4]	Cycle 4[4]	EOT	Surgery
week	-3 to 0	1	4	7	10	13	14
Medical and (family) breast cancer history (incl. concomitant medications)	x						
Central pathology review of diagnostic core biopsy	x						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x[2]	x	x	x	x	x	
Serum sample (biomarker analysis)	x[5]		x[5]			x[5]	
Radiology: • Chest X-ray • Bone scan • Liver imaging	x[3]						
Breast MRI (inclusion of patients without MRI is allowed)	x[5]		x[5]			x[5] prior to surgery	
Ultrasound	x		x	x		x	
Mammography	x[3]					x	
Clinical assessment	x[2]		x	x		x	
Pregnancy test	x						
ECG and LVEF[6]	x[3]						
Laboratory: • Hematology • Biochemistry	x	x	x	x	x	x	
Surgery							x
(Serious) Adverse Event		continuously					
Concomitant medication	x	continuously					

[1] prior to 2nd administration of study drug
[2] within 7 days prior to randomization
[3] within 3 months prior to randomization
[4] +/-3 days
[5] Optionally
[6] LVEF assessment during chemotherapy if indicated

Patient selection

ADAPT Triple Negative:

- ER negative (<1% positive cells in IHC), PR negative (<1% positive cells on IHC) and HER2 negative (i.e. IHC with DAKO score ≤ 1 or FISH negative) breast cancer in central pathology

General Inclusion Criteria:

- Female patients, age at diagnosis 18 years and above (consider *ADAPT Elderly* for patients at 70 years and above)
- Histologically confirmed unilateral primary invasive carcinoma of the breast
- Patients must qualify for neoadjuvant treatment:
  - Clinical cT1c - T4a-c (participation of patients with tumors >cT2 if cN0 is strongly recommended)
  - All clinical N (participation of patients with cN+, irrespective of tumor size is strongly recommended)
-
- No clinical evidence for distant metastasis (M0)
- Known HR status and HER2 status (local pathology)
- Tumor block available for central pathology review
- Performance Status ECOG ≤ 1 or KI ≥ 80 %
- Negative pregnancy test (urine or serum) within 7 days prior to registration in premenopausal patients
- Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements
- The patient must be accessible for treatment and follow-up

Additional Inclusion Criteria:

- Laboratory requirements for patients receiving chemotherapy (within 14 days prior to randomization):
  - Leucocytes ≥ 3.5 10^9/L
  - Neutrophils ≥1.5 10^9/L
  - Platelets ≥ 100 10^9/L
  - Hemoglobin ≥ 10 g/dL
  - Total bilirubin ≤ 1 x ULN
  - ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 x UNL
  - Creatinine ≤ 175 µmol/L (2 mg/dl)
  - AP<5.0 ULN
- LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization)

General Exclusion Criteria:

- Known hypersensitivity reaction to the compounds or incorporated substances
- Prior malignancy with a disease-free survival of < 10 years, except curatively treated basalioma of the skin or pTis of the cervix uteri
- Non-operable breast cancer including inflammatory breast cancer
- Previous or concurrent treatment with cytotoxic agents for any reason after consultation with the sponsor
- Concurrent treatment with other experimental drugs. Participation in another interventional clinical trial with or without any investigational not marketed drug within 30 days prior to study entry (concurrent participation in non-interventional post authorization safety studies not influencing the primary study endpoints is allowed, e.g. WSG

	PROTROCA for evaluation of primary/secondary G-CSF prophylaxis) • Male breast cancer • Concurrent pregnancy; patients of childbearing potential must implement a highly effective (less than 1% failure rate) non-hormonal contraceptive measures during the study treatment • Breast feeding woman • Sequential breast cancer • Reasons indicating risk of poor compliance • Patients not able to consent **Additional Exclusion Criteria:** • Known polyneuropathy ≥ grade 2 • Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study • Uncompensated cardiac function • Inadequate organ function including: o Leucocytes < 3.5 x 10^9/L o Neutrophils<1.5 x 10^9/L o Platelets < 100 x 10^9/L o Bilirubin above normal limits o Alkaline phosphatase ≥ 5 x UNL o ASAT and/or ALAT > 2.5 x UNL
Efficacy evaluation	An intention to treat (ITT) analysis will be conducted for all patients. An additional analysis will be conducted among the eligible patients (per protocol).
Statistical considerations	The ADAPT TN sub-trial seeks to identify early-response biomarkers, optimize novel chemotherapy regimens/combinations, and identify patient subgroups with primary drug resistance. Specifically the TN sub-trial aims to show a strong association between pCR and early response (17% better pCR rate in responders than in non-responders). It also will look for a difference of 15% in pCR under nab-paclitaxel + carboplatin (Arm B) compared to nab-paclitaxel + gemcitabine (Arm A). Patients are initially randomized in the ratio 1:1 to Arm A or Arm B. The study comprises a **Run-in phase** (n=130) and a **Main phase** (n=206), total: 336 patients. <u>Primary endpoints</u> The primary endpoint of the study is pCR as defined above. The trial will test **two co-primary hypotheses**. The family-wise error alpha is controlled for multiple testing at the level 0.05 by an unequal allocation of alpha (generalized Bonferroni according to Cook et al. 1993). <u>Hypothesis 1 (primary)</u>: • **Proportion achieving pCR is higher in responders (60 % of TN) t responders (about 40 % of TN).** Overall proportion of pCR with these medications in TNBC is estimated at about 25% including both responders (assumed 60% of TN patients) and non-responders (assumed 40% of TN patients). A difference of 17 % between pCR

proportion of responders and pCR proportion of non-responders is of clinical interest. A **one-sided test with alpha = 0.01** will be performed for a difference of 17 % between responders and non-responders (e.g., 31.8 % versus 14.8 %). Under the above assumptions, this test would reject the null hypothesis (no difference in proportions) with better than 80 % power with N = 320 patients (336 including drop-outs), even taking into account variability in the true percentage of responders.

Hypothesis 2 (primary):

- **Proportion achieving pCR is is different in the two arms**.

There is indirect evidence that pCR could be higher in the B (nab-paclitaxel + carboplatin) arm than in the A Arm (nab-paclitaxel + gemcitabine). A **two-sided hypothesis test will performed with alpha = 0.04** for a difference in pCR proportion between the B-Arm and the A-Arm. A difference of magnitude **15 %** would be clinically relevant for TNBC. Under these assumptions, there is 80% power with N = 320 patients (336 including dropouts) to reject the null hypothesis.

Secondary analyses

Hypothesis 3 (secondary)

- **Among responders, pCR is different in the two arms.**

There is indirect evidence that pCR could be higher in the B (nab-paclitaxel + carboplatin) arm. However, the test is two-sided because a difference in either direction would be clinically relevant.

Consistent with the first primary hypothesis, we assume about 60 % responders in the population. We assume that pCR proportion among responders (in A and B arms combined) will be 32 %. We test for a difference of 20 % or more in pCR proportion between the B-Arm (nab-paclitaxel + carboplatin) and the A-Arm (nab-paclitaxel + gemcitabine). A difference of this magnitude would be clinically relevant for TNBC.

If one of the two CTX combinations is superior by 20 % with respect to pCR proportion, then a two-sided test with alpha = 0.05 would reject the null hypothesis with better than 80 % power with N = 336 TN patients, taking into account the variability in the percentage of responders.

Hypothesis 4 (secondary):

- **Among non-responders, pCR is different in the two arms.**

Consistent with the first primary hypothesis, we assume about 40 % non-responders in the population. We estimate that pCR proportion among non-responders (in A and B arms combined) could be about 14 %. We can test for a clinically relevant difference of 19 % or more in pCR proportion between the B-Arm (nab-paclitaxel + carboplatin) and the A-Arm (nab-paclitaxel + gemcitabine).

	Under these assumptions, if one of the two CTX combinations is superior by 19 % with respect to pCR proportion, then a two-sided test with alpha = 0.05 would reject the null hypothesis with better than 80 % power with a total of N = 336 TN patients, taking into account the variability in the percentage of non-responders. <u>Secondary endpoints</u> The following secondary endpoints (defined below) will be prospectively evaluated: • Overall survival • Relapse free survival • Interim safety RFS and OS analyisis with regard to pCR and therapy after 3 years • Distant disease-free survival • Local/regional relapse-free survival • Evaluation of proliferation/apoptosis changes as surrogate marker for 5 year EFS. • Relation of survival to study arm.
Patient number/ Enrolment period	Run-in phase: 130 patients Main phase: 206 patients In total: 336 patients (including 5 %) drop-out Number of sites: 30 Enrolment start: Q2 2013 Enrolment stop: Q1 2015 Total patient number has been achieved in Q1 2015 and the recruitment for substudy was stopped. Follow-up period: 60 months, may be prolonged half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study

2 Introduction and Background ADAPT Triple Negative Breast Cancer

About 15% percent of breast cancers lack expression of ER and PR as well as amplification/over-expression of HER2 and are thus described as triple negative breast Substantial molecular heterogeneity is reported for this subtype, which includes most of basal like and hereditary breast cancers.

Standard treatment of TNBC

In the neoadjuvant setting, it has been shown that TNBC is sensitive to standard chemotherapy. Patients achieving pathological complete response (pCR) after standard chemotherapy have an excellent prognosis that is not significantly different from that observed in other breast cancer subtypes. However, patients with less responsive disease (i.e. residual disease after completion of neoadjuvant chemotherapy) have a significantly worse prognosis than non-TNBC[30] patients. The percentage of primarily resistant disease is high. Optimal subtype-specific chemotherapy remains to be defined.

Several adjuvant trials confirmed an increased benefit by taxane (particularly paclitaxel weekly) and anthracycline-based chemotherapy in patients with TNBC[21,162,16321,162,16321,162,16319, 153, 154]. Previous work from our group demonstrated an increased benefit from dose intensified, alkylating agent-containing chemotherapy vs. conventional dose-dense chemotherapy in patients with TNBC , which is in line with previous reports[164164164 [155][156]] . This indicates that some resistance mechanisms (e.g. mediated by YB-1) may be overcome by dose intensification of chemotherapy for high-risk early BC (for review see[56])

However, there is still no consensus about optimal non-anthracycline containing poly-chemotherapy in TNBC.

The incidence of BRCA mutations in TNBC varies from 16 % to 42 %[165]. Other mechanisms (epigenetic alterations and overexpression of BRCA1 inhibitors) resulting in downregulation of BRCA1/2, are also associated with TNBC and likely contribute to the characteristic aneuploidy and genomic instability observed in this subgroup.

The impact of BRCA status on chemotherapy sensitivity remains unclear. No prospective data regarding this issue have been published so far. Kriege et al. published response rates to first line therapy (CMF and anthracyclines) in BRCA mutated metastatic breast cancer with enhanced response in BRCA2 mutation carriers. They also observed and decreased response to different lines of taxane-based chemotherapy[166]. In contrast, Gonzales-Angulo et al. showed improved survival (OR 0.19) after anthracycline and taxane-based chemotherapy in BRCA1 or 2 mutation carriers with early BC compared to patients with sporadic TNBC[167]. A recent small study revealed no survival differences between carriers and non-carriers of BRCA1 in TNBC, if treated by alkylating chemotherapy[168]

Moreover TNBC is a biologically heterogeneous disease. Both definitions: genomic one: basal-like breast cancer (BLBC) and clinical: TNBC (defined by absence of ER, PR, HER2) are under discussion. Gene expression analysis demonstrates that the molecular signature of TNBC generally overlaps with BLBC, with concordance rates of ~ 70 % – 90 %[169]. There are several reports demonstrating that poor prognosis of TNBC is particularly due to the subgroup of BLBC[170].

Recently Lehmann et al. identified at least six different subtypes within the TNBC by gene expression analysis of 587 TNBC tumors[171]

Platinum compounds: association of TNBC with BRCA1 mutations as one mechanism of dysfunctional DNA repair may indicate an increased sensitivity towards DNA-damaging agents, such as platinum salts. One small study in BRCA1 carriers (mostly cT1, cN0) revealed excellent pCR rate for four cycles of cisplatin (of 71 %)[50] and lower response rates to other regimens[50]. Other trials in unselected patients with locally advanced TNBC showed significantly lower overall response rates but showed particular benefit from cisplatin in patients

with BRCA1 dysfunction (low BRCA1 mRNA expression, BRCA1 methylation[57]). However, one recent publication in 163 patients does not support the predictive value of BRCA1 dysfunction (methylation, mutation etc.) for efficacy of neoadjuvant anthracyclines and/or taxane-based treatment within TNBC. It showed a substantial predictive impact of a CGH classifier derived from *BRCA1*-mutated breast cancer in patients treated by high-dose platinum based chemotherapy[172]. A recent small study revealed 100 % RCB 0-1 in patients with BRCA1 mutation treated by 6 cycles of gemcitabine and carboplatinum/iniparib (a targeted compound with distinct response patterns in the BRCA1 cases) vs. 44 % in TN non-BRCA1 mutant cases[173].

A number of anthracycline-free combinations in small-size early phase studies of taxanes and platinum-compounds were highly effective in patients with TNBC resulting in excellent pCR rates ranging from 30 % to 62 %. The combination of weekly cisplatin added to weekly epirubicin and paclitaxel produced a pCR rate of 62 % and 5-year DFS and OS rates of 76 % and 89 %, respectively. In a phase II trial, a pCR rate of 67 % was observed in patients with TNBC after 16 weeks of paclitaxel weekly + carboplatin AUC6 q4w translating into excellent short-term survival. A second phase II neoadjuvant study using 4 cycles of docetaxel and carboplatin showed a pCR-rate of 55 % associated with improved survival[149]. In both studies, an increased response was observed in patients with TNBC and HER2 subtypes (the latter also receiving trastuzumab). To what extent these results reflect either an increased overall chemosensitivity of TNBC or rather mirror a particular efficacy of platinum salts in these particular subtypes remains unclear.

Regarding platinum agents in the metastatic setting, results are also controversial.

In a randomised phase II trial (N = 126, single institutional setting), cisplatin added to metronomic methotrexate and cyclophosphamide showed an improvement in median TTP of 6 months (from 7 to 13 months) and OS of 4 months (from 12 to 16 months) in second-line metastatic TNBC patients[174]. The toxicity profile was manageable.

Two recently published studies showed only very moderate efficacy profiles. So although Carey et al. reported increased response to carboplatinum+EGFR inhibitor cetuximab (6 % vs. 17 %) with a TTP of only 2.1 months in both study arms[175]. Baselga et al. reported similarly better response to the combination of cisplatin+cetximab (20 % vs. 10 %) and longer PFS of 3.1 vs. 1.5 months (all patients in first-multiple lines of therapy) - yet the overall PFS data are discouraging regardless the better response to the combination therapy[176].

However, if carboplatin was added to anthracyclines- and taxane-based combination chemotherapy (EC-Doc), no significant effect was seen (pCR 30 % vs. 35 %) in unselected TNBC patients[150]. However, O'Shaugnessy et al. used the combination of carboplatin and gemcitabine as a chemotherapy backbone for a targeted compound (iniparib) within two phase II and III studies in the TNBC[151], so that the combination of these both drugs is widely used standard in the treatment of TNBC.

Taxanes – nab-paclitaxel:

Nab-paclitaxel has been shown to be a potent taxane in TNBC, although its optimal combination partner to be still defined[45]. Over-expression of SPARC and/or caveolin-1 are being discussed as potential predictive markers for efficacy of nab-paclitaxel. Both proteins are frequently overexpressed in TNBC[56,152]

Serum albumin–bound nab-paclitaxel complexes safely deliver high intracellular concentrations of taxane to tumor cells by interacting with albumin receptors. Nab-paclitaxel can be administered over a shorter duration of infusion (30 minutes compared with 3 hours for standard paclitaxel), without pre-medication against hypersensitivity, and in higher doses compared to conventional paclitaxel. Several phase II-III studies were conducted regarding efficacy of nab-paclitaxel vs. conventional taxanes. Gradishar et al. reported in 2005 better efficacy of nab-paclitaxel 260 mg/m^2 every 3 weeks compared to the older standard of

paclitaxel q3w in mostly pretreated patients (overall response 33 % vs. 19 %, median OS 14.1 vs. 11.7 months, p = 0.024). Similarly to standard paclitaxel therapy[91], use of nab-paclitaxel has been shown to be more effective if used in the weekly setting.

In another study three schedules of nab-paclitaxel 300 mg/m2 (q3w, or 100, 150 mg/m^2 weekly, 3 weeks of 4) were compared with standard docetaxel 100 q3w. Significantly better investigator assessed overall response (74 % vs. 39 %), investigator-assessed PFS (14,6 vs. 7,8 months) and OS (33.3 vs. 26.6 months) were seen for the weekly 150 mg/m^2 schema vs. docetaxel (as well 3-weekly nab-paclitaxel and q21 or 100 mg/m^2 weekly)[101].

These data indirectly also favor nab-paclitaxel compared to older studies using paclitaxel weekly (reported ORR of 21 – 42 %[65], median PFS of 6-9 months[29,30]) or docetaxel q21 (ORR 35 – 46 %; median PFS up to 7,5 - 8,4 months[177]).

However, toxicity of nab-paclitaxel and comparably lower effiacacy when combined with targeted therapy still nedd to be adressed. Rugo et al. reported similar median PFS when comparing nab-paclitaxel 150 mg/m^2 combined with bevacizumab versus paclitaxel weekly+bevacizumab (9.2 vs. 10.6 months). No differences were observed in the TNBC patients but a significantly worse PFS was observed in the HR+ subgroup. No significant differences in OS were observed between the nab-paclitaxel and paclitaxel weekly arms (26 - 27 months)[102].

Use of nab-paclitaxel is associated with up to 44 – 47 % (if combined with bevacizumab)[102] neutropenia grade 3-4 (compared to 43[178]– 94 %[101] in the docetaxel q3w studies, up to 9 % in the paclitaxel weekly trials[179] or up to 18 % if combined with bevacizumab[180]). Peripheral neuropathy grade 3 was reported in 22 % of patients, compared to 12 % in the docetaxel arm (other studies reported 4 – 5 %[178,181] or in up to 16[102] - 21%[179]).

47 % of patients required nab-paclitaxel dose reduction in the Gradishar trial and 45 % vs. 15 % (in the paclitaxel weekly+bevacizumab arm) at cycle 3 in the CALBG trial. Outcome of patients with a reduced dose of nab-paclitaxel seemed to be not substantially different compared to the 150 mg/m^2 in the Gradishar trial. Thus, it is remarkable that in the the CALBG trial 48 % of patients in the nab-paclitaxel arm interrupted therapy at cycle 5, although not more than 10 % had progressive disease. In contrast, median number of cycles was 8 and 10 for dose-reduced and non dose-reduced patients in the Gradishar trial. Thus, further studies are urgently needed to clarify optimal taxane dosage and schedule in the treatment of BC and particurarly of TNBC.

Combination of carboplatin and nab-paclitaxel: Studies in non-small cell lung carcinoma reported higher ORR for the combination of nab-paclitaxel with carboplatin vs. solvent paclitaxel and carboplatin as well as better PFS and OS for the nab-paclitaxel combination[153]. Several small phase II studies evaluated the effect of nab-paclitaxel and carboplatin with/without bevacizumab/trastuzumab in the neoadjuvant and metastatic setting.

Hamilton et al. reported encouraging CBR of 88 % in 27 patients with TNBC in the first- and second-line setting for the combination of nab-paclitaxel 100 mg/m^2, carboplatin AUC2 (upper limit 300 mg) weekly and bevacizumab for 3 weeks with one week off[152].

Recently, a small phase II study examined the effect of 12 weeks of nab-paclitaxel together with carboplatin and bevacizumab. A pCR rate of 27 % in TNBC (55 % residual cancer burden 0 or 1) was reported after this short course of therapy. Although it could be increased to 81 % by the addition of four cycles of dose-dense AC, it remains a clinical important issue to identify patients with excellent response to taxane/carboplatin without anthracyclines[154].

Rationale for the use of nab-paclitaxel in patients with TNBC

TNBC as well as hereditary breast cancer has been demonstrated to frequently express Caveolin-1[182]. Caveolin-1 expression in patients with a basal-like subtype does furthermore

predict for significantly shorter overall (OS) and disease-free survival (DFS)[183]. Interestingly, Caveolin-1 is thought to mediate transcytosis of nanoparticle-albumin bound paclitaxel (nab-paclitaxel, ABI-007). This may serve as a rationale to specifically investigate the use of nab-paclitaxel in patients with TNBC ported for the 150 mg/m^2 arm for first-line setting.

Gemcitabine: gemcitabine is considered, particularly as a combination agent, as an active drug in the treatment of breast cancer. Although there is only limited efficacy of gemcitabine as a part of polychemotherapy used in the (neo)- or adjuvant setting, the combination of gemcitabine and taxanes (paclitaxel or docetaxel) is considered as a standard in the first line treatment of metastatic breast cancer. Nielsen et al. reported longer time to progression (TTP) for the combination of gemcitabine with docetaxel vs. docetaxel alone (10.3 vs. 8.3 months) but similar RR for the combination vs. taxane alone (34 – 36 %)[155]. Other phase III trials reported ORR of 40 % and median PFS of 7.9 months for the combination of docetaxel and gemcitabine[156] as well as prolongation of time to treatment failure (TTF) compared to gemcitabine and capecitabine. Albain et al. reported better TTF (6.1 months vs. 4 months), and better ORR of 41 % vs. 26 % for the combination of gemcitabine and 3-weekly paclitaxel vs. paclitaxel alone. Both studies were conducted in the first line setting[157].

Roy et al. reported significant efficacy for combination of nab-paclitaxel 125 mg/m^2 combined with gemcitabine 1000 mg/m^2 on day 1 and 8 (q21). Median PFS was 7.9 months and overall response of 50 % in 50 patients in the first-line setting[158]. Recently Lobo et al. reported encouraging ORR of 75.9 % in 30 patients with HER2-negative BC treated by the bi-weekly combination of nab-paclitaxel 150 mg/m^2 and gemcitabine 1500 mg/m^2. Clinical benefit rate was 93.1 % in the overall group and 86 % in the triple negative subgroup[159].

Von Hoff reported encouraging results for the combination of nab-paclitaxel and gemcitabine in metastatic pancreatic carcinoma. SPARC expression in the stroma was predictive for response of this combination therapy[160].

Thus, beside taxanes (nab-paclitaxel, docetaxel or solvent-based paclitaxel) as an important part of therapy in TNBC, there is an urgent need to evaluate the optimal combination therapy in TNBC (e.g. taxane +/- carboplatin/gemcitabine).

Dynamic measurement (breast MRI/tumor cell proliferation) as an early surrogate marker for pCR

Recently, neoadjuvant cytotoxic and/or tailored therapies have been suggested as an important tool for evaluation of response to a given systemic therapy *in vivo*. Clinical response measured by sequential evaluation of different proliferation markers (such as Ki-67) following a course of neoadjuvant chemotherapy significantly correlates with an increased risk of relapse in those patients who did not achieve a pCR[122]. Considering the different effects of chemotherapy on proliferation, it would be clinically relevant to also evaluate such proliferation tools for early prediction of combination therapy efficacy. Unfortunately, it is still unclear which method of proliferation measurement is the optimal marker for response evaluation with respect to chemotherapy.
However, measurement of proliferation and apoptosis as well as assessment of changes in PI3K/AKT, IGF and stem cell signaling after a short induction of therapy could provide a unique signature for *dynamic* response evaluation and selection of patients for mono vs. combined targeted treatment.
Another way to assess early response could be **molecular imaging** by MRI (or other functional dynamic imaging), given its strong evidence, particularly in TNBC[52,53].
Changes in contrast medium kinetics in contrast-enhanced MRI (DCE-MRI) or of the ADC (apparent diffusion coefficient) in the diffusion-weighted MRI or drop of the cholin peak in the ^{1}H-MR-Spektroskopy already after short induction therapy are possible measurement instruments for an imaging approach as an alternative non-invasive and complimentary method for dynamic patient stratification within the trial. A further advantage of breast MRI is

the analysis of the whole tumor (and not just a single biopsy area) thus better accounting for tumor heterogeneity.

Hence, for patients with TNBC it is particularly important to

(a) identify early markers of response
(b) optimize novel chemotherapy regimens/combinations
(c) identify patient subgroups, with primary drug resistance to the offered therapy and who would potentially benefit from an early change to non-cross-resistant drugs/ novel agents

ADAPT surrogate response markers may provide answers to these problems by showing a strong association between pCR and early response. To this end, the sub-trial is powered to detect a 17% better pCR rate between responders and non-responders. The TN sub-trial will also be able to explore possible better response under nab-paclitaxel + carboplatin compared to nab-paclitaxel + gemcitabine irrespective of responder status.

The ADAPT philosophy – A combined static and dynamic model

Early response assessment in eBC may be essential to separate sub-populations with large or marginal benefit from therapy.

Drop of proliferative activity after a short course of endocrine therapy (2 weeks to 4 months) as measured by proliferation marker Ki-67 is an excellent predictor for local as well as systemic outcome in HR+ disease. It allows the identification of groups of patients with excellent outcome in both low and higher risk groups independently from chemotherapy application[25-27]. ADAPT applies this dynamic model to all early breast cancer subtypes. First step is a broad baseline assessment (conventional central pathology, biomarker) of prognosis. Sequential tissue sampling is realized (3 week interval, core biopsies and surgery) after a short subtype specific treatment. Thus, besides baseline prognosis estimation (***static* assessment**), therapy efficacy is evaluated at an early time of treatment (***dynamic* assessment**).

Beyond baseline biomarker assessment, the primary endpoint of the ADAPT HER2+ and TN protocols is the definition of molecular surrogate markers predictive for pCR and 5 year event-free survival.

Surgery after neoadjuvant chemotherapy

Surgery and subsequent radiotherapy should be planned according to current AGO guidelines based on response of the tumor, patient choice etc. In the case of progressive disease (PD) during chemotherapy surgery should be performed immediately (within two weeks after diagnosis of PD) or a change to the dose-dense regime EC can be planned at the decision of the investigator.

In the case of clinically negative axilla (assessed by ultrasound) sentinel lymph node biopsy (SLNB) is recommended to be performed prior to the neoadjuvant chemotherapy. SLNB performed at the time of definitive surgery after neoadjuvant chemotherapy has resulted in lower rates of identifying the SLN and higher false negative rates compared with the same procedure performed before therapy[184]. A systematic review of 27 studies with a total of 2148 patients who had SLNB after neoadjuvant systemic therapy showed a pooled SLN identification rate of 91 % (95 % CI 88 - 93) and false-negative rate of 10.5 percent (95 % CI 8.1 - 13.6).

Data comparing neoadjuvant chemotherapy before or after SLNB are limited. In a consecutive series of 87 patients, the first 31 underwent SLNB after chemotherapy followed by completion axillary lymph node dissection (ALND), and the subsequent 58 patients underwent SLNB before chemotherapy followed by completion ALND. Performing SLNB before neoadjuvant systemic therapy was associated with a significantly higher rate of SLN identification (99 % versus 87 %) and a significantly lower false negative rate (0 % versus 16 %)[185].

ALND is recommended to be performed in all patients with positive SLN at the time of definitive surgery upon on current AGO guidelines. Axillary second look can be done in the case of progressive disease.

In any case axilla intervention should be performed according to the current AGO/S3 guidelines depending on evidence.

3 Rationale ADAPT triple negative breast cancer

ADAPT is designed to assess early response to therapy in all breast cancer subtypes. After a short subtype-specific three week “induction” treatment therapy response is assessed by dynamic biomarker assessment in tumor tissue derived from a second core biopsy.

Standard chemotherapy for patients with triple negative breast cancer (TNBC) is based on taxane-anthracycline containing poly-chemotherapy. However, there is a subgroup of patients with chemo-sensitive tumors achieving pathological complete response already after short course of neoadjuvant chemotherapy. Additionally there is a group of patients without benefit from anthracyclines with strong need for effective taxane-based combinations. At last but not at least the role of the optimal partner for modern taxane agents (e.g. nab-paclitaxel) as well as the role of platinum agents remain still unclear.

ADAPT TNBC will test 12week two-agent chemotherapy with nab-paclitaxel +/- carboplatin or gemcitabine. After 12 weeks of treatment surgery will be performed and pCR rates will be assessed. After surgery patients are recommended to receive standard treatment.

ADAPT TN seeks to identify an early biomarker (profile) for response to two different chemotherapy combination regimens with a taxane backbone. The trial primarily aims at the identification of good responders to carboplatin or gemcitabine with nab-paclitaxel. These patients would potentially need no further chemotherapy. The trial will also allow for exploratory biomarker analysis and for early switch of patients to non-cross-resistant further therapy.

Dosing rationale: TNBC is a chemosensitive subtype including a subgroup of patients experiencing pCR already after short course of therapy

- Gemcitabine (1000 mg/m2 d1-8 q3w) - cis- or carboplatin (among others AUC2, upper limit 300 mg, d1-8 q3w) containing regimens are shown to be particularly effective in TNBC[68] and are widely used in the metastatic TNBC;
- Nab-paclitaxel combinations with both gemcitabine and carboplatin are associated with promising activity in metastatic BC (all studies used dose-intensity of 75-84 mg/m^2 per week);
- Based on data from the neoadjuvant setting suggesting particular efficacy of taxanes if combination therapies are used (e.g. carboplatin), nab-paclitaxel dose of 125 mg/m^2 is used in this trial;
- Predictive markers (SPARC, BRCA-ness, caveolin-1 etc.) are urgently needed in the TNBC for targeting or individualizing therapy;
- Undertreatment will be omitted by recommendation for all patients to be treated by dose-dense EC after surgery.

4 Study Objectives ADAPT Triple Negative Breast Cancer

A total of 336 patients will be introduced to the ADAPT triple negative breast cancer sub-trial, which will have two phases, a run-in phase (130 patients) and a main phase (206 patients; whole trial). The objectives of both phases are listed below:

Run-in phase concept:

Primary objectives

- Identification of molecular markers correlating with early response/pCR,
- Feasibility/reproducibility of assessment of these markers,
- Validation of statistical assumptions made for the whole sub-trial.

Run-in and Main phase concept:

Primary objectives

- Comparison: pCR in nab-paclitaxel/carboplatin vs. nab-paclitaxel/gemcitabine,
- Comparison: pCR in responders vs. non-responders.

Secondary objectives

- Comparison of nab-paclitaxel/carboplatin vs. nab-paclitaxel/gemcitabine with regard to pCR in both responders and non-responders,
- Evaluation of proliferation/apoptosis changes as surrogate marker for 5 year EFS,
- Overall survival,
- Toxicity,
- EFS in pCR patients defined as responders by dynamic testing with no further therapy vs. low-risk HR+/HER2- with no chemotherapy,
- Definition of the molecular profile of non-responding patients,
- Comparison of imaging (changes in dynamic breast MRI after 3 weeks of therapy vs. dynamics of Ki-67/further proliferation markers).

5 Study Design ADAPT Triple Negative Breast Cancer

The ADAPT TN breast cancer sub-trial is a prospective, multi-center, controlled non-blinded randomized phase II trial. Following the diagnostic core biopsy and identification of a triple negative tumor, the patients meeting the inclusion/exclusion criteria will be registered for the trial, after informed consent was obtained. The patient will be randomized right from the beginning to either 4 x nab-Paclitaxel 125mg/m² + Gemcitabine 1000mg/m² d1/8 q3w or 4 x nab-Paclitaxel 125mg/m² + Carboplation AUC2 (upper limit 300 mg) d1/8 q3w. Patients will be treated for three weeks with the respective regimen as an induction treatment and will then undergo the second core biopsy for efficacy estimation and response assessment. After completion of 12 weeks of therapy with either of the three treatment arms, the patients will undergo surgery and pCR will be assessed. In case of disease progression, systemic treatment will be stopped and surgery will be performed immediately.
After 12-week neoadjuvant treatment, all patients will complete standard treatment (4 cycles Epirubicin 90 mg/m^2 / Cyclophosphamide 600 mg/m^2). In case of pCR, it will be at the investigator´s and patient´s discretion not to complete full chemotherapy treatment after surgery. The triple negative study design is depicted in figure 1 below.

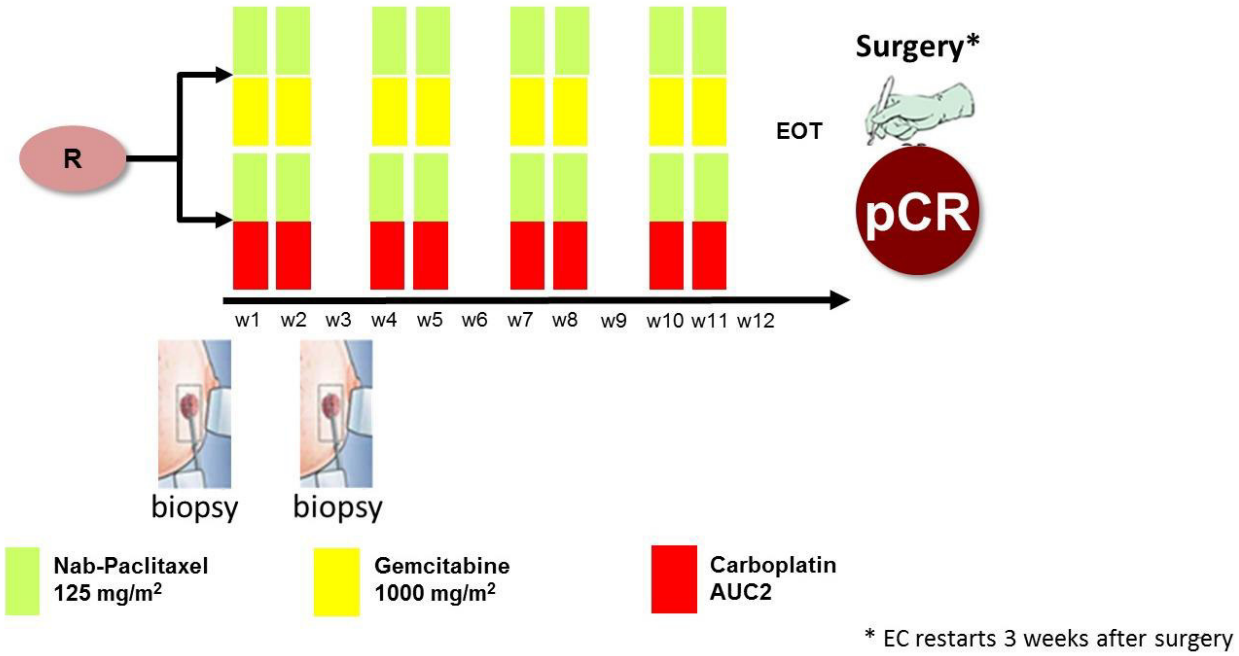


Figure 1: *Patient selection ADAPT Triple Negative Breast Cancer*

5.1 Run-in Phase and Main Phase

For further information please refer to the ADAPT umbrella protocol, chapter **5.1**. The run in phase of the triple negative protocol will include 130 patients and the main phase 206 patients.

5.2 Timing of Surgery

Surgery can be done 3 weeks after the last treatment cycle or after prolonged neoadjuvant chemotherapy, if indicated due to significant remaining tumor burden. In case of disease progression systemic treatment will be stopped and surgery will be performed immediately.
Surgery and subsequent radiotherapy should be planned according to current AGO guidelines based on response of the tumor, patient choice etc. In the case of progressive disease (PD) during chemotherapy surgery should be performed immediately (within two weeks after diagnosis of PD). In the case of clinically negative axilla (assessed by ultrasound) sentinel lymph node biopsy is recommended to be performed prior to the neoadjuvant chemotherapy. ALND is recommended to be performed in all patients with positive SLN at the time of definitive surgery upon on current AGO guidelines. Axillary second look can be done in the case of progressive disease.

6 Patient Enrollment ADAPT Triple Negative Breast Cancer

Following the diagnostic core biopsy and local pathology assessment, the patients meeting the inclusion/exclusion criteria will be informed about the ADAPT trial and triple negative sub-trial. After signing the informed consent patients will be registered and subsequently randomized to one of the two treatment arms. Patients will be only enrolled for randomization after central pathology assessment of HR and HER2 expression.
The following examinations are mandatory prior to randomization:

Table 1: *Study Evaluations for Participation in ADAPT Triple Negative Breast Cancer Trial*

	INVESTIGATIONS	TIMING
Negative ER and/or PR status **according to local pathology**	✔	Prior to registration (standard of care)
Negative HER2 status **according to local pathology**	✔	Prior to registration (standard of care)
Nodal status	Participation of patients with cN0 is strongly recommended, if cT≥2	Prior to registration (standard of care)
Grading		Prior to registration (standard of care)
Ultrasound	✔	Prior to registration (standard of care)
History[1] and physical exam for patients receiving chemotherapy	Physical examination including: • Height • Weight • Karnofsky index for performance status/vital signs	≤ 7 days prior to randomization
LVEF ≥ 50%	Echocardiography	Within 42 days prior to randomization

[1]Within 3 weeks prior to registration

6.1 Additional Inclusion Criteria ADAPT Triple Negative Breast Cancer

In order to be eligible for the participation in the ADAPT triple negative breast cancer trial, patients who meet the general inclusion/exclusion criteria of the ADAPT trial also have to meet the following additional inclusion criteria:

- [5]Laboratory requirements for patients receiving chemotherapy (within 14 days prior to randomization):
  - Leucocytes ≥ 3.5 x 10^9/L
  - Neutrophils ≥1.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Hemoglobin ≥ 10 g/dL
  - Total bilirubin ≤ 1 x ULN
  - ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 x ULN
  - AP<5.0 ULN
  - Creatinine ≤ 175 µmol/L (2 mg/dl)
- LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to randomization)

6.2 Additional Exclusion Criteria ADAPT Triple Negative Breast Cancer

In order to be eligible for the participation in the ADAPT triple negative breast cancer trial, patients, who meet the general exclusion criteria of the ADAPT trial **must** also **not** meet any of the following additional exclusion criteria:

- Known polyneuropathy ≥ grade 2
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study
- Uncompensated cardiac function
- Inadequate organ function including:
  - Leucocytes < 3.5 x 10^9/l
  - Platelets < 100 x 10^9/l
  - Bilirubin above normal limits
  - Alkaline phosphatase ≥ 5 x UNL

ASAT and/or ALAT associated with AP > 2.5 x UNL
The patients complying with inclusion and exclusion criteria will be randomized to one of the neoadjuvant chemotherapy arms.

6.3 Randomization to ADAPT Triple Negative Breast Cancer

After informed consent form is obtained, each eligible patient will be registered and subsequently randomized to receive either:
4 x nab-Paclitaxel 125mg/m² + Gemcitabine 1000mg/m² d1/8 q3w
or
4 x nab-Paclitaxel 125mg/m² + Carboplation AUC2 (upper limit 300 mg) d1/8 q3w
The randomization forms have to be filled in online in the e-CRF. After completion it has to be printed, signed by an investigator and faxed to the coordinator of the study:

Fax: +49 (0)611 160248 - 29

The following information will be requested:

- Institution name
- Investigator's name
- Patient's identifiers (site number, patient code)
- Patient's birth date (month/year)
- Type of tumor (HR+/HER2-, HER2+/HR-, HER2+/HR+ or TN)
- Date start of treatment planned

A patient who was not randomized prior to the first treatment administration will not be accepted for the study at a later date.
Investigators will be notified via the eCRF within 24 hours after complete information has been received from the site as per the randomization form.

6.3.1 **Arm A: nab-paclitaxel + gemcitabine**

Nab-paclitaxel

Dose: 125 mg/m², day 1 and day 8

Route: 30 minutes intravenous infusion

Schedule: Every 3 weeks

Gemcitabine

Dose: 1000 mg/m², day 1 and day 8

Route: 30 minutes intravenous infusion (as per hospital policy)

Schedule: Every 3 weeks

This cycle of treatment will be given four times. In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

6.3.2 **Arm B: nab-paclitaxel + carboplatin**

Nab-paclitaxel

Dose: 125 mg/m², day 1 and day 8

Route: 30 minutes intravenous infusion

Schedule: Every 3 weeks

Carboplatin

Dose: AUC 2 (mg/ml) · min, upper limit 300 mg, day 1 and day 8

Route: 15 to 60 minutes intravenous infusion (as per hospital policy)

Schedule: Every 3 weeks

This cycle of treatment will be given four times. In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

7 Study Plan ADAPT Triple Negative Breast Cancer

7.1 Definition of Study Medication ADAPT Triple Negative Breast Cancer

For the purpose of this sub-trial nab-paclitaxel will be labeled study-specific and is considered study medication. Gemcitabine as well as Carboplatin will be commercial ware and will not be labeled study-specific. Documentation of preparation and distribution of the study medication has to be documented in accordance with the Investigator's Brochure (nab-paclitaxel) or according to local guidelines (gemcitabine and carboplatin).

7.2 Study Treatment ADAPT Triple Negative Breast Cancer

For induction treatment patients will receive one cycle of either 4 x nab-Paclitaxel 125mg/m² + Gemcitabine 1000mg/m² d1/8 q3w or 4 x nab-Paclitaxel 125mg/m² + Carboplation AUC2 (upper limit 300 mg) d1/8 q3w.
After completion of induction treatment, patients will obtain the second core biopsy for efficacy estimation. The treatment regimen from induction treatment will be continued for three further cycles until end of treatment and surgery.
Study treatment should be discontinued in case of disease progression and the patient should undergo surgery.
In case of clinical tumor burden (non-pCR) after 12 weeks, neoadjuvant therapy may be prolonged as stated above. Chemotherapy may be applied as stated for adjuvant therapy. Total duration of anti-HER2 therapy (neoadjuvant and adjuvant) should be one year.
Post-study treatment with adjuvant chemotherapy is planned as standard of care at the discretion of investigator.

7.2.1 Dosing Rationale

TNBC is a chemosensitive subtype with a subgroup of patients experiencing pCR already after a short course of chemotherapy.

- Gemcitabine (1000 mg/m2 d1-8 q3w) - cis- or carboplatin (among others AUC2, upper limit 300 mg, d1-8 q3w) containing regimens are shown to be particularly effective in TNBC[68] and are widely used in the metastatic TNBC;
- Nab-paclitaxel combinations with both gemcitabine and carboplatin are associated with promising activity in metastatic BC (all studies used dose-intensity of 75-84 mg/m^2 per week);
- Based on data from the neoadjuvant setting suggesting particular efficacy of taxanes if combination therapies are used (e.g. carboplatin), nab-paclitaxel dose of 125 mg/m^2 is used in this study;
- Predictive markers (SPARC, caveolin-1, BRCA-ness etc) are urgently needed in the TNBC for targeting or individualizing of therapy;
- Undertreatment will be omitted by recommendation for all patients to be treated by dose-dense EC after surgery.

7.2.2 End of Treatment (EOT) Definition ADAPT Triple Negative Breast Cancer

End of treatment is defined as 21 days after the last application of study drug and prior to surgery. pCR will be the target endpoint of the study.
Any further treatment after surgery is at the discretion of the investigator, but it is recommended to apply anthracycline-containing adjuvant standard chemotherapy (4 cycles Epirubicin 90 mg/m^2 / Cyclophosphamide 600 mg/m^2).

7.2.3 Prophylactic Premedication Regimen for Taxanes, Epirubicin and Cyclophosphamid

Please refer to the ADAPT trial (chapter 7.9) for further information on prophylactic premedication, including use of antibiotics, G-CSF and antiemetics.

7.2.4 Concomitant Treatment during Chemotherapy

For permitted prophylactic premedication please refer to the previous chapter.

Ancillary treatments will be given as medically indicated. Any concomitant medication must be documented in the Case Report Form (CRF). Caution should be exercised with some drug combinations, e.g. carboplatin should not be given together with aminoglycosides, chelation or phenytoin. (Nab-)paclitaxel should not be given together with CYP2C8 and CYP3A4 inhibitors or inducers. Please refer to the SmPC.

7.3 Follow-up

For the follow-up please refer to the ADAPT protocol, chapter **7.10**.

7.4 Post-Chemotherapy Treatment

After completion of chemotherapy the patients can be treated with bisphosphonates at the discretion of the investigator (according with AGO guidelines):

- Zoledronic acid 4 mg every six months for three years,
- Clodronate 1600 mg/d p.o. for two years.

7.4.1 Therapy after Protocol Treatment is discontinued

In case of clinical tumor burden (non-pCR) after 12 weeks, neoadjuvant therapy may be prolonged as stated above. Chemotherapy may be applied as stated for adjuvant therapy. Total duration of anti-HER2 therapy (neoadjuvant and adjuvant) should be one year.
Except for study chemotherapy and radiotherapy as per protocol, no further antitumor therapy is allowed (surgery, chemotherapy, immunotherapy, etc.) before tumor relapse is documented. If patients are removed from the study because of disease relapse, further treatment is at the discretion of the investigator. The treatment regimen(s) given in case of metastatic disease will be documented in the Case Report Form.

8 Study Evaluations ADAPT Triple Negative Breast Cancer

8.1 Evaluation during Chemotherapy

While under chemotherapy, all patients must be examined according to the schedule outlined below until they come off chemotherapy.

Table 2: *Study Evaluations before each Cycle of Treatment*

ASSESSMENT	BL	Cycle 1[4]	Cycle 2[4]	Cycle 3[4]	Cycle 4[4]	EOT	Surgery
week	-3 to 0	1	4	7	10	13	14
Medical and family breast cancer history (incl. concomitant medications)	x						
Central pathology review of diagnostic core biopsy	x						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x[2]	x	x	x	x	x	
Serum sample (biomarker analysis)	x[5]		x[5]			x[5]	
Radiology: • Chest X-ray • Bone scan • Liver imaging	x[3]						
Breast MRI (inclusion of patients without MRI is allowed)	x[5]		x[5]			x[5] (prior to surgery)	
Ultrasound	x		x	x		x	
Mammography	x[3]					x	
Clinical assessment	x[2]		x	x		x	
Pregnancy test	x						
ECG and LVEF[6]	x[3]						
Laboratory: • Hematology • Biochemistry	x	x	x	x	x	x	
Surgery							x
(Serious) Adverse Event		continuously					
Concomitant medication	x	continuously					

[1] prior to 2nd administration of study drug
[2] within 7 days prior to randomization
[3] within 42 days prior to randomization
[4] +/-3 days
[5] Optionally
[6] LVEF assessment during chemotherapy if indicated

8.2 Evaluation at End of Induction Treatment

Please refer to chapter **7.8** of the ADAPT protocol for further information.

8.3 Evaluation at End of Treatment (EOT)

The End of Treatment evaluation has to be performed 21 days after the last treatment and prior to surgery. Work-up will include:

- Physical examination with Karnofsky Index or ECOG
- Hematology, biochemistry, urine analysis
- Documentation of toxicity
- Serum sample (biomarker analysis)
- Ultrasound
- Mammography
- Breast MRI (prior to surgery, optional)
- Quality of Life questionnaire

8.4 Evaluation in Follow-up after End of Treatment

Patients will be followed every 6 months for two years starting from registration and every 12 months thereafter until year 5 (corresponding to German aftercare plan) or until relapse to document:

- Event-free survival
- Overall survival
- Further therapy (and/or endocrine treatment/treatment with Herceptin)
- Long term toxicities
- Relapse (local relapse)
- 2nd primary malignancy
- First treatment for metastatic breast cancer or 2nd primary malignancy
- Results for biopsy of distant metastases
- Yearly evaluation of lifestyle parameter

Timing of follow-up visits is based on the date of registration. Follow-up visits will be scheduled at month 6, 12, 18, 24, 36, 48, and 60 after registration.
Patients who relapse or suffer from 2nd primary malignancy will only be followed for survival. For any distant metastasis occurring, if biopsied, IHC should be reported in the CRF.

Patients completing follow-up month 60 may be followed half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study, provided that an additional informed consent regarding prolongation of the follow-up was signed.

8.5 Response assessment

Clinical assessment should be performed at baseline, at the time of core biopsy/breast MRI (week 3), after 6 weeks and at the end of therapy (week 12). Clinical assessment at the week 9 is optional.

The clinical response is typically assessed by bidimensional clinical measurements of the primary breast tumor (i.e. clinical palpation). The clinical complete response (cCR) is defined as complete disappearance of all clinically detectable disease in the breast and regional lymph nodes.

Assessment by ultrasound or mammography will be performed according to the following criteria[186].

- Progressive Disease (PD): ≥20 percent increase of at least 5 mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameter recorded. In case of PD the therapy should be changed (or surgerry performed) at discretion of the investigator.

Response will be evaluated on an exploratory basis. The tumor needs to be marked with a clip before the first cycle of chemotherapy to be able to reliably identify the region of the former tumor at the time of surgery.
Pathological response assessment: The tumor ypT is measured as the largest single focus of invasive tumor, not including areas of fibrosis within the tumor bed. Pathological complete response (pCR) implies no histopathological evidence of residual invasive tumor cells, either in the breast or the axillary lymph nodes.

Recently Von Minckwitz et al compared different definitions of pCR (e.g. ypT0/ypN+, with or without don-invasive lesions etc.). They found adverse impact of remaining in situ lesions on prognosis of patients[73] (in contrast to prior reports[74]).

9 Dose Delays and Reduction/Modification ADAPT Triple Negative Breast Cancer

9.1 Treatment Dose Adjustments and Treatment Delays

Toxicities will be graded using the NCI Common Toxicity Criteria (NCI CTC), version 4.0.
Dose reduction is planned for each treatment arm in case of severe hematological and/or non-hematological toxicities. Chemotherapy dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. In case of several toxicities in one patient and conflicting recommendations, the most conservative dose adjustment has to be followed. Doses which have been reduced for toxicity must not be re-escalated.
Treatment with chemotherapy may be delayed no more than 2 weeks (up to day 35) to allow recovery from acute toxicity.

9.2 Toxicity Related Guidelines for Dose Reduction and Dose Modification of Nab-paclitaxel, Gemcitabine and Carboplatin

Please refer to the ADAPT protocol, **Appendix 1 – Treatment Dose Adjustments and** Treatment Delays for further information.

10 Safety Monitoring

10.1 Safety Plan

Overall safety will be assessed on an ongoing basis during the conduct of the study. The DSMB (IDMSC) will monitor cumulative safety data at least once every 6 months during the course of the study. In addition, data on serious adverse events and deaths will be monitored by the DSMB (IDMSC) at least once every 3 months.

10.2 Cardiac Safety Monitoring

There will be no specific recommendations for the cardiac safety monitoring for triple negative patients. Please refer to the ADAPT protocol, **Appendix 2 – Cardiac Safety Monitoring** for further information.

11 Data Analysis and Statistical Considerations

The ADAPT TN sub-trial seeks to identify early-response biomarkers, optimize novel chemotherapy regimens/combinations, and identify patient subgroups with primary drug resistance.

Specifically the TN sub-trial aims to show a strong association between pCR and early response (17% better pCR rate in responders than in non-responders). It also will look for a difference of 15% in pCR under nab-paclitaxel + carboplatin (Arm B) compared to nab-paclitaxel + gemcitabine (Arm A). Patients are initially randomized in the ratio 1:1 to Arm A or Arm B.

The study comprises a **Run-in phase** (n=130) and a **Main phase** (n=206), total: 336 patients.

11.1 Run-in Phase

The Run-in phase has the following objectives:

- Validation of statistical assumptions made for the ADAPT TN sub-trial as a whole
- Identification of molecular markers associated with early response* and with pCR
- Feasibility/reproducibility of assessment of these markers

* “Early response” during the run-in phase is defined in terms of Ki-67 measurements after 3 weeks, as in the ADAPT study as a whole.

11.2 Primary endpoints and hypothesis testing

The primary endpoint of the study is pCR as defined above. The trial will test **two co-primary hypotheses**. The family-wise error alpha is controlled for multiple testing at the level 0.05 by an unequal allocation of alpha (generalized Bonferroni according to Cook et al. 1993).

Hypothesis 1 (primary):

- **Proportion achieving pCR is higher in responders (60 % of TN) than in non-responders (about 40 % of TN).**

Overall proportion of pCR with these medications in TNBC is estimated at about 25% including both responders (assumed 60% of TN patients) and non-responders (assumed 40% of TN patients). A difference of 17 % between pCR proportion of responders and pCR proportion of non-responders is of clinical interest. A **one-sided test with alpha = 0.01** will be performed for a difference of 17 % between responders and non-responders (e.g., 31.8 % versus 14.8 %). Under the above assumptions, this test would reject the null hypothesis (no difference in proportions) with better than 80 % power with N = 320 patients (336 including drop-outs), even taking into account variability in the true percentage of responders.

Hypothesis 2 (primary):

- **Proportion achieving pCR is is different in the two arms**.

There is indirect evidence that pCR could be higher in the B (nab-paclitaxel + carboplatin) arm than in the A Arm (nab-paclitaxel + gemcitabine). A **two-sided hypothesis test will performed with alpha = 0.04** for a difference in pCR proportion between the B-Arm and the A-Arm. A difference of magnitude **15 %** would be clinically relevant for TNBC. Under these

assumptions, there is 80% power with N = 320 patients (336 including dropouts) to reject the null hypothesis.

Secondary analyses

Hypothesis 3 (secondary)

- **Among responders, pCR is different in the two arms.**

There is indirect evidence that pCR could be higher in the B (nab-paclitaxel + carboplatin) arm. However, the test is two-sided because a difference in either direction would be clinically relevant.

Consistent with the first primary hypothesis, we assume about 60 % responders in the population. We assume that pCR proportion among responders (in A and B arms combined) will be 32 %. We test for a difference of 20 % or more in pCR proportion between the B-Arm (nab-paclitaxel + carboplatin) and the A-Arm (nab-paclitaxel + gemcitabine). A difference of this magnitude would be clinically relevant for TNBC.

If one of the two CTX combinations is superior by 20 % with respect to pCR proportion, then a two-sided test with alpha = 0.05 would reject the null hypothesis with better than 80 % power with N = 336 TN patients, taking into account the variability in the percentage of responders.

Hypothesis 4 (secondary):

- **Among non-responders, pCR is different in the two arms.**

Consistent with the first primary hypothesis, we assume about 40 % non-responders in the population. We estimate that pCR proportion among non-responders (in A and B arms combined) could be about 14 %. We can test for a clinically relevant difference of 19 % or more in pCR proportion between the B-Arm (nab-paclitaxel + carboplatin) and the A-Arm (nab-paclitaxel + gemcitabine).

Under these assumptions, if one of the two CTX combinations is superior by 19 % with respect to pCR proportion, then a two-sided test with alpha = 0.05 would reject the null hypothesis with better than 80 % power with a total of N = 336 TN patients, taking into account the variability in the percentage of non-responders.

Secondary endpoints

The following secondary endpoints (defined below) will be prospectively evaluated:

- Overall survival
- Distant disease-free survival
- Local relapse-free survival
- Evaluation of proliferation/apoptosis changes as surrogate marker for 5 year EFS.
- Relation of survival to Chemotherapy.

For the definitions of event-free survival and overall survival, please refer to chapter 11 of the ADAPT umbrella protocol.

- Interim (exploratory) safety RFS and OS analyisis with regard to pCR and therapy after 3 years of median FU

Safety (see above):

- Toxicity

Further secondary objectives will be analyzed in an explorative manner.

Translational research:

- Definition of the molecular profile of non-responding patients,imagaing comparisons: (changes in dynamic breast MRI after 3 weeks of therapy vs. dynamics of Ki-67/further proliferation markers).

11.3 Ethical Considerations ADAPT Triple Negative

All participants will give written informed consent for participation in the trial. All participants will be protected by the insurance cover as standard in the clinical trials. Possible undertreatment should be excluded by the data from several trials. Transfer of tumor block to the central tumor bank is planned for further research purposes.

11.4 Allocation/Randomization

Eligible patients will be randomized to either 4 x nab-Paclitaxel 125mg/m² + Gemcitabine 1000mg/m² d1/8 q3w (Arm A) or 4 x nab-Paclitaxel 125mg/m² + Carboplatin AUC2 (upper limit 300 mg) d1/8 q3w (Arm B). In the TN sub-trial**,** randomization of eligible triple-negative patients is applicable **right from the beginning of study participation in the ratio 1:1**. Efficacy Evaluation

11.4.1 Primary efficacy parameters and ITT

The primary efficacy parameter for TN disease will be pCR, defined as no invasive patterns in the breast and lymph nodes at the time of surgery. The primary efficacy analysis for TN disease will be based on the ITT5 population.

11.4.2 Further efficacy parameters and populations

In addition to pCR, exploratory analyses will include RCB rates. Exploratory analyses will also be conducted in per-protocol populations.

11.5 Further statistical details

11.6 For further information please refer to the ADAPT umbrella protocol chapter 11.5.Safety Evaluations

11.6.1 Interim Safety Analysis

For further information please refer to the umbrella protocol chapter 11.4.3
RFS and OS analyisis with regard to pCR and therapy after 3 years of median follow up

12 Translational Research

An additional core-biopsy will be taken after 3 weeks from 50 patients (in addition to the biopsy at baseline) for further biomarker analysis (including but not limited to protein expression etc.) – please refer to the ADAPT protocol, chapter **10** for further information.

13 Adverse Events

The Sponsor will supply Celgene with a copy of all SAEs which involve *exposure* to a Celgene product within 24 hours of being made aware of the event regardless of whether or not the event is listed in the reference document (e.g. IB, SmPC). The Sponsor will provide Celgene with a copy of the annual periodic safety report e.g. Development Update Safety Report (DSUR) at the time of submission to the Regulatory Authority and Ethics Committee.

Please refer to the ADAPT protocol, chapter 12 for further information.

14 Definition of Study Medication

14.1 Study Medication

For the purpose of this sub-trial, nab-paclitaxel is the investigational medicinal product (IMP or IP). The combinations of nab-paclitaxel with gemcitabine and carboplatin will be regarded as investigational. Gemcitabine and carboplatin are regarded as study medication and will be labeled study-specific.

15 Administrative Aspects

Please refer to the ADAPT protocol, chapter **14** for further information.

The planned number of patients has been reached Q1 2015 and the recruitment into this substudy has been stopped.

ADAPT Elderly in HER2 negative Breast Cancer - Sub-trial for Patients beyond 70 years

(Recruitment for the substudy prematurely stopped)

A prospective, multicenter, open-label 12 week neoadjuvant phase II trial optimizing taxane therapy in *Elderly* patients with low response

Protocol Number:	WSG-AM06
EUDRA-CT Number:	2011-001462-17
SPONSOR:	WSG – Westdeutsche Studiengruppe GmbH
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Final Version 5.0, 11 November 2021

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Protocol title: A prospective, multicenter, open-label 12 week neoadjuvant phase II trial optimizing taxane therapy in *Elderly* patients with low response

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1 Study Summary ADAPT Elderly Breast Cancer

ADAPT Elderly	A prospective, multicenter, open-label comparison of pre-surgicalpre-surgical Myocet/ Cyclophosphamide (MC) q3w followed by either MC or Paclitaxel - depending on early response assessment by ultrasound or by toxicity for elderly non frail primary breast cancer patients with increased risk of relapse.
Study Overview	Germany has one of the highest incidences of *Elderly* breast cancer in the western world. According to the recently published data of the Robert-Koch-Institute, the incidence varies between 325,3-361,5 per 100.000 in age subgroups beyond age of 70 years. There is a risk of 6,3% to develop cancer for women aged >70 and a risk to die of 2,4% due to breast cancer. Despite of only moderate change in incidence between 1990 and 2000 in Germany (-5,0%), only weak survival advantage (7,3%) due to better therapies and diagnostics could be observed in Germany in this subgroup. These data highlight - a. the contrast to other countries (e.g. Switzerland: incidence increase of 27,9% and mortality decrease of 27,3%) - b. contrast to other age subgroups (e.g. in Germany change in incidence in 50-69 years old subgroup of +58% and decrease in mortality of 16%)[187]. *Elderly* women have more frequently tumors with HR expression, less HER2 expression, more often larger, node positive tumors[188,189]. Interestingly, node involvement is more often seen in smaller tumors, indicating possible higher aggressiveness in older patients. Yet, after adjusting for disease stage, older patients have lower relative survival compared to patients 40-70 years old due to suboptimal therapy, socioeconomic differences and limited access to cancer care[190]. Undoubtedly, there is a significant impact of co-morbidities onto mortality. Satariano et al. reported 20-time higher mortality from other causes than breast cancer in women with more severe diseases[191]. **Integrated oncogeriatric approach (IOGA)** An integrated oncogeriatric approach (IOGA) has developed as a top priority in the international oncology community over last 15 years[i]. IOGA focuses on the specific needs, values and preferences of geriatric cancer patients. Comprehensive geriatric assessments (CGA) is important in the IOGA concept[ii,iii], and is the most frequently used tool used within breast cancer studies. The consensus conference defined Comprehensive Geriatric Assessment as “a multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described and explained, if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan developed to focus interventions on the person’s problems”[iv]. A geriatric functional status measurement is different form the instruments used in oncology like ECOG performance status or Karnofsky Index. Stotter et al. reported data on pre-surgicalpre-surgical CGA in 152 patients and identified breast cancer patients with an estimated life expectancy of < 2 years, who should be treated by endocrine therapy alone[7] Within another study in 660 patients >65 years old CGA correctly identified patients with poor treatment tolerance and higher mortality. Hurria et al. reported successful implementation of CGA in this study setting for patient selection for chemotherapy[10]. In a trial published by Girre et al. in 105 patients with solid tumors (61% had breast cancer) CGA resulted in 39% change of treatment plan; no outcome data are reported so far[8]. However, while different tools have been used, no definitive consensus has yet been reached regarding assessment steps’, correct use and place[v]. Similar results were confirmed by others (for review see also Puts et al.[9]). Puts et al

emphasized the divergences between oncologists' and geriatricians' experience of it and Extermann et al. demonstrated that geriatric tools and oncology tools have only a weak correlation[4]. Oncologists usually carry out non-systematic and non-standardized CGA. Differences in perception between oncologists and geriatricians regarding the use of CGA tools have also been reported by other authors. Hurria et al concluded there is no consensus within the geriatric oncology community regarding a standard CGA instrument for older patients with cancer[10]. International Society of Geriatric Oncology (SIOG) experts have declared they cannot recommend any specific CGA. Hence, in spite of its advantages, CGA is not necessarily current practice for oncologists[1].
We are going to use the **Charlson comorbidity index** in our trial. The Charlson comorbidity index predicts the ten-year mortality for a patient who may have a range of comorbid conditions (a total of 22 conditions)[vi]. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality. Clinical conditions and associated scores are as follows:
1 each: Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease.
2 each: Hemiplegia, moderate or severe kidney disease, diabetes, diabetes with complication, tumor, leukemia, lymphoma.
3 each: Moderate or severe liver disease.
6 each: Malignant tumor, metastasis, AIDS.
Charlson scale ≤ 2 declared in additional inclusion criteria **ADAPT Elderly** as inclusion criteria.

Standard treatment of the *Elderly*
Older patients are underrepresented in clinical trials. Life expectancy is increasing and breast cancer incidence is increasing with age. In future we will be faced with a growing number of older patients and breast cancer with a limited number of optimal treatment guidelines.

Surgery: *Elderly* patients with early breast cancer should be treated by similar surgical procedures as younger patients (breast conserving surgery (BCS) with radiotherapy, mastectomy +/- radiotherapy), axillary surgery should be planned by similar criteria as in younger patients.

Radiotherapy: *Elderly* patients with early breast cancer should be treated by similar radiotherapeutic procedures as younger patients. 10 years results of CALGB 9343 trial showed reduction of local relapses by radiotherapy from 9% to 2% in *Elderly* women >70 years with clinical stage 1 ER+ breast cancer treated by lumpectomy + tam +/- radiotherapy. However, there is no survival difference between both study arms (breast cancer specific survival 98% vs. 96%, OS 63% vs. 61%) (for review[192].

Chemotherapy:
The standard chemotherapy treatment in elderly patients (≥65 yrs.) is Adriamycin/ cyclophosphamide x 4 q3w, or classical CMF for high risk, early stage breast cancer patients based on the results of the largest randomized trial conducted in the elderly that investigated the efficacy of AC or CMF versus capecitabine[193] Patients who were randomly assigned to capecitabine were twice as likely to have a relapse and almost twice as likely to die as patients treated with standard polychemotherapy AC or CMF. At 3 years, the rate of relapse-free survival was 68% in the capecitabine group versus 85% in the standard group. The overall survival rate was 86% versus 91%. The benefit was

pronounced in women with hormone-receptor-negative tumors. Only 62% of the patients, who were assigned to CMF could complete the six planned cycles. In the group, treated with doxorubicin plus cyclophosphamide 92% of the patients completed the four cycles.

Taxanes in the *Elderly* patient population

According to the recently published EBCTG metaanalysis four courses of AC or CMF are inferior to other anthracycline based chemotherapy[194]. A further improvement of outcome data is reported for taxane /anthracycline based last generation chemotherapies irrespective of nodal status, hormone receptor status and grading. There are relatively few data on the use of these agents in older patients. However, there are pharmacokinetic data, which demonstrate that taxanes can be used in *Elderly* patients without dose modifications. Only in case of an impaired liver function neither paclitaxel nor docetaxel should be applied due to their high liver metabolization[195,196].

Recent evidence supports the use of regimens incorporating taxanes with anthracyclines; at 5 years, the survival benefits of these regimens were similar for patients in all age groups, including those ≥ 60[197]. Loibl et al. published a systematic pooled analysis of tolerability for *Elderly* from different adjuvant and neoadjuvant German trials with taxane-containing regimens[198]. The patient cohort reflects clinical trial routine at that time and substantiates findings from other studies[199,200] demonstrating that even if the trials had no upper age limit, *Elderly* patients were generally included less frequently or were not included at all. In this analysis Paclitaxel had significantly less hematologic toxicity compared to Docetaxel, which is consistent with data from a prospective adjuvant trial directly comparing these taxanes[91], Moreover, in an adjuvant anthracycline–taxane sequential regimen, weekly Paclitaxel shows the same efficacy as Docetaxel. This might therefore, be the preferred taxane regimen, at least for Elderly patients.

The data published by Muss et al. showed that benefit from chemotherapy did not differ across age groups although treatment-related mortality was higher (1.5% *vs.* 0.42%) in the group aged > 65 years[193].

It has therefore become increasingly clear that neoadjuvant therapy concepts for *Elderly* patients should consider – next to oncological needs – the patient's physical and functional status, and should not be determined merely on the basis of their age.

Anthracyclines - Liposomal Anthracycline

Anthracyclines in combination with cyclophosphamide are one well evaluated standard in the elderly[193]. Beyond acute toxicity, long-term cardiotoxicity is one important concern in anthracycline based chemotherapy. For study populations cumulative doses of 550 mg/m^2 doxorubicin and of 950 mg/m2 epirubicin cause less than 5% of grade 3 to 4 carditoxicity. Beyond these cumulative doses risk increases exponentially. Taxane combinations seem to increase the cardiac risk as the 10 year data from BCIRG 001 document. Chronic heart failure from this trial, which involved patients up to 70 years, was reported after ten years for 3.5% of patients receiving TAC (docetaxel, adriamycin, cyclophosphamide) versus 2.3% in patients receiving F(5 fluoro-uracil)AC. SEERS data collected from 43 339 women - which may reflect much more daily routine- document that age is an important risk factor for anthracycline induced cardiotoxicity. The adjusted hazard ratio for chronic heart failure was 1.28 for women aged 66 to 70 treated with anthracycline compared to other chemotherapy. Furthermore, this analysis identified the following baseline characteristics as significant predictors of chronic heart failure: age (HR1.79), hypertension (HR 1.45), diabetes (HR 1.74) and coronary artery disease (HR 1.59) [201].

In many elderly patients comorbidity as described above is a frequent clinical problem. The liposome encapsulation of anthracyclines has the potential to decrease toxicity of anthracyclines, while preserving their antitumor efficacy. Liposome encapsulated doxorubicin (TLC D-99, Myocet©) at 75 mg/m^2 q3w has been compared to 75 mg/m^2 doxorubicin q3w in first line therapy of 224 patients with metastatic breast cancer. Median age of this group was 54 years. Protocol-defined cardiotoxicity was observed in 13% of patients receiving liposome encapsulated doxorubicin versus 29% in the doxorubicin arm. Median cumulative doses at onset of cardiotoxicity were 785 mg/m^2 and 570 mg/m^2 respectively again favoring the liposome encapsulated compound. Response rates were 26% in both arms[202]. In combination with cyclophosphamide (600 mg/m^2) liposome encapsulated doxorubicin or conventional doxorubicin both at a dose of 60 mg/m^2 were compared within a three week schedule in 297 patients in first line chemotherapy for metastatic breast cancer. Six versus 21% of patients developed cardiotoxicity in the liposome encapsulated anthracyline arm versus the conventional arm. Again response rates were identical (43% vs. 43%) as well as median time to treatment failure and median survival[203].
Another trial has been conducted in first line chemotherapy of metastatic breast cancer by Chan et al. comparing Myocet 75 mg/m^2 versus Epiadriamycin at the same dose in a three week schedule in 160 patients. Overall response rates were 46% versus 39% favoring the liposomal encapsulated compound as well as median time to progression (7.7. vs. 5.5 months). Median survival times were 18.3 vs. 16.0 months (p=0.504). Both Myocet and Epirubicin had low cardiotoxicity at the planned cumulative dose of 600 mg/m^2.[204]. In terms of non-cardiac toxicity liposome encapsulated doxorubicin induces significantly less neutropenia grade 4, diarrhea grade 3 and nausea grade 3 to 4 than doxorubicin as shown by Cochrane meta-analysis[205].

Specific problems in the Elderly:
Anthracyclines and taxanes are recommended as (neo)adjuvant polychemotherapy in high risk early breast cancer patients. Older women will less likely receive standard chemotherapy[193,206,207], because of more severe toxicity, comorbidities, and finally due to missing evidence from large scale clinical trials[198,208]. Under treatment as a result of not adhering to consensus guidelines, is associated with a higher recurrence rate likely resulting in a poorer quality of life and inferior survival In a meta-analyses by Muss et al. it could be demonstrated that Elderly women with node positive disease have a significant better disease-free and overall survival, if they receive adequately dosed chemotherapy[209].

Neoadjuvant chemotherapy of the *Elderly*
There are no randomized trials testing the efficacy of neoadjuvant chemotherapy in older patients so far.

The ADAPT philosophy – A combined static and dynamic model
Early response assessment in eBC may be essential to separate sub-populations with large or marginal benefit from therapy.
Drop of proliferative activity after a short course of endocrine therapy (2 weeks to 4 months) as measured by proliferation marker Ki-67 is an excellent predictor for local as well as systemic outcome in HR+ disease. It allows identifying groups of patients with excellent outcome in both low and higher risk groups independently from chemotherapy application[25-27]. Early prediction of chemotherapy outcome by sequential assessment of ki-67 is less well evaluated. Posttherapeutic Ki-67 after neoadjuvant chemotherapy nevertheless better correlates with outcome than baseline ki-67[210]. Early response assessment by

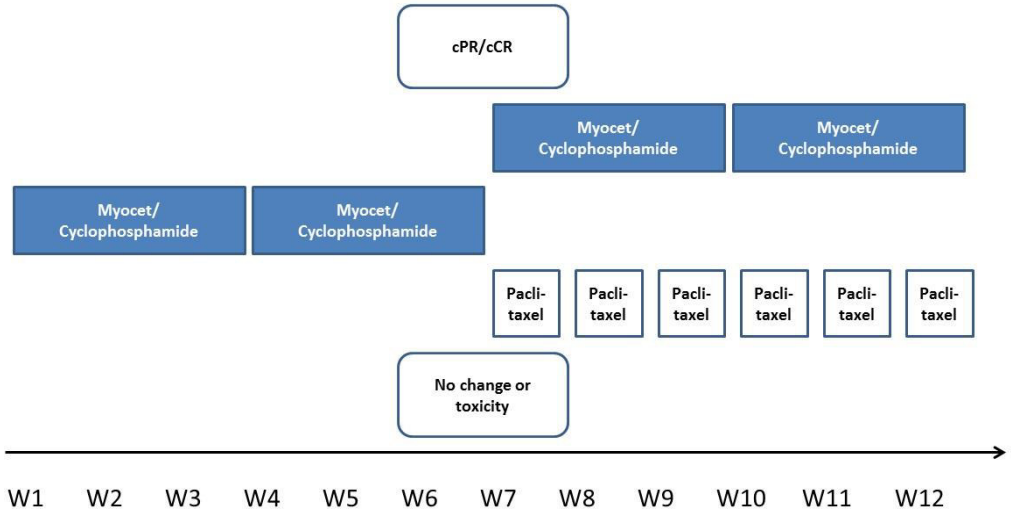
	ultrasound is according to GEPARTRIO another reliable predictive tool. Thus, besides baseline prognosis estimation (***static* assessment**), therapy efficacy is evaluated at an early time of treatment (***dynamic* assessment**). This approach is especially important in the elderly since risk – benefit evaluation is much more sensible than in younger, healthy patients.
Rationale	**Neoadjuvant** chemotherapy allows in vivo testing of chemotherapy regimens identifying good and poor responders. This information is of particular interest in the elderly since the risk- benefit evaluation is much more difficult in older populations due to increased toxicity and comorbidity and reduced life expectancy. **Rationale for Taxanes:** According to the last EBCTTG meta-analysis the addition of taxanes has improved adjuvant chemotherapy outcome in all age groups[194]. For patients beyond 70 years sample size is small. Sequential regimens are superior to combinations. Taxane based chemotherapy caused especially in the elderly undue toxicity, which may consistently influence the therapeutic ratio in this age group. **Myocet** Anthracyline based chemotherapy is standard of care in the elderly. Especially in this age group and in patients with comorbidity such as hypertension, diabetes and coronary artery disease - cardio toxicity profile is an important discriminant for the choice of a specific anthracycline derivative in primary therapy. With respect to long-term prognosis this is even more important in an adjuvant setting than in metastatic disease. In terms of cardiotoxicity Myocet© is safer than doxorubicin and as effective as doxorubicin or epi-doxorubicin. It is therefore the ideal candidate anthracycline partner for cyclophosphamide in the *ADAPT Elderly* protocol. **G-CSF primary prophylaxis** Based on the data from small trials indicating risk for febrile neutropenia of 15% in older patients G-CSF Prophylaxis is strongly recommended within the study[211]. **Early response assessment / early assessment of toxicity** The early assessment of response to NACT for breast cancer may allow to stop ineffective therapy regarding pCR or to modifiy this therapy or to continue an effective NACT. Some published data show that due to this procedure the DFS and OS can be improved. (von Minckwitz et al. 2005; 2008; von Minckwitz et al. 2011). The optimal method for early response assessment has not been established. The Response Evaluation Criteria In Solid Tumors (RECIST) guidelines recommend breast MRI as the preferred method. Ultrasound should not be used. Breast ultrasound results are highly dependend on the investigator and not enough reproducible (Eisenhauer et al. 2009). But the GEPARTRIO trial demonstrated improved patient outcomes due to early response assessment using breast ultrasound or palpation of tumor size. A metaanalysis of the value of MRI in pre-surgicalpre-surgical prediction of pCR showed that with breast ultrasound can be achieved the same results as compared with MRI. But there was no study with direct comparison. (Marinovich et al. 2012; 2013). Breast ultrasound has advantages compared with MRI like lower costs, widely available, shorter investigation time and no need of i.v. injections. Because of these data further studies are needed to analyse the predictive value of ultrasound in predicting pCR and other kinds of response after NACT in breast cancer patients.

	The GEPARTRIO -trial has shown that early response evaluation by ultrasound correlates strongly with outcome. Identification of non-responders allows sparing unnecessary toxicity to patients from non-effective chemotherapy. Early assessment of toxicity on the other hand allows identifying a subgroup of patients, who despite benefit from chemotherapy may have low therapeutic ratio due to enhanced toxicity. **Overall design:** 4 x MC is according to data from Muss considered to be an classical standard in the elderly, which might have the advantage of causing less cardiotoxicity than classical AC. As taxane based chemotherapy is not well tolerated in the elderly and since the metaanalysis only shows small survival differences, taxane use should be restricted to those patients, who are not sufficiently treated with MC alone. In an neoadjuvant setting early response assessment allows to identify patients with poor response to MC, who might benefit from the use of taxanes. The early switch allows an exploratory analysis of the benefit patients may have in terms of pCR by the addition of taxanes . The comparison of toxicity in the two arms (MC vs MC->pac) allows evaluating whether the presumed enhanced toxicity in the taxane containing arm may be outweighed by the higher response rate in poor responders.
Objectives	Primary objectives **Run-in Phase:** • Identification of molecular markers correlating with early response/pCR • Feasibility/reproducibility of assessment of these markers • Validation of statistical assumptions (toxicity, pCR) **Run-in phase + main phase** Primary objectives Comparison of pCR rates in patients with early response and no severe toxicity (Group 1) and in other patients (Group 2). Secondary objectives • Incidence of febrile neutropenia (FN) after 1 x MC in patients with primary prophylaxis (PP) vs. others. • Toxicity in the 4 x MC versus 2 x MC →6 x Pac arm • Number of pCR in non-responders to MC • Evaluation of dynamic test regarding prediction of pCR • Evaluation of 6 week US regarding prediction of pCR • Comparison of dynamic Ki-67 assessment with early ultrasound assessment for prediction of pCR • G-CSF use/FNP • Health-related quality of life (HRQL) (optional) • Rates of breast conserving therapy Exploratory analysis Survival of patients with pCR
Trial design	Prospective, multi-center, controlled, non-blinded, phase II
Treatment	**Neoadjuvant Treatment:** **2 cycles** Myocet 60 mg/m² / Cyclophosphamide 600 mg/m² (**MC) q3w followed by either 2 x MC or Paclitaxel 80 mg/m² q1w x 6** depending on early response assessment by ultrasound or on toxicity profile **Supportive therapy**: G-CSF according to AGO guidelines primary G-CSF prophylaxis is strongly recommended.

Toxicity assessment:
After the second course of MC: patients with any organ toxicity >°2 or hematotoxicity > °2 in patients with primary G- CSF prophylaxis should be switched to taxanes

Surgery:
After completion of 12 weeks of neoadjuvant treatment for all patients, surgery is planned. In case of disease progression treatment can be stopped prematurely and surgery will be performed immediately.

Adjuvant Treatment:
Patients, who do not achieve pCR after 12 weeks could cumulatively receive further treatment at decision of investigator. Patients achieving pCR after 12 week neoadjuvant chemotherapy can consider to stop chemotherapy



Response Assessment:
Primary efficacy (i.e. pCR) is defined at time of surgery according to NCCN guidelines (no invasive cancer in both breast and lymph nodes) and based on provided data regarding residual tumor size, proportion of vital cells within invasive carcinoma, number of positive lymph nodes and size of the largest lymph node metastasis and ductal carcinoma in situ.
Based on these criteria residual cancer burden (and other pCR classifications) will be defined for further analysis (Symmans et al, JCO 2007). Further chemotherapy may be omitted only in tumors with no invasive and DCIS patterns.

Safety:
Safety of paclitaxel and Myocet/cyclophosphamide chemotherapy will be measured by the incidence and severity of adverse events (AE) and serious adverse events (SAE). Frequency and reasons for discontinuation of therapy, modification and interruption will be evaluated in a prospective manner.

Dynamic test:
Drop of proliferation is considered as the key factor for efficacy of the combination therapy. During the run-in phase of the study, immunohistochemical measurement of Ki-67, can be performed on samples from diagnostic and sequential biopsy.
All tumors will undergo central pathology assessment (ER, PR, HER2) for randomization to the study (analysis by Prof. H. Kreipe, Hannover).

Study Examinations:
For timing of baseline examinations and examinations during neoadjuvant treatment please refer to table 1.

Table 1: Study Evaluations for *ADAPT Elderly* Breast Cancer Patients

week	-3 to 0 (BL)	1	4	7	10	13 (EOT)	14 (Surgery)
Medical history (incl. concomitant medications)	x						
Central pathology review of diagnostic core biopsy	x						
Charlson Score	x						
Recurrence Score (HR+ only)	x						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x[2]	x[5]	x[5]	x[5]	x[5]	x	
Serum sample (biomarker analysis, optionally)	x[2]		x			x	
Radiology: • Chest X-ray • Bone scan • Liver imaging • Mammography	x[3]						
MRI (optional)	x		x				
Ultrasound	x		x	x		x	
Clinical assessment	x[2]		x	x		x	
ECG and LVEF	x[3]			x			x (prior to surgery)
Laboratory: • Hematology • Biochemistry	x	x[5]	x[5]	x[5]	x[5]	x	
Surgery							x
(Serious) Adverse Event		continuously					
Concomitant medication		continuously					

[1] prior to 2nd administration of study drug
[2] within ≤ 7 days prior to allocation
[3] within 3 months prior to allocation
[4] +/-3 days
[5] prior to **any application of chemotherapy** (MC q3w or Paclitaxel q1w)

Selection of patients

General Inclusion Criteria for ADAPT:

- Female patients, age at diagnosis 18 years and above (consider patients at 70 years and above for *ADAPT Elderly*)
- Candidate for chemotherapy on the basis of conventional criteria
- Histologically confirmed unilateral primary invasive carcinoma of the breast
- Clinical T1 - T4a-c
- All clinical N (cN)
- No clinical evidence for distant metastasis (M0)
- Known HR status and HER2 status (local pathology)
- Tumor block available for central pathology review
- Performance Status ECOG ≤ 1 or KI ≥ 80%
- Written informed consent prior to beginning specific protocol procedures, including expected cooperation of the patients for the treatment and follow-up, must be obtained and documented according to the local regulatory requirements
- The patient must be accessible for treatment and follow-up
- Patients must qualify for neoadjuvant treatment

- LVEF $\geq$ 50%; LVEF within normal limits of each institution measured by echocardiography and normal ECG (within 42 days prior to chemotherapy)

- Laboratory requirements :
  - Leucocytes ≥ 3.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Hemoglobin ≥ 10 g/dL
  - Total bilirubin ≤ 1 x ULN
  - ASAT (SGOT) and ALAT (SGPT) ≤ 2.5 x UNL
  - Creatinine ≤ 175 µmol/L (2 mg/dl)

Additional inclusion criteria *ADAPT Elderly:*

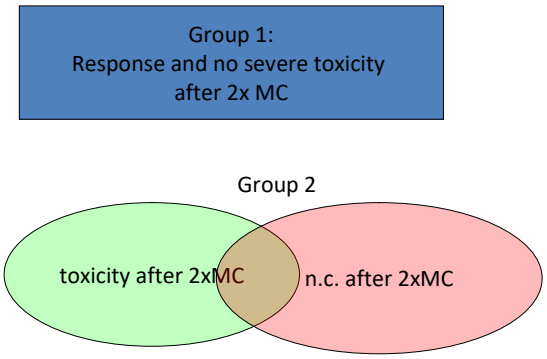
- ≥ 70 years old
- Charlson scale ≤ 2
- HR+/HER2- disease: if RS and sequential testing are available N0-1/RS 12-25/poor response or N0-1/RS ≥26 or G3 with Ki-67 ≥40% in tumors >1cm or cN2-3
- All TN qualifying for neoadjuvant treatment
-

General Exclusion Criteria for ADAPT:

- Known hypersensitivity reaction to the compounds or incorporated substances
- Prior malignancy with a disease-free survival of < 10 years, except curatively treated basalioma of the skin, pTis of the cervix uteri
- Non-operable breast cancer including inflammatory breast cancer
- Previous or concurrent treatment with cytotoxic agents for any reason after consultation with the sponsor
- Concurrent treatment with other experimental drugs. Participation in another clinical trial with any investigational not marketed drug within 30 days prior to study entry (concurrent participation in non-interventional post authorization safety studies not influencing the primary study endpoints is allowed, e.g. WSG PROTROCA for evaluation of primary/secondary G-CSF prophylaxis)
- Male breast cancer
- Sequential breast cancer
- Reasons indicating risk of poor compliance
- Patient not able to consent

Additional Exclusion Criteria *ADAPT Elderly*:

- Known polyneuropathy ≥ grade 2
- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study
- Inadequate organ function (e.g. hepatic impairment, pulmonary disease, etc.)
- Uncompensated cardiac function (current unstable ventricular arrhythmia requiring treatment, history of symptomatic CHF NYHA classes II-IV), history of myocardial infarction or unstable angina pectoris within 12 months of enrollment, history of severe hypertension, CAD – coronary artery disease)
- Severe dyspnea
- Pneumonitis

	• Abnormal blood values: • Thrombocytopenia > CTCAE grade 1 • Increases in ALT/AST > CTCAE grade 1 • Hypokalaemia > CTCAE grade 1 • Neutropenia > CTCAE grade 1 • Anaemia > CTCAE grade 1
Efficacy evaluation	An intention to treat (ITT) analysis will be conducted for all patients. An additional analysis will be conducted among the eligible patients (per protocol)
Statistical considerations	The non-randomized trial comprises a **Run-in phase** (n=130) and a **Main phase** (n=170), i.e., a total of 300 patients including dropouts. The trial is designed to test whether early response assessment could allow identification of patients with poor response to MC (or toxicity) who might benefit from the use of taxanes. **Primary Endpoint** The primary endpoint of the ADAPT Elderly trial is pCR. Early response and toxicity (particularly febrile neutropenia) are stratification criteria. The trial is designed to test whether therapy switch in patients with either toxicity or inadequate early response benefit from the addition of taxanes. To this end (see illustration Fig. 1), a non-inferiority hypothesis for this group (Group 2) compared to responders without toxicity (Group 1) will be tested with respect to the outcome pCR:  ***Figure 3: Group 1 is defined as patients with early response AND no severe toxicity. Group 2 is defined as patients with either "no change" or severe toxicity or both (i.e., all other patients). One expects roughly 150 patients in each group. A few patients in Group 2 could be non-responders with severe toxicity.*** Patients in Group 1 receive 4 x MC (2 x MC prior to early-response assessment, 2 x MC subsequently). Patients in Group 2 receive 2 x MC followed by Paclitaxel 80 mg/m^2 q1w x 6. The hypothesis to be tested is non-inferiority of Group 2 compared to Group 1 with regard to pCR, θ_1-θ_2<δ (respective pCR fractions defined as θ_1, θ_2) With a sample size of 150 patients in each group (1 and 2), this test will have 80% power to detect a **non-inferiority delta of 0.13** with one-tailed alpha=.05 assuming true pCR percentage in each group is 0.25. The power allows for 8% dropouts in each group. Patients of the run-in and main phases are included in this test. **Secondary Endpoints**

	Comparison of toxicity in the two arms (MC vs MC->pac) allows evaluating whether the presumed higher risk of toxicity in the taxane-containing arm may be outweighed by the higher response rate in poor responders. Febrile neutropenia: Primary prophylaxis (PP) with G-CSF for febrile neutropenia will be administered at investigator discretion (recommended according to AGO guidelines). Incidence of febrile neutropenia (FN) after 1xMC will be evaluated in these two (non-randomized) groups with formal 95% confidence intervals (CI). With an estimated N=200 patients receiving PP (based on experience from previous trials), the upper 95% confidence interval will extend to about 3.9% if the true FN rate in this group is 2%. In exploratory analysis (provided that 100 patients do not receive PP) incidence of FN will be compared in these two groups of patients after 1xMC. A difference of about 8% will be seen in a one-sided test with alpha=.05 and about 80% power (no correction for multiple testing). To support interpretation in this nonrandomized comparison, patient characteristics at study entry in the two groups will be compared. If subgroups of the PP group and of the non-PP group with comparable characteristics can be identified, FN incidence in these similar subgroups will also be compared in exploratory analysis. After 2xMC, there will be patients with G-CSF from the start, patients with no G-CSF, and patients with G-CSF beginning with the second cycle. Incidence of FN at 2xMC will be estimated with formal 95% CI in these groups. Incidence of FN after w12 will be reported as a whole and in all groups defined by G-CSF and study medication sequence. Toxicity rates will be generally computed with formal 95% CI in the 4 x MC and in the 2 x MC →6 x Pac arm. **Further objectives** Response and dynamic assessment: • Percentage of pCR in non-responders to MC will be estimated with 95% CI • Sensitivity, specificity, positive predictive value of dynamic test regarding prediction of pCR will be evaluated as a whole and in subgroups • Sensitivity, specificity, positive predictive value of 6-week US regarding prediction of pCR will be evaluated as a whole and in subgroups • Concordance measures of dynamic Ki-67 assessment with early ultrasound assessment will be computed. • Dynamic Ki-67 assessment will be compared to early ultrasound assessment for prediction of pCR Survival assessment: • The trial will perform descriptive (Kaplan-Meier) survival estimation in patient subgroups, particularly in subgroups with/without pCR, in terms of event-free and overall survival. Other assessments:

	• Breast-conserving therapy rates and (optionally) Health-related quality of life (HRQL) will be described.
Patient number/ Enrolment period	Run-in phase: 130 patients Main phase: 170 patients In total: 300 patients Number of sites: 30 Maximum patients per site: 15% of randomized patients Enrolment start: Q3 2013 Enrolment stop: Q4 2017 Due to very low enrolment numbers, the recruitment of new patients was prematurely stopped in Q4 2015. Follow-up period: 60 months, may be prolonged half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study

2 Introduction and Background ADAPT Elderly

Germany has one of the highest incidences of *Elderly* breast cancer in the western world. According to the recently published data of the Robert-Koch-Institute, the incidence varies between 325,3-361,5 per 100.000 in age subgroups beyond age of 70 years. There is a risk of 6,3% to develop cancer for women aged >70 and a risk to die of 2,4% due to breast cancer. Despite of only moderate change in incidence between 1990 and 2000 in Germany (-5,0%), only weak survival advantage (7,3%) due to better therapies and diagnostics could be observed in Germany in this subgroup. These data highlight
- a. the contrast to other countries (e.g. Switzerland: incidence increase of 27,9% and mortality decrease of 27,3%)
- b. contrast to other age subgroups (e.g. in Germany change in incidence in 50-69 years old subgroup of +58% and decrease in mortality of 16%)[187].
Elderly women have more frequently tumors with HR expression, less HER2 expression, more often larger, node positive tumors [188,189]. Interestingly, node involvement is more often seen in smaller tumors, indicating possible higher aggressiveness in older patients.
Yet, after adjusting for disease stage, older patients have lower relative survival compared to patients 40-70 years old due to suboptimal therapy, socioeconomic differences and limited access to cancer care[190].
Undoubtedly, there is a significant impact of co-morbidities onto mortality. Satariano et al. reported 20-time higher mortality from other causes than breast cancer in women with more severe diseases[191].

Integrated oncogeriatric approach (IOGA)

An integrated oncogeriatric approach (IOGA) has developed as a top priority in the international oncology community over last 15 years[vii]. IOGA focuses on the specific needs, values and preferences of geriatric cancer patients. Comprehensive geriatric assessments (CGA) is important in the IOGA concept[viii,ix], and is the most frequently used tool used within breast cancer studies. The consensus conference defined Comprehensive Geriatric Assessment as “a multidisciplinary evaluation in which the multiple problems of older persons are uncovered, described and explained, if possible, and in which the resources and strengths of the person are catalogued, need for services assessed, and a coordinated care plan developed to focus interventions on the person’s problems”[x]. A geriatric functional status measurement is different form the instruments used in oncology like ECOG performance status or Karnofsky Index. Stotter et al. reported data on pre-surgicalpre-surgical CGA in 152 patients and identified breast cancer patients with an estimated life expectancy of < 2 years, who should be treated by endocrine therapy alone[7]
Within another study in 660 patients >65 years old CGA correctly identified patients with poor treatment tolerance and higher mortality. Hurria et al. reported successful implementation of CGA in this study setting for patient selection for chemotherapy[10]. In a trial published by Girre et al. in 105 patients with solid tumors (61% had breast cancer) CGA resulted in 39% change of treatment plan; no outcome data are reported so far[8].
However, while different tools have been used, no definitive consensus has yet been reached regarding assessment steps’, correct use and place[xi]. Similar results were confirmed by others (for review see also Puts et al.[9]). Puts et al emphasized the divergences between oncologists’ and geriatricians’ experience of it and Extermann et al. demonstrated that geriatric tools and oncology tools have only a weak correlation[4]. Oncologists usually carry out non-systematic and non-standardized CGA. Differences in perception between oncologists and geriatricians regarding the use of CGA tools have also been reported by other authors. Hurria et al concluded there is no consensus within the geriatric oncology community regarding a standard CGA instrument for older patients with cancer[10]. International Society of Geriatric Oncology (SIOG) experts have declared they cannot recommend any specific CGA. Hence, in spite of its advantages, CGA is not necessarily current practice for oncologists[1].

We are going to use the **Charlson comorbidity index** in our trial. The Charlson comorbidity index predicts the ten-year mortality for a patient who may have a range of comorbid conditions (a total of 22 conditions)[xii]. Each condition is assigned a score of 1, 2, 3, or 6, depending on the risk of dying associated with each one. Scores are summed to provide a total score to predict mortality. Clinical conditions and associated scores are as follows:
1 each: Myocardial infarct, congestive heart failure, peripheral vascular disease, dementia, cerebrovascular disease, chronic lung disease, connective tissue disease, ulcer, chronic liver disease.
2 each: Hemiplegia, moderate or severe kidney disease, diabetes, diabetes with complication, tumor, leukemia, lymphoma.
3 each: Moderate or severe liver disease.
6 each: Malignant tumor, metastasis, AIDS.
Charlson scale ≤ 2 declared in additional inclusion criteria **ADAPT Elderly** as inclusion criteria.

Standard treatment of the *Elderly*
Older patients are underrepresented in clinical trials. Life expectancy is increasing and breast cancer incidence is increasing with age. In future we will be faced with a growing number of older patients and breast cancer with a limited number of optimal treatment guidelines.

Surgery: *Elderly* patients with early breast cancer should be treated by similar surgical procedures as younger patients (breast conserving surgery (BCS) with radiotherapy, mastectomy +/- radiotherapy), axillary surgery should be planned by similar criteria as in younger patients.
Radiotherapy: *Elderly* patients with early breast cancer should be treated by similar radiotherapeutic procedures as younger patients. 10 years results of CALGB 9343 trial showed reduction of local relapses by radiotherapy from 9% to 2% in *Elderly* women >70 years with clinical stage 1 ER+ breast cancer treated by lumpectomy + tam +/- radiotherapy. However, there is no survival difference between both study arms (breast cancer specific survival 98% vs. 96%, OS 63% vs. 61%) (for review[192].
Chemotherapy:
The standard chemotherapy treatment in elderly patients (≥65 yrs.) is Adriamycin/ cyclophosphamide x 4 q3w, or classical CMF for high risk, early stage breast cancer patients based on the results of the largest randomized trial conducted in the elderly that investigated the efficacy of AC or CMF versus capecitabine[193] Patients who were randomly assigned to capecitabine were twice as likely to have a relapse and almost twice as likely to die as patients treated with standard polychemotherapy AC or CMF. At 3 years, the rate of relapse-free survival was 68% in the capecitabine group versus 85% in the standard group. The overall survival rate was 86% versus 91%. The benefit was pronounced in women with hormone-receptor-negative tumors. Only 62% of the patients, who were assigned to CMF could complete the six planned cycles. In the group, treated with doxorubicin plus cyclophosphamide 92% of the patients completed the four cycles.

Taxanes in the *Elderly* patient population
According to the recently published EBCTG metaanalysis four courses of AC or CMF are inferior to other anthracycline based chemotherapy[194]. A further improvement of outcome data is reported for taxane /anthracycline based last generation chemotherapies irrespective of nodal status, hormone receptor status and grading. There are relatively few data on the use of these agents in older patients. However, there are pharmacokinetic data, which demonstrate that taxanes can be used in *Elderly* patients without dose modifications. Only in case of an impaired liver function neither paclitaxel nor docetaxel should be applied due to their high liver metabolization[195,196].
Recent evidence supports the use of regimens incorporating taxanes with anthracyclines; at 5 years, the survival benefits of these regimens were similar for patients in all age groups, including those ≥ 60[197]. Loibl et al. published a systematic pooled analysis of tolerability for *Elderly* from different adjuvant and neoadjuvant German trials with taxane-containing

regimens[198]. The patient cohort reflects clinical trial routine at that time and substantiates findings from other studies[199,200] demonstrating that even if the trials had no upper age limit, *Elderly* patients were generally included less frequently or were not included at all. In this analysis Paclitaxel had significantly less hematologic toxicity compared to Docetaxel, which is consistent with data from a prospective adjuvant trial directly comparing these taxanes[91], Moreover, in an adjuvant anthracycline–taxane sequential regimen, weekly Paclitaxel shows the same efficacy as Docetaxel. This might therefore, be the preferred taxane regimen, at least for Elderly patients.

The data published by Muss et al. showed that benefit from chemotherapy did not differ across age groups although treatment-related mortality was higher (1.5% *vs.* 0.42%) in the group aged > 65 years[193].
It has therefore become increasingly clear that neoadjuvant therapy concepts for *Elderly* patients should consider – next to oncological needs – the patient's physical and functional status, and should not be determined merely on the basis of their age.

Anthracyclines - Liposomal Anthracycline
Anthracyclines in combination with cyclophosphamide are one well evaluated standard in the elderly[193]. Beyond acute toxicity, long-term cardiotoxicity is one important concern in anthracycline based chemotherapy. For study populations cumulative doses of 550 mg/m^2 doxorubicin and of 950 mg/m2 epirubicin cause less than 5% of grade 3 to 4 carditoxicity. Beyond these cumulative doses risk increases exponentially. Taxane combinations seem to increase the cardiac risk as the 10 year data from BCIRG 001 document. Chronic heart failure from this trial, which involved patients up to 70 years, was reported after ten years for 3.5% of patients receiving TAC (docetaxel, adriamycin, cyclophosphamide) versus 2.3% in patients receiving F(5 fluoro-uracil)AC. SEERS data collected from 43 339 women - which may reflect much more daily routine- document that age is an important risk factor for anthracycline induced cardiotoxicity. The adjusted hazard ratio for chronic heart failure was 1.28 for women aged 66 to 70 treated with anthracycline compared to other chemotherapy. Furthermore, this analysis identified the following baseline characteristics as significant predictors of chronic heart failure: age (HR1.79), hypertension (HR 1.45), diabetes (HR 1.74) and coronary artery disease (HR 1.59) [201].
In many elderly patients comorbidity as described above is a frequent clinical problem. The liposome encapsulation of anthracyclines has the potential to decrease toxicity of anthracyclines, while preserving their antitumor efficacy. Liposome encapsulated doxorubicin (TLC D-99, Myocet©) at 75 mg/m^2 q3w has been compared to 75 mg/m^2 doxorubicin q3w in first line therapy of 224 patients with metastatic breast cancer. Median age of this group was 54 years. Protocol-defined cardiotoxicity was observed in 13% of patients receiving liposome encapsulated doxorubicin versus 29% in the doxorubicin arm. Median cumulative doses at onset of cardiotoxicity were 785 mg/m^2 and 570 mg/m^2 respectively again favoring the liposome encapsulated compound. Response rates were 26% in both arms[202]. In combination with cyclophosphamide (600 mg/m^2) liposome encapsulated doxorubicin or conventional doxorubicin both at a dose of 60 mg/m^2 were compared within a three week schedule in 297 patients in first line chemotherapy for metastatic breast cancer. Six versus 21% of patients developed cardiotoxicity in the liposome encapsulated anthracyline arm versus the conventional arm. Again response rates were identical (43% vs. 43%) as well as median time to treatment failure and median survival[203].
Another trial has been conducted in first line chemotherapy of metastatic breast cancer by Chan et al. comparing Myocet 75 mg/m^2 versus Epiadriamycin at the same dose in a three week schedule in 160 patients. Overall response rates were 46% versus 39% favoring the liposomal encapsulated compound as well as median time to progression (7.7. vs. 5.5 months). Median survival times were 18.3 vs. 16.0 months (p=0.504). Both Myocet and Epirubicin had low cardiotoxicity at the planned cumulative dose of 600 mg/m^2.[204]. In terms of non-cardiac toxicity liposome encapsulated doxorubicin induces significantly less neutropenia grade 4,

diarrhea grade 3 and nausea grade 3 to 4 than doxorubicin as shown by Cochrane meta-analysis[205].

Specific problems in the Elderly:
Anthracyclines and taxanes are recommended as (neo)adjuvant polychemotherapy in high risk early breast cancer patients. Older women will less likely receive standard chemotherapy[193,206,207], because of more severe toxicity, comorbidities, and finally due to missing evidence from large scale clinical trials[198,208]. Under treatment as a result of not adhering to consensus guidelines, is associated with a higher recurrence rate likely resulting in a poorer quality of life and inferior survival In a meta-analyses by Muss et al. it could be demonstrated that Elderly women with node positive disease have a significant better disease-free and overall survival, if they receive adequately dosed chemotherapy[209].

Neoadjuvant chemotherapy of the *Elderly*
There are no randomized trials testing the efficacy of neoadjuvant chemotherapy in older patients so far.

The ADAPT philosophy – A combined static and dynamic model
Early response assessment in eBC may be essential to separate sub-populations with large or marginal benefit from therapy.
Drop of proliferative activity after a short course of endocrine therapy (2 weeks to 4 months) as measured by proliferation marker Ki-67 is an excellent predictor for local as well as systemic outcome in HR+ disease. It allows identifying groups of patients with excellent outcome in both low and higher risk groups independently from chemotherapy application[25-27]. Early prediction of chemotherapy outcome by sequential assessment of ki-67 is less well evaluated. Posttherapeutic Ki-67 after neoadjuvant chemotherapy nevertheless better correlates with outcome than baseline ki-67[210]. Early response assessment by ultrasound is according to GEPARTRIO another reliable predictive tool. Thus, besides baseline prognosis estimation (***static* assessment**), therapy efficacy is evaluated at an early time of treatment (***dynamic* assessment**). This approach is especially important in the elderly since risk – benefit evaluation is much more sensible than in younger, healthy patients.

3 Rationale ADAPT Elderly

Neoadjuvant chemotherapy allows in vivo testing of chemotherapy regimens identifying good and poor responders. This information is of particular interest in the elderly since the risk-benefit evaluation is much more difficult in older populations due to increased toxicity and comorbidity and reduced life expectancy.
Rationale for Taxanes:
According to the last EBCTTG meta-analysis the addition of taxanes has improved adjuvant chemotherapy outcome in all age groups[194]. For patients beyond 70 years sample size is small. Sequential regimens are superior to combinations. Taxane based chemotherapy caused especially in the elderly undue toxicity, which may consistently influence the therapeutic ratio in this age group.
Myocet
Anthracyline based chemotherapy is standard of care in the elderly. Especially in this age group and in patients with comorbidity such as hypertension, diabetes and coronary artery disease - cardio toxicity profile is an important discriminant for the choice of a specific anthracycline derivative in primary therapy. With respect to long-term prognosis this is even more important in an adjuvant setting than in metastatic disease. In terms of cardiotoxicity Myocet© is safer than doxorubicin and as effective as doxorubicin or epi-doxorubicin. It is therefore the ideal candidate anthracycline partner for cyclophosphamide in the *ADAPT Elderly* protocol.

G-CSF primary prophylaxis
Based on the data from small trials indicating risk for febrile neutropenia of 15% in older patients G-CSF Prophylaxis is strongly recommended within the study[211].

Early response assessment / early assessment of toxicity
The early assessment of response to NACT for breast cancer may allow to stop ineffective therapy regarding pCR or modifying this therapy or to continue an effective NACT. Some published data show that due to this procedure the DFS and OS can be improved. (von Minckwitz et al. 2005; 2008; von Minckwitz et al. 2011). The optimal method for early response assessment has not been established. The Response Evaluation Criteria In Solid Tumors (RECIST) guidelines recommend breast MRI as the preferred method. Ultrasound should not be used. Breast ultrasound results are highly dependent from the investigator and not enough reproducible (Eisenhauer et al. 2009). But the GEPARTRIO trial demonstrated improved patient outcomes due to early response assessment using breast ultrasound or palpation of tumor size. A metaanalysis of the value of MRI in pre-surgical prediction of pCR showed that with breast ultrasound can be achieved the same results as compared with MRI. But there was no study with direct comparison. (Marinovich et al. 2012; 2013). Breast ultrasound has advantages compared with MRI like lower costs, widely available, shorter investigation time and no need of i.v. injections. Because of these data further studies are needed to analyse the predictive value of ultrasound in predicting pCR and other kinds of response after NACT in breast cancer patients.
The GEPARTRIO -trial has shown that early response evaluation by ultrasound correlates strongly with outcome. Identification of non-responders allows sparing unnecessary toxicity to patients from non-effective chemotherapy. Early assessment of toxicity on the other hand allows identifying a subgroup of patients, who despite benefit from chemotherapy may have low therapeutic ratio due to enhanced toxicity.

Overall design:
4 x MC is according to data from Muss considered to be an classical standard in the elderly, which might have the advantage of causing less cardiotoxicity than classical AC. As taxane based chemotherapy is not well tolerated in the elderly and since the metaanalysis only shows small survival differences, taxane use should be restricted to those patients, who are not sufficiently treated with MC alone. In an neoadjuvant setting early response assessment allows to identify patients with poor response to MC, who might benefit from the use of taxanes. The early switch allows an exploratory analysis of the benefit patients may have in terms of pCR by the addition of taxanes . The comparison of toxicity in the two arms (MC vs MC->pac) allows evaluating whether the presumed enhanced toxicity in the taxane containing arm may be outweighed by the higher response rate in poor responders.

4 Study Objectives ADAPT Elderly

Primary objectives
Run-in Phase:

- Identification of molecular markers correlating with early response/pCR
- Feasibility/reproducibility of assessment of these markers
- Validation of statistical assumptions (toxicity, pCR)

Run-in phase + main phase
Primary objectives
Comparison of pCR rates in patients with early response and no severe toxicity (Group 1) and in other patients (Group 2).

Secondary objectives

- Incidence of febrile neutropenia (FN) after 1xMC in patients with primary prophylaxis (PP) vs. others.
- Toxicity in the 4 x MC versus 2 x MC →6 x Pac arm
- Number of pCR in non-responders to MC
- Evaluation of dynamic test regarding prediction of pCR
- Evaluation of 6 week US regarding prediction of pCR
- Comparison of dynamic Ki-67 assessment with early ultrasound assessment for prediction of pCR
- G-CSF use/FNP
- Rates of breast conserving therapy

Exploratory analysis
- Survival of patients with pCR

Exploratory analysis
Survival of patients with pCR

5 Study Design ADAPT Elderly

The *ADAPT Elderly* breast cancer sub-trial is a modern biomarker-based neoadjuvant, prospective, multi-center, controlled, non-blinded, phase II

The *Elderly* study design is depicted in figure 1 below.

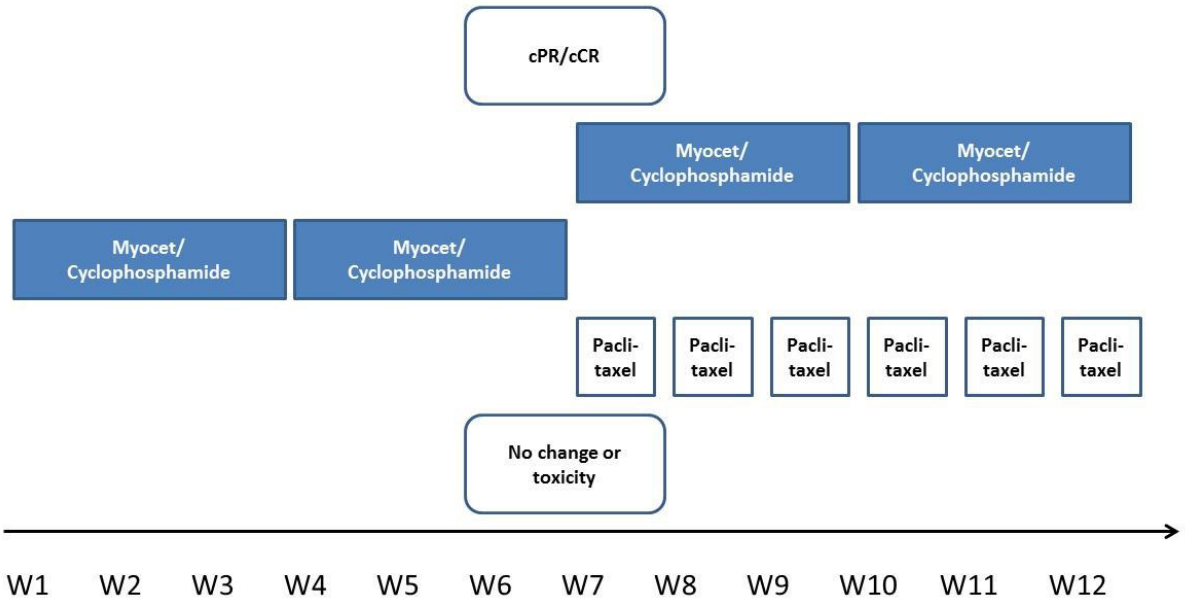


Figure 1: *Study Design for ADAPT Elderly Breast Cancer*

5.1 Run-in Phase and Main Phase

The run-in phase of the *Elderly* protocol will include 130 patients and the main phase 170 patients. For further information please refer to the *ADAPT umbrella* protocol, chapter 5.1.

5.2 Timing of Surgery

The surgery is to be done after 12 weeks of chemotherapy, i.e. following end of therapy.

6 Patient Enrollment

Following the diagnostic core biopsy and local pathology assessment, the patients meeting the inclusion/exclusion criteria will be informed about the *ADAPT umbrella* trial and *ADAPT Elderly* sub-trial. After signing the informed consent patients will be registered.
The following examinations are mandatory prior to registration:

Table 1: *Study Evaluations for Participation in ADAPT Elderly Breast Cancer Trial*

	INVESTIGATIONS	TIMING
Negative HER2 status **according to local pathology**	✔	Prior to registration (standard of care)
Nodal status	N0-1 / RS 12-25 / poor response N0-1 / RS ≥ 26 Clinical N ≥ 2	Prior to allocation
Grading	Must be known G3 with Ki-67 ≥40% in tumors >1cm	Prior to registration (standard of care)
Age	≥ 70 years old	Prior to registration
Performance	Charlson scale ≤ 2	Prior to registration
Ultrasound	✔	Prior to registration (standard of care)
Recurrence Score (HR+ only)	Tumor sample obtained from diagnostic core biopsy (standard of care) of primary tumor	Prior to registration
History[1] and physical exam for patients receiving chemotherapy	Physical examination including: • Height • Weight • Karnofsky index for performance status/vital signs	≤ 7 days prior to allocation
LVEF ≥ 50%	Echocardiography	Within 42 days prior to allocation

[1]Within 3 weeks prior to registration

6.1 Additional Inclusion Criteria *ADAPT Elderly*

In order to be eligible for the participation in the *ADAPT Elderly* trial, patients, who meet the general inclusion criteria of the *ADAPT umbrella* trial also have to meet the following additional inclusion criteria:

- ≥ 70 years old
- Charlson scale ≤ 2
- HR+/HER2- disease: if RS and sequential testing are available N0-1/RS 12-25/poor response or N0-1/RS ≥26 or G3 with Ki-67 ≥40% in tumors >1cm or cN2-3
- All TN qualifying for neoadjuvant treatment

Concurrent participation in the WSG post authorization safety study PROTROCA for evaluation of primary/secondary G-CSF prophylaxis is allowed.

6.2 Additional Exclusion Criteria *ADAPT Elderly*

In order to be eligible for the participation in the *ADAPT Elderly* trial, patients, who meet the general exclusion criteria of the *ADAPT umbrella* trial **must** also **not** meet any of the following additional exclusion criteria:

- Known polyneuropathy ≥ grade 2

- Severe and relevant co-morbidity that would interact with the application of cytotoxic agents or the participation in the study
- Inadequate organ function (e.g. hepatic impairment, pulmonary disease, etc.)
- Uncompensated cardiac function (current unstable ventricular arrhythmia requiring treatment, history of symptomatic CHF NYHA classes II-IV), history of myocardial infarction or unstable angina pectoris within 12 months of enrollment, history of severe hypertension, CAD – coronary artery disease)
- Severe dyspnea
- Pneumonitis
- Abnormal blood values:
    - Thrombocytopenia > CTCAE grade 1
    - Increases in ALT/AST > CTCAE grade 1
    - Hypokalaemia > CTCAE grade 1
    - Neutropenia > CTCAE grade 1
    - Anaemia > CTCAE grade 1

6.3 Registration to *ADAPT Elderly* Sub-trial

Each eligible patient will be registered and after informed consent was obtained she will receive

Neoadjuvant Treatment:
2 cycles Myocet 60 mg/m² / Cyclophosphamide 600 mg/m² (**MC) q3w followed by either 2 x MC or Paclitaxel 80 mg/m² q1w x6** depending on early response assessment by ultrasound or on toxicity profile.

Supportive therapy: G-CSF according to AGO guidelines primary G-CSF prophylaxis is strongly recommended.

Ultrasound assessment for response:
The tumor (marker lesion) is measured in all three dimensions. The two longest diameters must be documented.

- Complete Response (CR): disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm.
    - Complete MC, if no contraindication by toxicity

- Partial Response (PR): ≥50 percent decrease in the product of the longest diameters of the target lesions compared with baseline.
    - Complete MC, if no contraindication by toxicity

- Progressive Disease (PD): ≥20 percent increase of at least 5 mm in the sum of the longest diameters of the target lesions compared with the smallest sum of the longest diameter recorded.
    - Change regimen to Pac or stop treatment prematurely and perform surgery immediately

- Stable Disease (SD) (no change): Neither PR nor PD.
    - Change regimen to Pac

A responder is defined to have Complete Response at the time of the second ultrasound. The tumor needs to be marked with a clip before the first cycle of chemotherapy to be able to reliably identify the region of the former tumor at the time of surgery.

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Toxicity assessment after the second course of MC: patients with any organ toxicity > °2 or hematotoxicity > °2 in patients with primary G-CSF prophylaxis should be switched to taxanes.

Surgery:
After completion of 12 weeks of neoadjuvant treatment for all patients, surgery is planned. In case of disease progression treatment can be stopped prematurely and surgery will be performed immediately. If there was a clip placed before or during the NACT this clip has to be marked with a wire and a mammographic control of correct localization of the tip of the wire near the clip has to be performed. After lumpectomy or segmental resection a radiography of the resected specimen has to be done to identify the clip.

Adjuvant Treatment:
Patients, who do not achieve pCR after 12 weeks could cumulatively receive further treatment at decision of investigator. Patients achieving pCR after 12 week neoadjuvant chemotherapy can consider to stop chemotherapy.

Response Assessment:
Primary efficacy (i.e. pCR) is defined at time of surgery according to NCCN guidelines (no invasive cancer in both breast and lymph nodes) and based on provided data regarding residual tumor size, proportion of vital cells within invasive carcinoma, number of positive lymph nodes and size of the largest lymph node metastasis and ductal carcinoma in situ.
Based on these criteria residual cancer burden (and other pCR classifications) will be defined for further analysis (Symmans et al, JCO 2007). Further chemotherapy may be omitted only in tumors with no invasive and DCIS patterns.

Safety:
Safety of paclitaxel and Myocet/cyclophosphamide chemotherapy will be measured by the incidence and severity of adverse events (AE) and serious adverse events (SAE). Frequency and reasons for discontinuation of therapy, modification and interruption will be evaluated in a prospective manner.

Dynamic test:
Drop of proliferation is considered as the key factor for efficacy of the combination therapy. During the run-in phase of the study, immunohistochemical measurement of Ki-67, can be performed on samples from diagnostic and sequential biopsy.
All tumors will undergo central pathology assessment (ER, PR, HER2) for allocation to the study (analysis by Prof. H. Kreipe, Hannover).

The registration forms have to be filled in online in the e-CRF. After completion it has to be printed, signed by an investigator and faxed to the coordinator of the study:

Fax: +49 (0)611 160248 - 29

The following information will be requested:

- Institution name
- Investigator's name
- Patient's identifiers (site number, patient code)
- Patient's birth date (month/year)
- Type of tumor (HR+/HER2- or TN)

A patient who was not registered prior to the first treatment administration will not be accepted for the study at a later date.

6.3.1 Arm A: Myocet/Cyclophosphamide

Myocet

Dose:	60 mg/m², day 1
Route:	1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule:	Every 3 weeks

This is called a cycle of treatment and is to be given four times.

Cyclophosphamide
Dose: 600 mg/m², day 1
Route: 5 to 60 minutes intravenous bolus injection (as per hospital policy)
Schedule: Every 3 weeks

This is called a cycle of treatment and is to be given four times.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

6.3.2 **Arm B: Myocet/Cyclophosphamide → Paclitaxel**

Myocet
Dose: 60 mg/m², day 1
Route: 1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule: Every 3 weeks

This is called a cycle of treatment and is to be given two times.

Cyclophosphamide
Dose: 600 mg/m², day 1
Route: 5 to 60 minutes intravenous bolus injection (as per hospital policy)
Schedule: Every 3 weeks

This is called a cycle of treatment and is to be given two times. In case of no change (NC) or toxicity the patient will be allocated to a non-cross resistant regimen.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

Paclitaxel
Dose: 80 mg/m², day 1
Route: 1 hour intravenous infusion. During the first 5 minutes, the infusion must be done drop by drop in order to reduce the incidence of acute hypersensitivity reaction (AHSR).
Schedule: Every week

This is called a cycle of treatment and is to be given six times.

In the event of relapse during treatment, unacceptable toxicities or withdrawn consent, treatment shall finish earlier.

7 Study Plan ADAPT Elderly

7.1 Study Treatment *ADAPT Elderly*

For induction treatment patients will receive one cycle of Myocet 60 mg/m² / Cyclophosphamide 600 mg/m² (MC) q3w**.**
After completion of induction treatment, patients will obtain the second core biopsy for efficacy estimation. The treatment regimen from induction treatment will be continued for three further cycles until end of treatment and surgery, in case of cCR or cPR. In case of no change (NC) or toxicity the patient will be allocated to a non-cross resistant regimen.
Study treatment should be discontinued in case of disease progression and the patient should undergo surgery.
Post-study treatment with adjuvant chemotherapy is planned as standard of care at the discretion of investigator.

7.1.1 Myocet Formulation, Preparation and Storage

Please refer to the Investigator's Brochure.

7.1.2 Dosing and Administration – Myocet

Myocet will be administered on day 1 of a 3-week cycle every 3 weeks at a dose of 60 mg/m² as intravenous infusion. The total dose will be calculated based on the patient's weight on day 1 of (or up to 3 days before) each cycle with upper limit of 2.0m².
Myocet doses may be reduced to as low as 30 mg/m², according to the dose-modification guidelines in chapter 9.1.1 of the *ADAPT Elderly* sub-protocol. Dose delays of up to 42 days from last administered dose are permitted.
If the timing of a protocol-mandated procedure such as administration of Myocet coincides with a holiday that precludes the procedure, the procedure should be performed within 3 business days of the scheduled date and, when possible, on the earliest following date, with subsequent protocol-specified procedures rescheduled accordingly.
The first infusion of Myocet will be administered over 90 minutes (± 10 minutes). Infusions may be slowed or interrupted for patients experiencing infusion-associated symptoms. Vital signs must be assessed before and after dose administration. Following the initial dose, patients will be observed for at least 60 minutes for fever, chills, or other infusion-associated symptoms. If prior infusions were well tolerated (without any signs or symptoms of infusion reactions) subsequent doses of Myocet may be administered over 30 minutes (± 10 minutes), with a minimum 30-minute observation period after infusion.
Local health authority guidelines must be followed with regard to further observation and monitoring, if applicable.

7.1.3 Dosing and Administration – Paclitaxel / Cyclophosphamide

Please administer Paclitaxel and/or Cyclophosphamide according to SmPC and the protocol-specific dosage.

7.1.4 End of Treatment (EOT) Definition *ADAPT Elderly*

End of treatment is defined as 21 days after the last application of study drug and prior to surgery. pCR will be the target endpoint of the study.

7.1.5 End of Study

End of study is defined as database closure.

7.1.6 Prophylactic Premedication Regimen

Premedication for nausea and infusion reactions (e.g., acetaminophen or other analgesics, anti-histamines such as diphenhydramine or corticosteroids) may be given at the investigator's discretion.

7.2 Follow-up

For the follow-up please refer to the *ADAPT umbrella* protocol, chapter 7.10.

7.2.1 Therapy after Protocol Treatment is discontinued

Except for study therapy and radiotherapy as per protocol (see 6.3), no further antitumor therapy is allowed (surgery, chemotherapy, immunotherapy, etc.) before tumor relapse is documented.
If patients are removed from the study because of disease relapse, further treatment is at the discretion of the investigator. The metastatic regimen(s) used will be documented in the Case Report Form.

8 Study Evaluations ADAPT Elderly

8.1 Evaluation during Treatment

While under treatment, all patients must be examined according to the schedule outlined below until they come off therapy.

Table 2: *Study Evaluations before each Cycle of Treatment*

week	-3 to 0 (BL)	1	4	7	10	13 (EOT)	14 (Surgery)
Medical history (incl. concomitant medications)	x						
Central pathology review of diagnostic core biopsy	x						
Charlson Score	x						
Recurrence Score (HR+ only)	x						
Second core biopsy (efficacy estimation)			x[1]				
Physical Examination	x[2]	x[5]	x[5]	x[5]	x[5]	x	
Serum sample (biomarker analysis, optioanlly)	x[2]		x			x	
Radiology: • Chest X-ray • Bone scan • Liver imaging • Mammography	x[3]						
MRI (optional)	x		x				
Ultrasound	x		x	x		x	
Clinical assessment	x[2]		x	x		x	
ECG and LVEF	x[3]			x			x (prior to surgery)
Laboratory: • Hematology • Biochemistry	x	x[5]	x[5]	x[5]	x[5]	x	
Surgery							x
(Serious) Adverse Event		continuously					
Concomitant medication		continuously					

[1] prior to 2nd administration of study drug
[2] within ≤ 7 days prior to allocation
[3] within 3 months prior to allocation
[4] +/-3 days
[5] prior to **any application of chemotherapy** (MC q3w or Paclitaxel q1w)

Physical examination will include:

- Weight
- ECOG or Karnofski index for performance status
- Clinical tumor assessment

Laboratory work-up will include:
Hematology:

- Hemoglobin
- WBC
- Neutrophils
- Platelets count

Biochemistry:

- Alkaline phosphatase
- ASAT (SGOT)
- ALAT (SGPT)
- Bilirubin
- Serum creatinine
- Creatinine clearance
- Electrolytes: Na^+, K^+, Cl^-

8.2 Evaluation at End of Induction Treatment

Please refer to chapter 7.8 of the *ADAPT umbrella* protocol for further information.

8.3 Evaluation at End of Treatment (EOT)

To be performed at latest 21 days after the last treatment and/or prior to surgery. Work-up will include:

- Physical examination with Karnofsky Index or ECOG
- Hematology, biochemistry
- Documentation of toxicity

8.4 Evaluation in Follow-up after End of Treatment

Patients will be followed every 6 months for two years starting from registration and every 12 months thereafter until year 5 (corresponding to German aftercare plan) or until relapse to document:

- Event-free survival
- Overall survival
- Further therapy
- Relapse (local relapse)
- 2nd primary malignancy
- First treatment for metastatic breast cancer or 2nd primary malignancy
- Results for biopsy of distant metastases
- Yearly evaluation of lifestyle parameter

Timing of follow-up visits is based on the date of registration. Follow-up visits will be scheduled at month 6, 12, 18, 24, 36, 48, and 60 after registration. Patients completing follow-up month 60 will be followed for survival once a year thereafter within a registry program.
Patients who relapse or suffer from 2nd primary malignancy will only be followed for survival. For any distant metastasis occurring, if biopsied, IHC should be reported in the CRF.

Patients completing follow-up month 60 may be followed half-yearly for survival, relapse, or 2nd primary malignancy status until end of the study, provided that an additional informed consent was signed.

9 Dose Delays and Reduction/Modification ADAPT Elderly

9.1 Treatment Dose Adjustments and Treatment Delays

Toxicities will be graded using the NCI Common Toxicity Criteria (NCI CTC), version 4.0.

Dose reduction is planned for each treatment arm in case of severe hematological and/or non-hematological toxicities. Dose adjustments are to be made according to the organ system showing the greatest degree of toxicity. In case of several toxicities in one patient and conflicting recommendations, the most conservative dose adjustment has to be followed.
Doses which have been reduced for toxicity must not be re-escalated.

Treatment with chemotherapy may be delayed no more than 2 weeks (up to day 35) to allow recovery from acute toxicity.

9.1.1 Dose Adjustments and Treatment Delays

Patients should be assessed for toxicity prior to each dose. Dosing will occur only, if the clinical assessment and laboratory test values are acceptable.
Dose delays and reductions are designed to maximize treatment for those, who derive clinical benefit from treatment, while ensuring patient safety.
Dose delays for Paclitaxel, Myocet and Cyclophosphamide toxicity are specified in Appendix 1 – Treatment Dose Adjustments and Treatment Delays for *ADAPT Elderly*.

9.1.2 Dose Adjustments and Treatment Delays – Paclitaxel

The following dose-reduction levels are applicable for treatment with Paclitaxel:

Dose level: **0** 80 mg/m²
-1 60 mg/m²
-2 50 mg/m²
Indication for further dose reduction → withdrawal from study treatment

9.1.3 Dose Adjustments and Treatment Delays – Myocet

The following dose-reduction levels are applicable for treatment with Myocet:

Dose level: **0** 60 mg/m²
-1 45 mg/m²
-2 30 mg/m²
Indication for further dose reduction → withdrawal from study treatment

9.1.4 Dose Adjustments and Treatment Delays – Cyclophosphamide

The following dose-reduction levels are applicable for treatment with Cyclophosphamide:

Dose level: **0** 600 mg/m²
-1 450 mg/m²
-2 300 mg/m²
Indication for further dose reduction → withdrawal from study treatment

9.2 Toxicity Related Guidelines for Dose Reduction and Dose Modification

Please refer to the *ADAPT umbrella* protocol, Appendix 1 – Treatment Dose Adjustments and Treatment Delays for further information.

10 Safety Monitoring

10.1 Safety Plan

Overall safety will be assessed on an ongoing basis during the conduct of the study. The DSMB (IDMSC) will monitor cumulative safety data at least once every 6 months during the course of the study. In addition, data on serious adverse events and deaths will be monitored by the DSMB (IDMSC) at least once every 3 months.

10.2 Safety Parameters and Definitions

Safety assessments will consist of monitoring and recording of protocol-defined adverse events (AEs) and serious adverse events (SAEs); measurement of protocol-specified hematology, clinical chemistry, and urine analysis variables; measurement of protocol-specified vital signs and other protocol-specified tests that are deemed critical to the safety evaluation of the study drugs.

The sponsor or its designee is responsible for reporting relevant SAEs to the Competent Authority, other applicable regulatory authorities and participating investigators, in accordance with ICH guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements.

The sponsor or its designee is responsible for reporting unexpected fatal or life-threatening events associated with the use of the study drug to the regulatory agencies and competent authorities by telephone or fax within 7 calendar days after being notified of the event.

The sponsor or its designee will report other relevant SAEs associated with the use of the study medication to the appropriate competent authorities (according to local guidelines), investigators, and central IRBs/ECs (except in the United States where investigators are responsible for reporting to their IRBs per local requirements) by a written safety report within 15 calendar days of notification.

10.3 Adverse Event Reporting

The investigator is responsible for ensuring that all AEs and SAEs (as defined in chapter 12 of the *ADAPT umbrella* protocol) are recorded in the e-CRF and reported to the sponsor in accordance with protocol instructions. Additional reference document for AE reporting is the respective IB/SmPC in its current version. For patient safety, all AEs that are graded as grade 2-5 by CTCAE must be documented in the e-CRF**.** Coding of AEs will be done according to MedDRA.

Investigators should use correct medical terminology/concepts when recording AEs or SAEs in the e-CRF. Avoid colloquialisms and abbreviations. There is one e-CRF page for recording AEs and a hardcopy printout page for recording SAEs. Only one medical concept should be recorded in the event field on the (Serious) Adverse Event report.

10.3.1 **Adverse Event Reporting Period**

After informed consent, but prior to initiation of study treatment, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as blood draws or no treatment run-in).

After initiation of study treatment, all AEs and SAEs regardless of attribution will be collected until 30 days following the last administration of study treatment or study discontinuation/termination, whichever is later. After this period, investigators should report only SAEs that are felt to be related to prior study treatment (see chapter 12.3 of the *ADAPT umbrella* protocol).

10.3.2 **Eliciting Adverse Events**

A consistent methodology of non-directive questioning for eliciting AEs at all patient evaluation time points should be adopted. Examples of non-directive questions include:
“How have you felt since your last clinic visit?”
“Have you had any new or changed health problems since you were last here?”

10.3.3 **Type and Duration of Follow-up of Patients after Adverse Events**

The investigator should follow all unresolved AEs and SAEs until the events are resolved or stabilized, the patient is lost-to-follow-up, or it has been determined that the study treatment or participation is not the cause of the AE/SAE. Resolution of AEs and SAEs (with dates) should be documented on the Adverse Event e-CRF and in the patient’s medical record to facilitate source data verification (SDV).
For some SAEs, the Sponsor or its designee may follow-up by telephone, fax, electronic mail, and/or a monitoring visit to obtain additional case details deemed necessary to appropriately evaluate the SAE report (e.g., hospital discharge summary, consultant report, or autopsy report).

10.3.4 **Post-Study Adverse Events**

At the last scheduled visit, the investigator should instruct each patient to report to the investigator any subsequent SAEs that the patient’s personal physician believes could be related to prior study treatment.
The investigator should notify the sponsor of any death or other SAE occurring at any time after a patient has discontinued or terminated study participation, if deemed to be related to prior study treatment. The sponsor should also be notified, if the investigator should become aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a patient that participated in this study. The investigator should report these events to the sponsor on the study e-CRF. If the study e-CRF is no longer available, the investigator should report the event directly to the sponsor via telephone.

10.3.5 **Adverse Events Occurring Secondary to Other Events**

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the e-CRF.
However, medically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the e-CRF.
For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the e-CRF.

10.3.6 **Persistent or Recurrent Adverse Events**

A persistent AE is one that extends continuously, without resolution between patient evaluation time points. Such events should only be recorded once in the e-CRF. The persistent AE will be only documented once with the highest CTC Grade occurring.
A recurrent AE is one that occurs and resolves between patient evaluation time points and subsequently recurs. All recurrent AEs should be recorded on Adverse Event e-CRF.

10.3.7 **Abnormal Laboratory Values**

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the e-CRF (e.g., abnormalities that require study drug dose

modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).
If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event e-CRF.
If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the e-CRF.
If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."
Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the e-CRF, unless the seriousness, or etiology changes.

10.3.8 **Deaths**

Deaths that occur during the protocol-specified AE reporting period (see chapter 10.3.1 of the *ADAPT Elderly* sub-protocol) that are attributed by the investigator solely to progression of breast cancer will be recorded only on the Death Report Form (DRF) in the e-CRF. All other on-study deaths, regardless of attribution, will be recorded on an e-CRF and expeditiously reported to the Sponsor. An independent monitoring committee will monitor the frequency of deaths from all causes.
When recording a death on the e-CRF, the event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the e-CRF. If the cause of death is unknown and cannot be ascertained at the time of reporting, record "Unexplained Death" on the DRF in the e-CRF.
During post-study survival follow-up, deaths attributed to progression of breast cancer will be recorded only on the Survival e-CRF.

10.3.9 **Relevant Medical History**

Relevant medical history includes any preexisting medical condition that is present at the start of the study. Such conditions should be recorded on the respective e-CRF page.
A preexisting medical condition should be only recorded as an AE or SAE if the frequency, severity, or character of the condition worsens during the study.
When recording such events on an Adverse Event, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

10.3.10 **Worsening of Breast Cancer**

Worsening and/or progression of breast cancer should not be recorded as an AE or SAE. These data will be captured as efficacy assessment data only.

10.3.11 **Hospitalization, Prolonged Hospitalization or Surgery**

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE unless specifically instructed otherwise in this protocol. There are some hospitalization scenarios that do not require reporting as an SAE when there is no occurrence of an AE. These scenarios include a planned hospitalization or prolonged hospitalization to:

- Perform an efficacy measurement for the study
- Undergo a diagnostic or elective surgical procedure for a preexisting medical condition that has not changed

- Receive scheduled therapy for the target disease of the study

11 Data Analysis and Statistical Considerations

The non-randomized trial comprises a **Run-in phase** (n=130) and a **Main phase** (n=170), i.e., a total of 300 patients including dropouts. The trial is designed to test whether early response assessment could allow identification of patients with poor response to MC (or toxicity) who might benefit from the use of taxanes.

11.1 Run-in phase

The Run-in phase will pursue the following objectives:

- Validation of statistical assumptions (toxicity, pCR)
- Identification of molecular markers correlating with early response/pCR
- Feasibility/reproducibility of assessment of these markers

11.2 Primary endpoints and hypothesis testing *ADAPT Elderly*

The primary endpoint of the ADAPT Elderly trial is pCR. Early response and toxicity (particularly febrile neutropenia) are stratification criteria. The trial is designed to test whether therapy switch in patients with either toxicity or inadequate early response benefit from the addition of taxanes. To this end (see illustration Fig. 1), a non-inferiority hypothesis for this group (Group 2) compared to responders without toxicity (Group 1) will be tested with respect to the outcome pCR:

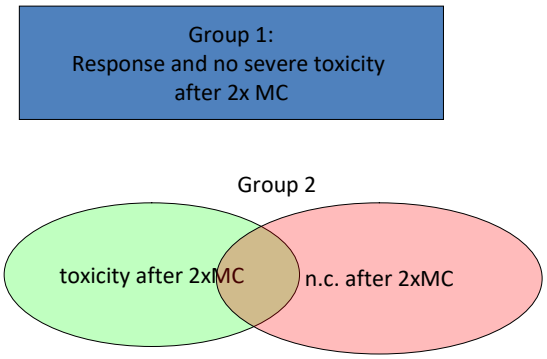

Figure 4: Group 1 is defined as patients with early response AND no severe toxicity. Group 2 is defined as patients with either "no change" or severe toxicity or both (i.e., all other patients). One expects roughly 150 patients in each group. A few patients in Group 2 could be non-responders with severe toxicity.

Patients in Group 1 receive 4 x MC (2 x MC prior to early-response assessment, 2 x MC subsequently). Patients in Group 2 receive 2 x MC followed by Paclitaxel 80 mg/m^2 q1w x 6.

The hypothesis to be tested is non-inferiority of Group 2 compared to Group 1 with regard to pCR, θ_1-θ_2<δ (respective pCR fractions defined as θ_1, θ_2) With a sample size of 150 patients in each group (1 and 2), this test will have 80% power to detect a **non-inferiority delta of 0.13** with one-tailed alpha=.05 assuming true pCR percentage in each group is 0.25. The power allows for 8% dropouts in each group. Patients of the run-in and main phases are included in this test.

11.3 Secondary Objectives: Toxicity

Comparison of toxicity in the two arms (MC vs MC->pac) allows evaluating whether the presumed higher risk of toxicity in the taxane-containing arm may be outweighed by the higher response rate in poor responders.

Febrile neutropenia:

Primary prophylaxis (PP) with G-CSF for febrile neutropenia will be administered at investigator discretion (recommended according to AGO guidelines). Incidence of febrile neutropenia (FN) after 1xMC will be evaluated in these two (non-randomized) groups with formal 95% confidence intervals (CI). With an estimated N=200 patients receiving PP (based on experience from previous trials), the upper 95% confidence interval will extend to about 3.9% if the true FN rate in this group is 2%.

In exploratory analysis (provided that 100 patients do not receive PP) incidence of FN will be compared in these two groups of patients after 1xMC. A difference of about 8% will be seen in a one-sided test with alpha=.05 and about 80% power (no correction for multiple testing).

To support interpretation in this nonrandomized comparison, patient characteristics at study entry in the two groups will be compared. If subgroups of the PP group and of the non-PP group with comparable characteristics can be identified, FN incidence in these similar subgroups will also be compared in exploratory analysis.

After 2xMC, there will be patients with G-CSF from the start, patients with no G-CSF, and patients with G-CSF beginning with the second cycle. Incidence of FN at 2xMC will be estimated with formal 95% CI in these groups. Incidence of FN after w12 will be reported as a whole and in all groups defined by G-CSF and study medication sequence. Toxicity rates will be generally computed with formal 95% CI in the 4 x MC and in the 2 x MC →6 x Pac arm.

11.4 Further objectives

Response and dynamic assessment:

- Percentage of pCR in non-responders to MC will be estimated with 95% CI
- Sensitivity, specificity, positive predictive value of dynamic test regarding prediction of pCR will be evaluated as a whole and in subgroups
- Sensitivity, specificity, positive predictive value of 6-week US regarding prediction of pCR will be evaluated as a whole and in subgroups
- Concordance measures of dynamic Ki-67 assessment with early ultrasound assessment will be computed.
- Dynamic Ki-67 assessment will be compared to early ultrasound assessment for prediction of pCR

Survival assessment:

- The trial will perform descriptive (Kaplan-Meier) survival estimation in patient subgroups, particularly in subgroups with/without pCR, in terms of event-free and overall survival.

Other assessments:

- Breast-conserving therapy rates and (optionally) Health-related quality of life (HRQL) will be described.

11.5 Ethical Considerations *ADAPT Elderly*

All participants will give written informed consent for participation in the trial. All participants will be protected by the insurance cover as standard in the clinical trials. Possible under-treatment should be excluded by the data from several trials. Donating of tumor block to the central tumor bank is planned for further research purposes.

11.6 Allocation

The *ADAPT Elderly* trial is a non-randomized trial: Eligible patients are to receive Myocet / Cyclophosphamide for two cycles and will be classified according to response (cCR/cPR or NC) and toxicity. Subsequently, in case of cPR or cCR, patients will be allocated to continue MC. In case of NC or toxicity (or both), patients will be further treated by Paclitaxel.

11.7 Efficacy Evaluation

11.7.1 Efficacy Parameters

The primary efficacy parameter is pCR, defined as no invasive patterns in the breast and lymph nodes at the time of surgery. Descriptive statistics regarding RCB will also be evaluated as available.

11.7.2 Safety Evaluations

Incidence of febrile neutropenia (FN) will be evaluated in the two (non – randomized) groups.

12 Translational Research

Please refer to the *ADAPT umbrella* protocol, chapter 10 for further information.

13 Adverse Events

Please refer to the *ADAPT umbrella* protocol, chapter 12 for further information.

14 Definition of Study Medication ADAPT Elderly

14.1 Definition of Study Medication

For the purpose of this sub-trial Myocet will be labeled study-specific and is considered study medication. Paclitaxel and Cyclophosphamide will be commercial ware and will not be labeled study-specific.
Documentation of preparation and distribution of the study medication has to be documented in accordance with the Investigator's Brochure.

15 Administrative Aspects

Please refer to the *ADAPT umbrella* protocol, chapter 14 for further information.

Due to very low enrolment numbers of patients, it was decided to prematurely stop the recruitment of new patients for the elderly study.. The follow-up for the patients who are already enrolled in the study will be continued as described in the ***ADAPT umbrella*** protocol, chapter 7.10.
The limited data obtained so far does not allow for a change of the risk benefit evaluation.

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