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Supplementary information

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Neoadjuvant atezolizumab in combination with dual HER2 blockade plus epirubicin in women with early HER2-positive breast cancer: the randomized phase 2 ABCSG-52/ATHENE trial

In the format provided by the authors and unedited

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	3
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	4-5
	2b	Specific objectives or hypotheses	5
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	12
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	12
	4b	Settings and locations where the data were collected	6
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	12-13
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	14
	7b	When applicable, explanation of any interim analyses and stopping guidelines	14-15
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	12
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	12
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	12
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	12

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	14-15
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	14-15
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	6
	13b	For each group, losses and exclusions after randomisation, together with reasons	6
Recruitment	14a	Dates defining the periods of recruitment and follow-up	6
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	22
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	6-7
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	6-7
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	7
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	7-9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	22-23
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	8-11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	8-11
Other information			
Registration	23	Registration number and name of trial registry	12
Protocol	24	Where the full trial protocol can be accessed, if available	Suppl.
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	18

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

ABCSG 52 / ATHENE: An open-label, two-arm, randomized, single-stage phase II study of **AT**ezolizumab in combination with dual **HE**R2 blockade plus epirubicin as **NE**oadjuvant therapy for HER2-positive early breast cancer.

Study sponsor: Austrian Breast & Colorectal Cancer Study Group (ABCSG)

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PROTOCOL SIGNATURE PAGE

ABCSG 52 / ATHENE Site ID: _ _ _ _

Protocol Title: **ATHENE:** An open-label, two-arm, randomized, single-stage phase II study of **AT**ezolizumab in combination with dual **HE**R2 blockade plus epirubicin as **NE**oadjuvant therapy for HER2-positive early breast cancer.

Protocol Number:	ABCSG 52 / ATHENE
EudraCT Number:	2019-002364-27
Study Sponsor:	Austrian Breast & Colorectal Cancer Study Group (ABCSG)

Declaration of Principal Investigator

I confirm that I have read this study protocol and agree to conduct the study in accordance with the current protocol and its appendices.

In addition, I agree to adhere to the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (ICH-GCP) and the applicable national laws and regulations.

I agree to handle all information concerning the study confidentially.

_____

First Name, Last Name of Principal Investigator (in capital letters or typewrite)

_____ _____

Signature Date

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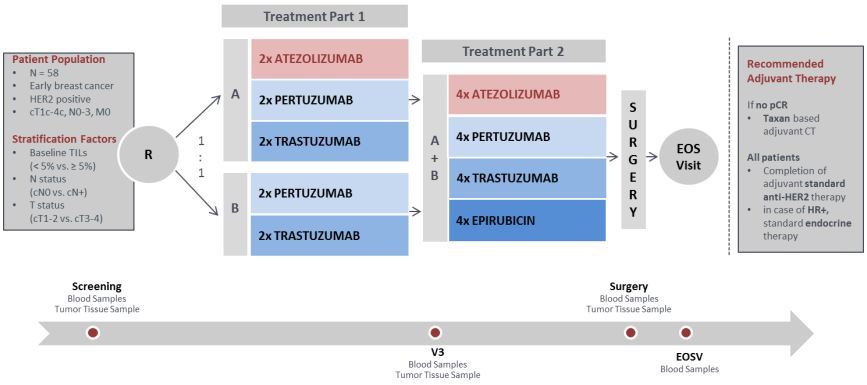
2 Study Synopsis

Study Title	**ABCSG 52 / ATHENE:** An open-label, two-arm, randomized, single-stage phase II study of **AT**ezolizumab in combination with dual **HE**R2 blockade plus epirubicin as **NE**oadjuvant therapy for HER2-positive early breast cancer.
Study Code	ABCSG 52
EudraCT Number	2019-002364-27
Study Sponsor	Austrian Breast & Colorectal Cancer Study Group (ABCSG)
Phase	Phase II
Background & Rationale	Approximately 15 % of all breast cancer cases belong to the HER2-positive subtype as defined by HER2 protein overexpression and/or HER2/neu gene amplification [1]. Addition of trastuzumab, a humanized monoclonal antibody targeting HER2 to conventional adjuvant chemotherapy, however, resulted in a significant and clinically relevant reduction of breast cancer recurrences (HR 0.54) [2]. Besides trastuzumab, further HER2-directed drugs such as the antibody pertuzumab, the drug-antibody conjugate trastuzumab-emtansine and tyrosine-kinase inhibitors such as lapatinib and neratinib are available today, allowing for targeted combination therapy or sequential administration of non-cross resistant drugs. In the neoadjuvant setting, dual HER2-inhibition with trastuzumab and pertuzumab resulted in pathological complete response (pCR) rates in breast and axilla of approximately 50 % despite the parallel reduction of chemotherapy intensity [3]. As pathological complete response (pCR) is associated with long-term outcome on an individual patient level in high-risk breast cancer subtypes [4], neoadjuvant chemo-immunotherapy is widely accepted as the preferred treatment approach today in HER2-positive breast cancer even when primary breast conservation appears feasible. Patients without pCR, however, still have a dismal prognosis; therefore, novel treatment approaches are being urgently sought to further improve patients' outcomes. While breast cancer was often regarded as "non-immunogenic", the presence of dense infiltrations of tumor-infiltrating lymphocytes (TILs) was reported in triple-negative and HER2-positive disease; importantly, presence of TILs is associated with improved outcome [5-8]. Furthermore, TILs may predict for trastuzumab activity [5]. The presence of TILs in residual disease after neoadjuvant chemotherapy is associated with better prognosis in TNBC patients [9]. Controversially, in HER2-positive breast cancer patients who did not achieve pCR after neoadjuvant therapy, TILs were associated with higher residual tumor burden and a worse disease-free survival [10]. These data clearly indicate an important role of immune mechanisms in breast cancer and serve as rationale for the use of immune-checkpoint modulators especially in the HER2-positive and triple-negative subtype. Combining these drugs with conventional chemotherapy or HER2-

	directed antibodies may further increase treatment activity. An appropriate combination of chemotherapy and checkpoint inhibitors could augment the efficacy of PD-(L)1 blockade, particularly in less immunogenic, chemo-sensitive tumors. Indeed, two recent phase III trials in squamous and non-squamous non-small cell lung cancer (NSCLC) patients reported an improved overall survival (OS) with the PD-1 antibody pembrolizumab in combination with a carboplatin-based chemotherapy compared to chemotherapy alone in the first-line setting [59, 60]. Similarly, atezolizumab in combination with chemotherapy and bevacizumab has been shown to be superior to chemotherapy alone as first-line therapy in NSCLC (IMpower150) [61]. In metastatic triple-negative breast cancer (mTNBC), the combination of nab-paclitaxel and atezolizumab in first-line showed promising activity in a phase Ib trial with an overall response rate (ORR) of 70.8 % [62]. A corresponding phase III trial (IMpassion130) comparing atezolizumab plus nab-paclitaxel vs. placebo plus nab-paclitaxel showed a significantly longer PFS by the addition of atezolizumab in the intention-to-treat (ITT) population [39]. Conventional chemotherapeutic agents are also known to harbour immunogenic properties. Doxorubicin was shown to enhance dendritic cell (DC) maturation [47], promote the antibody-presenting abilities of murine DCs [48], and induce the expression of heat shock proteins *in vitro* [49]. Next to doxorubicin, also other anthracyclines (i.e. epirubicin, and idarubicin) can trigger immunogenic cell death, a regulated cell death that engages the adaptive immune system [52]. These data again suggest a sound rationale for the combination of an anthracyclin with immune-checkpoint modulators. In immune-checkpoint-inhibitor combination trials in breast cancer patients, only a subset of patients had a benefit from the addition of a PD-1 or PD-L1 inhibitor. To identify patients who might benefit from the treatment regimen investigated in the ABCSG 52 trial, and to identify patients who do not benefit and for whom other treatment strategies should be investigated, a translational research project investigating predictive biomarkers will accompany the ABCSG 52 trial. The evaluation of safety and tolerability of atezolizumab in combination with trastuzumab, pertuzumab and epirubicin as well as of QoL is an essential part of phase II trials and is in line with International Conference on Harmonization (ICH) and regulatory authorities (including EU Clinical Trials Directive). These endpoints are pivotal in order to establish the safety profile of this regimen.
Primary Objective	To evaluate the efficacy of a neoadjuvant immunochemotherapy regimen consisting of atezolizumab, trastuzumab, pertuzumab and epirubicin in regards to pathologic complete response (pCR = ypT0/is, ypN0) which is assessed in the overall study population at the time of surgery
Secondary Objectives	To evaluate efficacy in regards to • Residual Cancer Burden (RCB) • Overall Response Rate (ORR)

	which are assessed in the overall study population at the time of surgery.
Safety Objective	To evaluate the safety and tolerability of a neoadjuvant immunochemotherapy regimen consisting of atezolizumab, trastuzumab, pertuzumab and epirubicin which is assessed in the overall study population
Patient Reported Outcome (PRO) Objective	To evaluate Quality of Life (QoL) of a neoadjuvant immunochemotherapy regimen consisting of atezolizumab, trastuzumab, pertuzumab and epirubicin which is assessed in the overall study population at baseline, V3, the surgery visit and the EOSV
Exploratory Objectives	• To evaluate the endpoints radiographic complete response (rCR) and radiographic partial response (rPR) which are assessed in the overall study population at the time of surgery • To evaluate the endpoints early rCR, rPR, mCR, and mPR at V3 which are assessed in the overall study population as well as between the two treatment arms • To evaluate the rate of patients considered as not suitable for breast conserving surgery at baseline but finally performed breast conserving surgery assessed at the EOSV in the overall study population • To evaluate surgery-associated and any other perioperative complications at the EOSV in the overall study population
Translational Objective	To explore signals of magnitude of association in regards to changes from baseline to V3 in immunological and genetic biomarkers which are assessed in the overall study population as well as between the two treatment arms
Trial Design and Schema	This is an open-label, two-arm, randomized, single-stage phase II study of atezolizumab with dual HER2 blockade (trastuzumab and pertuzumab) and epirubicin as neoadjuvant immunichemotherapy in patients with HER2-positive, HR positive/negative early breast cancer.  58 patients will be randomized in a 1:1 ration to receive either • 2 cycles of atezolizumab q3w + 2 cycles of pertuzumab q3w and trastuzumab q3w (arm A)

	• or 2 cycles of pertuzumab q3w and trastuzumab q3w (arm B) in treatment part 1. Treatment part 2 (consisting of 4 cycles of atezolizumab q3w, pertuzumab q3w, trastuzumab q3w and epirubicin q3w) will apply to all patients regardless of previous treatment assignment
Inclusion Criteria	**Patients must meet the following criteria for study entry:** <u>Patient / Disease Specifics</u> (1) Signed informed consent obtained prior to any study specific assessments and procedures which are not performed as part of standard of care (2) Female patients, age ≥ 18 years at the time of signing informed consent form (ICF) (3) Histologically confirmed invasive, unilateral adenocarcinoma of the breast with the following characteristics: - cT1c-4a-d, N0–3, M0 per AJCC (American Joint Committee on Cancer) Breast Cancer Staging version 8 (refer to section 23.3, Appendix III) - In the case of a multifocal tumor (defined as the presence of two or more foci of cancer within the same breast quadrant), the largest lesion must be > 1 cm and designated as the “target” lesion for all subsequent tumor evaluations - In the case of a multicentric tumor (defined as the presence of two or more foci of cancer within different quadrants), the largest lesion must be > 1 cm and designated as the “target” lesion for all subsequent tumor evaluations - histologically confirmed HER2 positivity; HER2 measurement to be assessed locally as 3+ by immunohistochemistry or 2+ by immunohistochemistry with HER2 amplification by In Situ Hybridization (ISH) according to the ASCO/CAP guideline (refer to section 23.4, Appendix IV) - If biopsies were taken from more than one focus, all histologically confirmed invasive breast cancer foci have to be HER2 positive. In case of a multicentric tumor, at least two foci in different breast quadrants have to be histologically confirmed HER2 positive breast cancer. - Hormone receptor positive or negative tumors (4) Tumor tissue from FFPE core-needly biopsy of breast tumor measuring at least 3x1 mm must be transmitted to a central sample repository and feedback on central TIL assessment must be available prior to randomization (5) Neoadjuvant chemotherapy indicated (at the discretion of the investigator) (6) ECOG performance status 0-1 (7) In women of childbearing potential, urine or serum pregnancy test must be negative within 28 days prior to randomization. In postmenopausal women or hysterectomized patients, pregnancy tests do not need to be performed.

	Note: Women of childbearing potential must agree to remain abstinent or use adequate contraception that result in a failure rate < 1 % per year during the study treatment and for a period of 7 months following the last administration of study drug. Adequate contraception is defined as one highly effective form (abstinence, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusion cap with spermicidal foam / gel / film / cream / suppository). Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. (8) Adequate left ventricular ejection fraction (LVEF) at baseline, defined as LVEF ≥ 55 % by either echocardiogram or MUGA. Adequate hematologic and end-organ function, defined by the following laboratory results: <u>Baseline body function specifics</u> (9) ANC ≥ 1.5 x 10^9/L (1500/µL) without granulocyte colony-stimulating factor support (10) Lymphocyte count ≥ 0.5 x 10^9/L (500/µL) (11) Platelet count ≥ 100 x 10^9/L (100,000/µL) without transfusion (12) Hemoglobin ≥ 90 g/L (9 g/dL). Patients may be transfused to meet this criterion (13) For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 x ULN. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen. (14) Aspartate amino transferase (AST), alanine amino transferase (ALT), and alkaline phosphatase (ALP) ≤ 2.5 x ULN (15) Serum bilirubin ≤1.5 x ULN with the following exception: Patients with known Gilbert's syndrome: serum bilirubin level ≤ 3 x ULN (16) Serum creatinine ≤ 1.5 x ULN AND creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula) (17) Ability to understand and fill out PRO questionnaires
Exclusion Criteria	**Patients who meet any of the following criteria must be excluded from study entry:** (1) Metastatic or locally advanced disease (without loco-regional treatment options with curative intention) (2) Patient receiving any prior cancer therapy for invasive breast cancer and/or the same disease (3) Bilateral invasive breast cancer (4) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti- Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways (5) History of other malignancy; patients who have been disease-free for 5 years or patients with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible (6) Pregnant or lactating women (7) Serious medical or psychiatric disorders that would interfere with

	the patient's safety or informed consent (at the discretion of the investigator) (8) Clinically significant cardiovascular disease, requiring medication during the study and which might interfere with regularity of the study treatment, or not controlled by medication (at the discretion of the investigator) (9) Clinically relevant, active bacterial, viral or fungal infection (at the discretion of the investigator) (10) History of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, uncontrolled inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible. Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible as well (11) Prior allogeneic stem cell or solid organ transplantation (12) Concurrent participation in another clinical trial with the same primary endpoint and/or concurrent participation in another clinical trial with an investigational product (13) Known hypersensitivity to the study drugs (14) Active tuberculosis (15) Patients receiving live, attenuated vaccine within 4 weeks prior to Cycle 1 Day 1 (= V1) AND not fit for study participation as per investigator's assessment. Note: Patients may receive influenza vaccination if individual risk-benefit-assessment leads to investigator's decision that harmful effects would be otherwise anticipated during study participation (16) Treatment with therapeutic oral or iv antibiotics within 2 weeks prior to randomization Note: Patients receiving prophylactic antibiotics (e.g. to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible (17) Known uncontrolled HIV, HCV and HBV infection
Investigational Medicinal Products	Atezolizumab (treatment part 1 and treatment part 2), pertuzumab (treatment part 1), trastuzumab (treatment part 1)
Background Treatments	Pertuzumab (treatment part 2), trastuzumab (treatment part 2), epirubicin (treatment part 2)
Analysis Populations	Three analysis populations are considered: Intention-to-Treat (ITT) population (all patients who were randomized), safety (SAF) population (all patients who were randomized and received at least one dose of study treatments) and efficacy assessment (EA) population (all patients who were randomized, were treated with at least two cycles of study treatment and were assessable for pCR status).

Sample Size Calculation	A sample size calculation was performed for the primary endpoint, the pCR proportion in the overall study population, and yielded a required sample size of n=58. Based on clinical data from the NeoSphere trial [23] and statistical and medical expert opinion, a pCR proportion of 40 % in the overall study population is assumed
Estimated Recruitment Period	Approximately 18 months
Estimated Study Duration (per patient)	Approximately 6-8 months
Estimated Study Duration (overall)	Approximately 26 months
Estimated First Patient In	QIV 2019
Estimated Last Patient – Last Visit	QI 2022
Number of sites	Approximately 8 trial sites

3 List of Abbreviations

The following abbreviations are used in this Clinical Study Protocol.

Abbreviation	Explanation
1L	First-line
2L	Second-line
2L+	Second-line and beyond
ABCSG	Austrian Breast & Colorectal Cancer Study Group
ACTH	Adrenocorticotropic hormone
ADA	anti-drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AJCC	American Joint Committee on Cancer
ALK	Anaplastic lymphoma kinase
ALP	Alkaline Phosphatase
AL(A)T/ GPT	Alanine Aminotransferase/ Glutamic Pyruvic Transaminase
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
ARR	Administration-related reactions
ASCO	American Society of Clinical Oncology
AS(A)T/ GOT	Aspartate Aminotransferase/ Glutamic Oxaloacetic Transaminase
AUC	Area under the curve
$AUC_{0\text{-}inf}$	AUC from time zero to infinity
BAL	Bronchoscopic alveolar lavage
BUN	Blood Urea Nitrogen
CAP	College of American Pathologists
CCOD	Clinical Cut Off Date
cCR	Complete Clinical Response
CD80	Cluster of differentiation 80
CHF	Congestive heart failure
CHO	Chinese Hamster Ovary
CI	Confidence Interval
CISH	Chromogenic in situ hybridization
c_{max}	Maximum serum concentration

Abbreviation	Explanation
c_{min}	Minimum serum concentration
CR	Complete Response
CRA	Clinical Research Associate
CRC	Colorectal Cancer
CRF	Case Report Form
CRP	C-reactive protein
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
CV	Coefficient of variation
CV (%)	(percent) coefficient of variation (geometric mean)
D	Day
DC	Dendritic cells
DCE-MRI	Dynamic contrast-enhanced-MRI
DCIS	Ductal carcinoma in situ
DCR	Disease control rate
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DOR	Duration of response
DWI	Diffusion-weighted imaging
eCRF	electronic Case Report Form
ECG	Electrocardiogram
ECHO	Echocardiogram
ECMO	Extracorporeal membrane oxygenation
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eEOT	Early end of treatment
EGFR	Epidermal growth factor receptor
EMA	European Medicines Agency
EORTC	European Organization of Research and Treatment of Cancer
EOS	End of Study
EOSV	End of Study Visit

Abbreviation	Explanation
EOT	End of Treatment
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration
FFPE	Formalin-Fixed, Paraffin-Embedded
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FNA	Fine needle aspiration
FPI	First Patient In
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GLP	Good Laboratory Practice
GM	Geometric mean
GmbH	Gesellschaft mit beschränkter Haftung
GMP	Good Manufacturing Practice
H	Height
Hb	Haemoglobin
HBsAg	Hepatitis B surface antigen
HbcAb	Hepatitis B core antibody
HCV	Hepatitis C virus
HER	Human Epithelial Growth Factor Receptor
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
HR	Hormone receptor
IB	Investigator’s Brochure
IC	Tumor-infiltrating immune cell
ICF	Informed Consent Form
ICH	International Conference on Harmonization
iDFS	Invasive disease-free survival
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IL	Interleukin

Abbreviation	Explanation
IMP	Investigational Medicinal Product
INR	International Normalized Ratio
IPD	Important Protocol Deviation
irPR	Immune related partial response
IRR	Infusion Related Reaction
irRC	Immune related response criteria
ISH	In Situ Hybridisation
ITC	Isolated tumor cells
ITT	Intention to treat
iv	Intravenous
IVIG	Intravenous immunoglobulin
KLH	Keyhole limpet hemocyanin
LBW	Lean body weight
LCIS	Lobular carcinoma in situ
LDH	Lactic dehydrogenase
LFT	Liver Function Test
LOQ	Limit of quantification
LVEF	Left ventricular ejection fraction
MBC	Metastatic breast cancer
mCR	Complete metabolic response
MedDRA	Medical Dictionary for Regulatory Activities
MM	Medical Monitor
mPR	Partial metabolic response
MRI	Magnetic Resonance Imaging
mUC	Metastatic urothelial carcinoma
MUGA	Multigated Acquisition
NCCN	National Comprehensive Cancer Network
NCI CTC	National Cancer Institute – Common Toxicity Criteria
NCI CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NE	Not evaluable
NR	Not reported
NSCLC	Non-small Cell Lung Cancer

Abbreviation	Explanation
NYHA	New York Heart Association
OcRR	Overall Clinical Response Rate
ORR	Overall Response Rate
OS	Overall Survival
pCR	Pathological Complete Response (pathological response rate)
PD	Protocol Deviation
PD-1	Programmed death - 1
PD-L1	Programmed death - ligand 1
PERCIST	PET Response Criteria in Solid Tumors
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetics
PR	Progesterone Receptor
PR	Partial Response
Pro-BNP	Pro-brain natriuretic peptide
QLQ	Quality of Life Questionnaire
QoL	Quality of Life
q3w	Once every three weeks
RANKL	Receptor activator of nuclear factor kappa-B ligand
RBC	Red Blood Cell
RCB	Residual Cancer Burden
RCC	Renal Cell Carinoma
rCR	Radiographic complete response
rPD	Radiographic progressive disease
rPR	Radiographic partial response
rSD	Radiographic stable disease
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase polymerase chain reaction
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Explanation
SC	Steering Committee
SD	Stable Disease
SDV	Source Data Verification
SOP	Standard Operating Procedures
T	Tesla
$t_{1/2}$	Terminal half-life
T-DM1	Trastuzumab-emtansine
TIL	Tumor-infiltrating lymphocytes
TKI	Tyrosine kinase inhibitor
TMP	Trial Monitoring Plan
TNBC	Triple Negative Breast Cancer
TNF	Tumor necrosis factor
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
V	Visit
VAD	Ventricular Assist Device
Vss	Volume of distribution at steady state
W	Weight
WBC	White Blood Cell
WT	Wilde-type

4 Definition of Study Terms

Title of Terms	Definition
Day 1	Actual first day of treatment administration in each cycle
Visit 1 (V1)	Cycle 1/day 1, due within a maximum of 10 days after the day of randomization
Visit 3 (V3)	Cycle 3/day 1
End of study (EOS), common	After formal closure of all study sites and database closure
End of study (EOS), Patient	At the time of EOS visit or early EOS of a single patient
End of study visit (EOSV)	Patient's last formal visit according to "Schedule of Assessments" (please refer to section 21)
End of treatment (EOT)	Date of last dose of neoadjuvant study treatment, irrespective if the patient completed study treatment or stopped study treatment earlier than scheduled. If patient discontinues study treatment earlier than scheduled, this is defined as early end of treatment (eEOT)
First Patient In (FPI)	Randomization of the first patient
Investigational Medicinal Product (IMP)	Atezolizumab (treatment part 1 and treatment part 2), pertuzumab (treatment part 1), trastuzumab (treatment part 1)
Background treatments	Pertuzumab (treatment part 2), trastuzumab (treatment part 2), epirubicin (treatment part 2)
Study treatments	Neoadjuvant treatment; comprises IMP and background treatments
Last dose of neoadjuvant treatment	Day of last administration of study specific neoadjuvant treatment
Study timelines	In case the protocol lists time periods/durations (i.e. within 10 days after the day of randomization), the date of assessment (i.e. randomization) is always excluded and the timeline starts the day after the date of assessment (i.e. day of randomization + 10 additional calendar days).

5 Introduction and Background

5.1 HER2-positive breast cancer - Rationale for Patient Population

Approximately 15 % of all breast cancer cases belong to the HER2-positive subtype as defined by HER2 protein overexpression and/or HER2/neu gene amplification [1]. Traditionally, HER2-positive breast cancer is regarded as the most aggressive subtype and a high rate of recurrences were

observed before the introduction of modern targeted therapies. Addition of trastuzumab, a humanized monoclonal antibody targeting HER2 to conventional adjuvant chemotherapy, however, resulted in a significant and clinically relevant reduction of breast cancer recurrences (HR 0.54) [2]. Besides trastuzumab, further HER2-directed drugs such as the antibody pertuzumab, the drug-antibody conjugate trastuzumab-emtansine and tyrosine-kinase inhibitors such as lapatinib and neratinib are available today, allowing for targeted combination therapy or sequential administration of non-cross resistant drugs.

In the neoadjuvant setting, dual HER2-inhibition with trastuzumab and pertuzumab resulted in pathological complete response (pCR) rates in breast and axilla of approximately 50 % despite the parallel reduction of chemotherapy intensity [3]. As pathological complete response (pCR) is associated with long-term outcome on an individual patient level in high-risk breast cancer subtypes [4], neoadjuvant chemo-immunotherapy is widely accepted as the preferred treatment approach today in HER2-positive breast cancer even when primary breast conservation appears feasible. Patients without pCR, however, still have a dismal prognosis; therefore, novel treatment approaches are being urgently sought to further improve patients' outcomes.

In contrast to melanoma or lung cancer, development of immunotherapy was markedly delayed in breast cancer and only recently interest has surged with clinical trials focusing on triple-negative and – to a lesser extent – HER2-positive disease.

While breast cancer was often regarded as "non-immunogenic", the presence of dense infiltrations of tumor-infiltrating lymphocytes (TILs) was reported in triple-negative and HER2-positive disease; importantly, presence of TILs is associated with improved outcome [5-8]. Furthermore, TILs may predict for trastuzumab activity [5]. The presence of TILs in residual disease after neoadjuvant chemotherapy is associated with better prognosis in TNBC patients [9]. Controversially, in HER2-positive breast cancer patients who did not achieve pCR after neoadjuvant therapy, TILs were associated with higher residual tumor burden and a worse disease-free survival [10].

These data clearly indicate an important role of immune mechanisms in breast cancer and serve as rationale for the use of immune-checkpoint modulators especially in the HER2-positive and triple-negative subtype. Combining these drugs with conventional chemotherapy or HER2-directed antibodies may further increase treatment activity.

In line with this assumption, an immunocompetent transgenic HER2-positive breast cancer mouse model showed that enhancement of T-cell response with PD-1 directed antibodies in combination with anti-HER2 antibodies yielded synergistic effects and was more effective than either treatment alone [11]. In a phase 1b–2 clinical trial, 58 patients with trastuzumab resistant metastatic breast cancer were treated with trastuzumab in combination with the anti-PD1-antibody pembrolizumab [12]. PD-L1-positive patients achieved an objective response in 15 %, while no objective responders were seen among the PD-L1-negative patients. The safety profile of this chemotherapy-free combination was favorable, wherefore further studies less heavily pretreated patients are planned.

5.2 **Targeted Treatments in HER2-positive Breast Cancer**

5.2.1 Monoclonal Antibodies

Three monoclonal antibodies targeting HER2 are currently approved by the FDA both for the treatment of early and metastatic breast cancer: trastuzumab, pertuzumab and T-DM1.

The first studies that led to trastuzumab's approval for the treatment of HER2-positive metastatic or locally advanced breast cancer tested trastuzumab in combination with various monochemotherapies, especially taxanes showing a significant improvement in survival [13, 14]. In early HER2-positive breast cancer, several large randomized phase III trials showed a significant improvement in disease-free and overall survival by the addition of trastuzumab to standard

adjuvant chemotherapy [2, 15-18], making 1 year of adjuvant trastuzumab the gold standard for the treatment of this disease. In the neoadjuvant setting, the NOAH trial showed among other trials that the addition of trastuzumab to chemotherapy increased clinical and pathological complete response [19]. Furthermore, long-term follow-up of the NOAH trial revealed a significant improvement in event-free survival by the addition of trastuzumab [20].

The introduction of pertuzumab, a monoclonal antibody inhibiting the dimerization of HER2 with other HER receptors, further improved the prognosis of this breast cancer subtype. The CLEOPATRA trial compared the combination of pertuzumab, trastuzumab and docetaxel with the combination of docetaxel and trastuzumab in patients with metastatic HER2-positive breast cancer [21]. PFS increased from 12.4 months to 18.5 months (HR 0.68; 95 % CI 0.58 to 0.80; p<0.001), and OS increased from 40.8 to 56.5 months (HR 0.68; 95 % CI 0.56 to 0.84; p<0.001) [21, 22]. This established the combination of taxanes with dual inhibition of HER2 as the first choice for first-line therapy in metastatic HER2-positive breast cancer. In the neoadjuvant setting, the NeoSphere trial similarly showed that the addition of pertuzumab to docetaxel plus trastuzmab significantly increased the pCR rate (46 % vs. 29 %; p=0.014) [23], which led to the approval of the neoadjuvant use of pertuzumab. These neoadjuvant results were certified in the TRYPHAENA trial where pCR rates between 55 % and 64 % were achieved when pertuzumab was added to different chemotherapy backbones [3]. In the adjuvant placebo-controlled APHINITY trial, patients with node-positive or high-risk node-negative HER2-positive, operable breast cancer were randomized between standard chemotherapy plus trastuzumab for 1 year or the same therapy combined with 1 year of pertuzumab [24]. The 3-year rates of invasive-disease-free survival were slightly increased by the addition of pertuzumab (94.1 % vs. 93.2 %; HR 0.81; 95 % CI 0.66 to 1.00; p=0.045). In the cohort of patients with node-positive disease, the difference was more pronounced (3-year iDFS rate 92.0 % vs. 90.2 %; HR 0.77; 95 % CI, 0.62 to 0.96; P=0.02) [24]. Based on these results pertuzumab was recently approved for the adjuvant treatment of high-risk patients with HER2-positive early breast cancer.

The third monoclonal antibody approved for the treatment of HER2-positive breast cancer is T-DM1, an antibody-drug conjugate of trastuzumab and the microtubule inhibitory agent emtansine (a derivative of maytansine) connected by a stable linker. Approval in metastatic disease was based on the results of the phase 3 registration trials EMILIA [25] and THERESA [26] comparing T-DM1 with capecitabine plus lapatinib and treatment of physicians choice, respectively. Both trials showed an improved OS by the antibody-drug conjugate (HR 0.68; 95 % CI 0.55 to 0.85; p<0.001 and HR 0.68; 95 % CI 0.54 to 0.85; p<0.001, respectively) [27, 28]. These data clearly demonstrated the acitivity and good tolerability of this drug, making it to the treatment of choice in pretreated patients with HER2-positive metastatic breast cancer. Recently, results of the phase 3 trial KATHRINE were published [29]. Here, adjuvant T-DM1 was compared to trastuzumab in HER2-positive patients with residual disease after neoadjuvant chemotherapy and anti-HER2 treatment. The risk of recurrence of invasive breast cancer or death (iDFS) was 50 % lower with adjuvant T-DM1 than with trastuzumab (HR 0.50; 95 % CI 0.39 to 0.64; p<0.001) [29]. Based on these study results, T-DM1 was recently approved by the FDA for this indication.

5.2.2 Tyrosine Kinase Inhibitors

Besides the three monoclonal antibodies trastuzumab, pertuzumab and T-DM1, two orally active small molecules, lapatinib and neratinib, are approved by the FDA for the treatment of HER2-positive breast cancer. Unlike the antibodies, these drugs inhibit the intracellular protein kinase domain of HER2 (and EGFR), thereby preventing self-phosphorylation and subsequent activation of the signaling pathway. Lapatinib has shown to improve the pCR rate when combined with neoadjuvant trastuzumab and chemotherapy compared to chemotherapy plus trastuzumab alone [30-32], however, the drug has not received approval for this indication. Today, lapatinib is approved in combination with capecitabine for the treatment of patients with locally advanced or metastatic HER2-positive breast cancer, who have received prior therapy with an anthracycline, a

taxane and trastuzumab. Neratinib was approved by the FDA and the EMA for the extended adjuvant treatment of patients with early stage HER2-overexpressed/amplified breast cancer after 1 year of adjuvant trastuzumab based on the results of the ExteNET trial [33].

5.3 **Atezolizumab Mechanism of Action**

Atezolizumab is a humanized immunoglobulin (IgG1) monoclonal antibody that is produced in Chinese hamster ovary (CHO) cells. Atezolizumab targets programmed death-ligand 1 (PD-L1) on tumor-infiltrating immune cells or tumor cells and prevents interaction with the programmed death-1 (PD-1) receptor and B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells and other immune cells. Interference of the PD-L1:PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function. Atezolizumab was engineered to eliminate Fc-effector function via a single amino acid substitution at position 298 on the heavy chain, which results in a non-glycosylated antibody that has minimal binding to Fc receptors and, consequently, eliminates detectable Fc-effector function. By eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity, antibody-mediated clearance of activated effector T cells is also eliminated.

Expression of PD-L1 is prevalent among many human tumors [8], and its overexpression is associated with poor prognosis for patients with certain cancers [10;34-36]. Therefore, interruption of the PD-L1/PD-1 pathway represents an attractive strategy to reinvigorate tumor-specific T-cell immunity.

A complete description of the activity and safety of atezolizumab can be found in the current version of the atezolizumab Investigator's Brochure (IB).

5.4 **Pre-clinical Data of Atezolizumab**

5.4.1 Toxicology and Safety Pharmacology

The toxicology program consisted of a 2-week, non-GLP repeat-dose pilot study in mice with a 4-week recovery period; 8- and 26-week, GLP repeat-dose studies in cynomolgus monkeys with 12- and 13-week recovery periods, respectively; an immunotoxicoloy study in cynomologus monkeys which elevated the T cell and T cell-dependent antibody response to KLH; an in vitro cytokine release assay; a GLP in vitro hemolytic potential and blood compatibility assay; and a GLP tissue cross-reactivity study using human and cynomolgus monkey tissues. The results of the toxicology program designed to support the administration of atezolizumab to oncology patients are as follows:

- Atezolizumab was well tolerated in C57BL/6 and CD-1 mice at doses of up to 50 mg/kg weekly for 2 weeks (total of 3 doses). Microscopic findings attributed to atezolizumab were observed in the sciatic nerve and consisted of minimal neuropathy noted in C57BL/6 mice at ≥ 10 mg/kg which is consistent with the observation that female NOD-H2$^{b/b}$ Pdcd$^{-/-}$ mice (PD-1-deficient) spontaneously developed autoimmune inflammation in multiple tissues, including peripheral nerves, between 20 and 25 weeks of age [65]. No atezolizumab-related microscopic findings were observed in CD-1 mice

- Atezolizumab was well tolerated in cynomolgus monkeys following iv or sc doses of up to 50 mg/kg for 8 weeks (total of 9 doses) or 26 weeks (iv only: total of 27 dosesdoses) respectively.

- Atezolizumab-related minimal-to-mild chronic-active, and multifocal arteritis/periarteritis within the interstitium of multiple parenchymal organs or within the submucosa or muscularis of tubular organs, such as the gastrointestinal and female reproductive tracts, was observed in a few animals each within the ≥ 15 mg/kg (iv or sc) dose groups; these findings were not present at the end of the dose-free recovery period, indicating either resolution during the recovery period or lack of occurrence in the recovery cohorts.

Arteritis/periarteritis in animals given atezolizumab may reflect an exacerbation of an immune-mediated condition that occurs in cynomolgus monkeys. As such, this finding is consistent with the primary pharmacology of PD-L1 inhibition and the dysregulation of peripheral tolerance.

- A microscopic change at the injection sites related to the sc administration of atezolizumab was noted at terminal necropsy in animals administered ≥ 15 mg/kg. The lesion was characterized as a minimal, focal to multifocal, and often perivascular, mononuclear cell infiltrate in the sc tissue of injection sites. The microscopic injection site lesions were not present at the recovery necropsy timepoint, suggesting reversibility and were not considered adverse.

- An atezolizumab-related effect on menstrual cycles (irregular cycle pattern) was observed during the dosing phase in all sexually mature females in the 50 mg/kg group, which corresponds to an estimated AUC approximately 6 times the AUC in patients receiving the recommended dose. This effect showed reversibility as the 2 females given 50 mg/kg of atezolizumab designated to the recovery group demonstrated a return to normal menstrual during the recovery phase.

- Administration of atezolizumab at 50 mg/kg by iv injection for up to 26 weeks was well tolerated in cynomologus monkeys challenged with the T cell-dependent antigen KLH. There were no unexpected or novel toxicities in KLH-challenged cynomologus monkeys. Chronic administration of atezolizumab resulted in a non-significant decrease of the primary anti-KLH IgM and the primary and secondary anit-KLH IgG responses. Although the toxicological significance is uncertain due to the low number of animals used in this study and the high interanimal variability, atezolizumab may decrease primary and secondary IgG responses to T cell-dependent antigens.

- Atezolizumab, at concentrations up to 125 mg/mL (the highest testable concentration), did not cause hemolysis of human or cynomolgus monkey erythrocytes.

- In human tissues, biotin-atezolizumab-specific staining was detected in the placenta, lymph node, tonsil, and thymus by immunohistochemistry. In cynomolgus monkey tissues, biotin-atezolizumab-specific staining was detected only in the lymph node. This staining is consistent with the reported expression of PD-L1 on lymphoid and non-lymphoid tissues [66-67].

- Atezolizumab alone, over a concentration range of 0.25-250 µg/mL, did not induce cytokine release from isolated human peripheral blood mononuclear cells (PBMCs).

Overall, the risks identified in the nonclinical studies conducted with atezolizumab are consistent with the primary pharmacology of PD-L1/PD-1 pathway inhibition.

The entire pre-clinical experience is fully described in the current version of the atezolizumab IB.

5.4.1.1 Safety Data of Atezolizumab

As of 17 May 2019 > 21,000 patients with solid tumors or hematologic malignancies have received atezolizumab as a single agent or in combination with cytotoxic chemotherapy and/or targeted therapy through participation in a clinical trial.

Safety findings of single-agent atezolizumab across multiple tumor types in the clinical development program are consistent with the known mechanism of action of atezolizumab and the underlying disease. Overall, treatment with atezolizumab is well tolerated, with a manageable adverse event profile. Currently, no maximum tolerated dose, no dose-limiting toxicities (DLTs), and

no clear dose-related trends in the incidence of adverse events (AEs) have been determined. Among 3075 patients treated with single-agent atezolizumab for whom pooled safety data are available, the most commonly reported AEs (≥ 10 %) include fatigue, decreased appetite, nausea, cough, dyspnea, constipation, pyrexia, diarrhea, anemia, back pain, vomiting, asthenia, arthralgia, pruritus, rash, headache, urinary tract infection and peripheral edema.

The AEs observed with atezolizumab in combination with chemotherapy and/or targeted therapies are consistent with the known risks of the individual study treatment.

Immune-mediated AEs are consistent with the role of the PD-L1/PD-1 pathway in regulating peripheral tolerance. Given the mechanism of action of atezolizumab, events associated with inflammation and/or immune-mediated AEs are closely monitored during the atezolizumab clinical program. As of 17 May 2018, immune-mediated AEs associated with atezolizumab include pneumonitis, hepatitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome/myasthenia gravis, meningoencephalitis, myocarditis, nephritis and myositis. Further safety-related information can be found in the current version of the atezolizumab IB.

5.5 **Pharmacokinetics of Atezolizumab in Humans**

5.5.1 Clinical Pharmacology

There have been no dedicated clinical pharmacology studies conducted for atezolizumab. Atezolizumab pharmacokinetics and other data have been analysed from the following atezolizumab monotherapy studies: PCD4989g, JO28944, IMvigor 210, IMvigor 211, BIRCH, POPLAR, FIR, and OAK. Atezolizumab pharmacokinetics after combination administrations with other anti-cancer agensts were comparable to those following atezolizumab monotherapy administrations.

The key PK findings from the above-listed atezolizumab monotherapy clinical studies are summarized below:

- The pharmacokinetics of atezolizumab monotherapy have been characterized in patients in Study PCD4989g at doses 0.01 mg/kg to 20 mg/kg q3w, including the fixed dose 1200 mg (equivalent to 15 mg/kg). Exposure to atezolizumab increased dose proportionally over the dose range of 1 mg/kg to 20 mg/kg. While a subset of anti-drug antibody (ADA)-positive patients in Study PCD4989g receiving 0.3 to 3 mg/kg atezolizumab q3w experienced a reduction of atezolizumab C_{min} to below the PK assay lower limit of quantification (LOQ), patients receiving 10 to 20 mg/ kg atezolizumab, including the fixed 1200 mg dose, maintained geometric mean C_{min} that was in excess of both the LOQ and the target serum concentration of 6 µg/mL

- A Phase I popPK analysis that included 472 patients from Studies PCD4989g and JO28944 described atezolizumab pharmacokinetics for the dose range 1-20 mg/kg with a linear two-compartment disposition model with first-order elimination. The popPK analysis indicated that central compartment volume of distribution (V1) was 3.28 L and the V_{ss} was 6.91 L in the typical patient. Further, the CL of atezolizumab was 0.20 L/day and the t 1/2 was 27 days. Steady state was obtained after 6 to 9 weeks (2 to 3 cycles) of repeated dosing. The systemic accumulation in AUC, C_{max}, and C_{min} was 1.91, 1.46, and 2.75-fold, respectively.

- Based on an analysis of exposure, safety, and efficacy data, the following factors had no clinically relevant effect: age (21-89 years), body weight, sex, albumin levels, tumor burden, region or race, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status. Positive ADA status against atezolizumab led to approximately 13 % reduction in overall exposure.

- The effect of moderate or severe hepatic impairment on the pharmacokinetics of atezolizumab is unknown.

5.5.1.1 Atezolizumab Monotherapy - Phase Ia Study PCD4989g

A PK assessment of available data (from patients enrolled at dose levels of 0.03-20 mg/kg, with data cutoff of 2 December 2014) was performed for Cycle 1 serum concentration-time data through use of standard non-compartmental PK methods. PK parameters following atezolizumab administration based on Cycle 1 are summarized in Table 1.

Table 1 Study PCD4989g: Summary Statistics for Serum Atezolizumab PK Parameters in Cycle 1

Atezolizumab Dose Group	Atezolizumab PK Parameters in Cycle 1 GM (%CV)			
	Cmax (ug/mL)	Cmin (pg/mL)	$AUC_{0\text{-}inf}$[a] (day»pg/mL)	$t_{1/2}$[b] (Days)
0.03 mg/kg (n = 1)	0.37	NA	NA	NA
0.1 mg/kg (n = 1)	0.96	NA	1.62	NA
0.3 mg/kg (n = 3)	6.49(19) n = 3	NA	33.0 (7.9) n = 2	NA
1 mg/kg (n = 3)	25.8(17) n = 3	3.80(160) n = 3	225 (2.8) n = 2	26.6 n = 1
3 mg/kg (n = 3)	75.6 (26) n = 3	12.2(62) n = 3	651 (22) n = 2	21.8 n = 1
10 mg/kg (n = 36)	265(16) n = 36	54.1 (25) n = 34	2780 (22) n = 9	22.7 (56) n = 10
15 mg/kg (n=235)	332 (53) n = 232	67.1 (73) n = 214	3280 (35) n = 17	18.0(39) n = 29
20 mg/kg (n = 145)	472 (35) n = 145	91.1 (36) n = 132	4860 (23) n = 10	23.7 (36) n = 28
1200mg(n=45)	405 (50) n = 40	95.5(51) n = 30	NA	NA

NA = PK parameter is not available due to insufficient data
Notes: The CCOD for these data was 2 December 2014.
PK parameters were not calculated for the 0.01-, 0.03-, and 1200-mg dose groups due to insufficient data. Intensive PK sampling was used for all doses except the 1200 mg dose, which was characterized by a C max and C min only.
[a] Given the 18.0 - 26.6 day $t_{1/2}$ and that $AUC_{0\text{-}inf}$ was calculated using only up Day 21 data in Cycle 1, AUC 0-inf is considered to be approximate in nature.
[b] $t_{1/2}$ was calculated only for patients with 3 or more consecutive end-of-treatment samples after 3 or more cycles of therapy and reported as harmonic mean (pseudo standard deviation). $t_{1/2}$ was estimated for patient data ranging from Cycle 3 to 36.

5.5.2 Effect of ADA on Atezolizumab Monotherapy Pharmacokinetics

A summary of the C_{max} and C_{min} of atezolizumab following multiple doses of atezolizumab (10 to 20 mg/kg and 1200 mg q3w) by ADA status in Study PCD4989g is shown in Table 2. A subset of ADA-positive patients in the lower dose groups (i.e., 0.3, 1, and 3 mg/kg) experienced a reduction of atezolizumab C_{min} to below the PK assay LOQ following multiple atezolizumab q3w dosing. However, patients receiving 10 to 20 mg/kg atezolizumab, including the fixed 1200 mg dose of atezolizumab, maintained an average C_{min} that was in excess of both the LOQ and the target serum concentration of 6 µg/mL, regardless of the ADA status. The similar C_{min} concentrations observed in ADA-positive and ADA-negative patients at doses ≥ 10 mg/kg suggest ADA positivity has little effect on atezolizumab exposure at these doses.

Table 2 Study PCD4989g: Geometric Mean (%CV) Serum Atezolizumab C min and C max Concentration across Treatment Cycles Stratified by ADA Status

Atezolizumab PK Parameters Stratified by ADA Status GM (%CV)							
Dose	ADA Status	C_{max} C1 Postdose (µg/mL)	C_{min} C2 Predose (µg/mL)	C_{min} C4 Predose (µg/mL))	C_{min} C5 Predose (µg/mL)	C_{min} C8 Predose (µg/mL)	C_{max} C8 Postdose (µg/mL)
10 mg/kg	+	235 (20) n=12	47.4 (22) n = 12	91.1 (62) n = 10	118(26) n = 3	NR	NR
	-	260 (24) n = 22	58.2 (23) n=22	105(32) n = 17	140(13) n=4	112(65) n = 3	NR
	All	249 (23) n = 35	54.1 (25) n = 34	99.5 (44) n = 27	130(20) n = 7	112(65) n = 3	NR
15 mg/kg	+	297(150) n = 82	54.5(110) n = 87	95(190) n = 60	107(280) n = 35	176(67) n=22	516(24) n = 9
	-	306 (240) n = 128	77.4(41) n = 127	144(46) n = 93	146(150) n = 69	196(55) n = 33	386 (63) n = 5
	All	306(190) n=222	67.1 (73) n = 214	122(110) n = 153	132 (190) n = 104	188 (60) n = 55	465(41) n = 14
20 mg/kg	+	435(21) n = 26	70.9 (35) n=27	132(53) n = 23	168(80) n = 11	163(130) n = 13	388 n = 1
	-	505 (24) n = 104	97.2 (33) n = 105	180(48) n = 90	206 (58) n=49	237 (59) n = 30	614 n = 1
	All	488 (24) n = 138	91.1 (35.8) n = 132	169 (50) n = 113	198 (62) n = 60	212 (82) n=43	488 n=2
1200 mg	+	392 (27) n=3	56.9 (45) n=3	56.9 (45) N=3	143 n=1	NR	NR
	-	458 (22) N=26	101 (48) n=27	139 (43) n=7	142 n=1	NR	NR
	All	455 (23) N=37	95.5 (51) n=30	139 (40) n=8	176 (50) n=4	NR	NR

Note: The CCOD of these data was 2 December 2014.
Patients with missing ADA status are included in the “All” group.

5.5.3 Population Pharmacokinetics

The population pharmacokinetics of atezolizumab was first assessed based on Phase I data from two clinical studies: Study PCD4989g and Study JO28944 (n=472 patients). The popPK model was subsequently subjected to an external validation for mUC and NSCLC, separately, using PK data collected from IMvigor210 (n=423 patients) and IMvigor211 (n=455) for mUC, and from BIRCH, POPLAR, and FIR (n=920 patients) and later OAK (n=596 patients) for NSCLC.

For the Phase I popPK model, serum pharmacokinetics of atezolizumab across the two studies PCD4989g and JO28944 (dose range: 1-20 mg/kg q3w, including the fixed 1200 mg dose of atezolizumab q3w) were described by a linear two-compartment disposition model with first-order elimination. The estimated typical population CL was 0.200 L/day and the typical V1 was 3.28 L for a male patient with 40 g/L of albumin.

The typical V_{ss} and terminal $t_{1/2}$ estimates were 6.9 L and 27 days. Based on simulations in the current population, 90 % of steady state was attained after the following median (range) number of cycles: 3 cycles (1-6), 2 cycles (1-4), and 3 cycles (1-5) for C_{min} , C_{max} , and AUC, respectively. Interindividual variability was estimated to be 29 %, 18 %, and 34 % for CL, V1, and V2, respectively.

The following statistically significant parameter-covariate relationships were identified as body weight, tumor burden, sex, ADA, and albumin. In patients who were positive for ADA, CL was estimated to be 16 % higher than in patients without ADA. In females, volume of distribution would be 13 % and 27 % lower than in males for V1 and V2, respectively. No covariate induced more than a 27 % change from the typical PK model parameter for extreme values.

A sensitivity analysis was performed to examine the influence of the statistically significant covariates on steady-state exposure (AUC_{ss} , $C_{max,ss}$ and $C_{min,ss}$) of atezolizumab.

Overall, females had a moderately higher exposure compared with males. Patients with low albumin tended to have a lower exposure with a larger effect on $C_{min,ss}$. Baseline tumor burden and positive ADA had a minor impact on exposure over the dose range investigated in this analysis (i.e., 1 to 20 mg/kg of atezolizumab q3w or the fixed 1200 mg dose q3w). Overall, no covariate effect induced more than a 30 % change in exposure from the typical patient (the typical patient is a male without positive ADA, weighing 77 kg, with an albumin level of 40 g/L and a tumor burden of 63 mm) except for body weight when evaluated at the lowest extreme of weight (i.e., 10^{th} percentile). Patients with body weight lower than 54 kg would have up to a 32 %, 28 %, and 40 % higher AUC_{ss}, $C_{max,ss}$, or $C_{min,ss}$, respectively, than the typical patient. None of these covariate effects would be expected to result in a $C_{min,ss}$ that would be lower than a targeted serum concentration of 6 µg/mL.

No new unexpected covariate effect was identified in IMvigor 210, BIRCH, FIR, POPLAR, or OAK. The atezolizumab PK data obtained in IMvigor 210, BIRCH, FIR, POPLAR, and OAK in patients with mUC and patients with NSCLC were consistent with the popPK model estimates.

An analysis of exposure-efficacy and exposure-safety relationships indicates that the following factors have no clinically relevant effect on atezolizumab pharmacokinetics: age (21-89 years), body weight, sex, positive ADA status, albumin levels, tumor burden, region or ethnicity, renal impairment, mild hepatic impairment, level of PD-L1 expression, or ECOG status.

Further PK-related information can be found in the current version of the atezolizumab IB.

5.6 **Clinical Data of Atezolizumab**

5.6.1 Clinical Trials of Atezolizumab in malignant Diseases

As of 17 May 2018, efficacy data were most extensive for patients with non-small cell lung cancer (NSCLC; 3134 patients enrolled in BIRCH, POPLAR, OAK, IMpower 150, IMpower 131, GO28625 [FIR], and the NSCLC cohort of PCD4989g) and patients with metastatic urothelial carcinoma (mUC; 1104 efficacy-evaluable patients in studies PCD4989g, IMvigor210 and IMvigor211 who were administered atezolizumab.

Efficacy parameters (ORR in Cohort 1 [CCOD 12 July 2017]and ORR, PFS, and OS in Cohort 2 [CCOD 12 July 2017]) observed in the Phase II IMvigor 210 study after an additional 10 months, from the original CCOD and 26 months of follow-up (Cohorts 1 and 2, respectively) were consistent with those obtained at primary analyses of each cohort. Similar response rates and consistency between primary and updated analyses were seen in the mUC cohort of Study PCD4989g. In both studies higher ORR results in the IC2/3 expression group suggest that higher levels of PD-L1 expression on ICs may be associated with increased benefit. The primary analysis of IMvigor211 (CCOD 13 March 2017) showed a clinically meaningful OS improvement for atezolizumab treatment compared to chemotherapy, but the results werde not statistically significant. The results with IMvigor211 are consistent with those of IMvigor210.

The results from the 5 studies evaluating atezolizumab as monotherapy in patients with locally advanced or metastatic NSCLC (PCD4989g, FIR, OAK, POPLAR, and BIRCH) single-agent treatment with atezolizumab resulted in clinically meaningful OS improvement in the 2L/3L NSCLC ITT population, in comparison with standard of care, in both non-squamous and squamous histologies, and across all PD-L1 expression subgroups. Higher PD-L1 expression on tumor cells or immune cells

was associated with higher ORRs and longer median PFS and OS duration. Responses were highly durable across all PD-L1 expression groups.

Other available efficacy data suggested that treatment with atezolizumab as a single agent or in combination with other therapeutic agents resulted in anti-tumor activity across a range of other tumor types and hematologic malignancies (including pediatric-type tumors), across lines of therapy, and across PD-L1 expression subgroups.

5.6.1.1 Summary Monotherapy

- In 2L/3L NSCLC patients, atezolizumab treatment resulted in clinically meaningful OS improvement in the ITT population and across all PD-L1 expression subgroups when compared to docetaxel.

- Among 1L cisplatin-ineligible and 2nd line metastatic urothelial carcinom responders, there were high numbers of complete responses, and responses appeared durable when compared to historical chemotherapy.

- Encouraging clinical outcomes were seen in patients with mTNBC following treatment with atezolizumab, in particular for those with PD-L1 IC2/3 expression and those who had received atezolizumab in the 1L setting.

5.6.1.2 Summary Combination Treatment

- Improvement in PFS was observed for atezolizumab+nab-placitaxel compared with placebo+nab-placitaxel in patients with locally advanced or metastatic TNBC. OS in the ITT population did not cross the pre-specified p-value boundary at the first and second interim analyses, but clinically meaningful improvement was observed in the PD-L1 positive population.

- Atezolizumab+bevacizumab showed clinical benefit in terms of ORRs and PFS for IC1/2/3 patients in 1L RCC as compared to monotherapy with sunitinb, as well as in ORRs in 2L+ CRC patients.

- Atezolizumab + cobimetinib + vemurafenib showed ORRs in the 45 % - 65.8 % range in 1L/1L+ metastatic melanoma patients.

- End of induction data for atezolizumab+obinutuzumab showed a 56.5 % response rate per Lugano criteria for patients with relapsed/refractory FL although there were few responders in diffuse large B-cell lymphoma.

- The benefit-risk profile of atezolizumab with bevacizumab, carboplatin, and paclitaxel is favorable for 1L patients with metastatic, non-squamous NSCLC, including patients with EGFR mutation or ALK positive NSCLC who had failed prior TKI therapy.

- Statistically and clinically meaningful improvement in OS and statistically significant improvement in PFS were demonstrated for atezolizumab+carboplatin+nab-paclitaxel compared with carpoplatin+nab-paclitaxel for chemotherapy-naïve pateints with stage IV non-squamous NSCLC, in both the ITT-WT and ITT populations.

5.6.2 Clinical Trials of Atezolizumab in Breast Cancer

5.6.2.1 Single-Agent Atezolizumab in 1L and 2L+ Metastatic TNBC: Phase 1a Study PCD4989g

The TNBC cohort of the single-arm phase Ia trial PCD4989g included 116 patients with metastatic TNBC evaluable for efficacy, 115 of these had measurable disease at baseline and were objective-response evaluable per RECIST v1.1. [37]. Investigator-assessed confirmed ORR was 10 % (95 % CI 5 to 16) with 3 complete responses (CRs) and 8 partial responses (PRs). Median duration of response (DOR) was 21 months (range 3-38+) and all-patient median OS was 8.9 months (95 % CI 7.0 to 12.6), with a median follow-up duration of 25.3 months. Median PFS duration was 1.4 months (95 % CI 1.3 to 1.6). These data suggest a similarity to or advantage over standard of care treatment.

Patients with higher PD-L1 expression had better responses than patients with lower PD-L1 expression. ORR was 12 % in the IC2/3 subgroup vs. 5 % in the 0/1 subgroup. Longer median OS was observed in IC2/3 patients (10.5 months; 95% CI 7.1 to 14.7) compared with those in the PD-L1 IC0/1 subgroup (7.0; 95 % CI 5.1 to 12.6) and the overall cohort.

More treatment benefit was also observed in patients receiving first-line atezolizumab than in patients receiving 2L+ atezolizumab. ORR was 24 % among 1L patients vs. 6 % among 2L+ patients. Median OS in 1L patients was 17.6 months (95 % CI 10.2–NE), vs. 7.3 months (95 % CI 6.1–10.8) in 2L+ patients. Median PFS was consistent regardless of PD-L1 expression subgroup or line of therapy [37].

It should be noted that immunotherapeutic agent activity and clinical benefit are not fully characterized in TNBC by RECIST criteria alone; patient responses in this cohort were assessed separately by immune-related response criteria (irRC). A higher proportion of patients were shown to have CR, PR or SD per irRC compared with that by RECIST v1.1 and all the patients with PD per RECIST v1.1 but irPR per irRC were still alive at the time of data cutoff [37].

Table 3 Key Efficacy Endpoints in Study PCD4989g (TNBC Cohort)

	PD-L1 Expression Subgroup			All Patients	1L	2L+
	ICO/1	IC2/3	Unknown			
INV-ORR[a]	n=37	n=74	n=4	n=115	n=21	n=94
Responders (%) (95% Cl)	2 (5.4) (0.7, 18.2)	9 (12.2) (5.7,21.8)	0	11 (9.6) (4.9, 16.5)	5 (23.8) (8.2, 47.2)	6 (6.4) (2.4, 13.4)
CR n (%)	0	3(4.1)	0	3 (2.6)	2 (9.5)	1 (1.1)
PR n (%)	2 (5.4)	6(8.1)	0	8 (7.0)	3(14.3)	5 (5.3)
INV-DOR	n=2	n=9	-	n=11	n=5	n=6
Patients with event (%)	1 (50.0)	6 (66.7)	-	7 (63.6)	3 (60.0)	4 (66.7)
Median DOR (mos) (95% Cl)	NE (9.9, NE)	21.1 (9.6, NE)	-	21.1 (9.6, NE)	21.1 (9.6, NE)	19.1 (4.2, 28.3)
INV-PFS	n=38	n=74	n=4	n=116	n=21	n=95
Patients with event (%)	36 (94.7)	69 (93.2)	4(100.0)	109 (94.0)	17 (81.0)	92 (96.8)
Median PFS (mos) (95% Cl)	1.4 (1.4,1.5)	1.4 (1.4, 1.9)	2.0 (1.0, 2.7)	1.4 (1.4, 1.6)	1.6 (1.4, 10.8)	1.4 (1.4, 1.4)
OS	n=38	n=74	n=4	n=116	n=21	n=95
Patients with event (%)	31 (81.6)	54 (73.0)	4(100.0)	89 (76.7)	11 (52.4)	78(82.1)
Median OS (mos) (95% Cl)	7.0 (5.1,12.6)	10.5 (7.1, 14.7)	9.8 (1.0,20.5)	8.9 (7.0, 12.6)	17.6 (10.1, NE)	7.3 (6.1, 10.8)

Notes: Patients were administered one of the following doses of atezolizumab: 15 mg/kg q3w, 20 mg/kg q3w, 1200 mg q3w.
The CCOD for the data was 31 December 2016.
The radiographic endpoints were assessed by the investigator per RECIST v1.1.
[a] ORR based on patients with measurable disease at baseline.

5.6.2.2 Atezolizumab plus Nab-Paclitaxel in 1-3L Metastatic TNBC: Phase 1b Study GP28328

This phase 1b multicohort study included 33 women with metastatic or locally recurrent TNBC who had received 0 to 2 lines of prior chemotherapy in the metastatic setting [38]. Patients were treated with 800 mg atezolizumab on day 1 and 15 in combination with 125 mg/m^2 nab-paclitaxel on day 1, 8 and 15 every 4 weeks for a minimum of 4 cycles. The primary end point was safety and tolerability. Secondary endpoints included best overall response rate by RECIST 1.1, ORR, DOR, disease control rate (DCR), PFS, OS and biomarker analyses.

The 33 women had a median age of 55 years (range 32-84 years). Thirteen patients had received no prior systemic therapy for metastatic disease, 20 patients were treated in the second-line or later setting. All patients (100 %) experienced at least 1 treatment-related adverse event, 24 patients (73 %) experienced grade 3/4 adverse events, and 7 patients (21 %) had grade 3/4 adverse events of special interest, including an increase of liver enzymes (3 patients), pneumonitis, type 1 diabetes and colitis (1 patient, respectively). Grade 3/4 events attributed, at least in part, to atezolizumab were observed in 24 patients (73 %). The most frequent grade 3/4 events were neutropenia (46 % [n = 15]), thrombocytopenia (9 % [n = 3]), pneumonia (6 % [n = 2]), anemia (6 % [n = 2]), diarrhea (6 % [n = 2]) and leucopenia (6 % [n = 2]). Febrile neutropenia was observed in 1 patient (3 %). The most common grade 3/4 AEs attributed exclusively to atezolizumab were diarrhea (6 % [n = 2]) and colitis (3% [n = 1]). No deaths were related to study treatment.

At a median follow-up of 24.4 months (95 % CI 22.1 to 28.8 months) the ORR was 39 % (95 % CI 22.9 % to 57.9 %) with 1 CR and 12 PR. Responses were durable, with a median DOR of 9.1 months (95% CI 2.0 to 20.9 months). The DCR was 52 % (95 % CI 33.5 % to 69.2 %). Responses were also seen in patients previously treated with a taxane. Median PFS and OS were 5.5 months (95 % CI 5.1 to 7.7 months) and 14.7 months (95 % CI 10.1 not reached), respectively.

The efficacy was numerically but not statistically better in untreated patients vs. previously treated patients: ORR 54 % vs. 30 %; median PFS 8.6 vs 5.1 months, median OS 24.2 vs 12.4 months. The same effect was observed in PD-L1-positive (defined as ≥1 % of immune cells expressing PD- L1) vs PD-L1-negative patients: ORR 41.4% vs 33.3%; median PFS 6.9 vs 5.1 months; median OS 21.9 vs 11.4 months [38].

5.6.2.3 Atezolizumab plus Nab-Paclitaxel in 1L Metastatic TNBC: Phase III Study IMpassion130

Based on the data of the GP28328 phase Ib study, the phase III study IMpassion130 was conducted, evaluating the combination of atezolizumab and nab-paclitaxel as first-line treatment for metastatic triple negative breast cancer (TNBC). In total, 902 patients were randomized 1:1 to nab-paclitaxel 100 mg/m^2 i.v. (on day 1, 8 and 15 of a 28-day cycle) plus atezolizumab 840 mg i.v. every 2 weeks or nab-paclitaxel plus placebo [39]. The study showed a significantly longer PFS by the addition of atezolizumab in the intention-to-treat (ITT) population (median PFS 7.2 vs. 5.5 months; HR 0.80; 95 % CI 0.69 to 0.92; p=0.002). In patients with PD-L1 expression in at least 1 % of tumor-infiltrating immune cells (PD-L1-positive) the influence on PFS was more pronounced (median PFS 7.5 vs. 5.0 months; HR 0.62; 95 %CI 0.49 to 0.78; p<0.001). The first interim OS analysis showed no statistical difference in the ITT population between the two study arms. Therefore, according to the protocol, no statistical analysis of OS in the PD-L1-positive subgroup was allowed. Nevertheless, an absolute survival difference between the two study arms of almost 10 months between the two study arms was observed in the PD-L1 IC+ subgroup (25.0 vs. 15.5 months; HR 0.62; 95 % CI 0.45 to 0.86) [39].

At the San Antonio Breast Cancer Symposium (SABCS) 2018 a more detailed biomarker-analysis beyond PD-L1 was presented [40]. For the PD-L1-negative subgroup, absolutely no benefit by the addition of atezolizumab to nab-paclitaxel was shown both regarding PFS and OS. Within the PD-L1 positive subgroup, however, no difference between low (IC1; PFS HR 0.59; 95 % CI 0.44 to 0.78) and intermediate or strong staining (IC2/3; PFS HR 0.64; 95 % CI 0.43 to 0.97) was observed.

Beyond PD-L1 on immune cells, stromal tumor-infiltrating lymphocytes (sTILs) and tumor-infiltrating cytotoxic T cells (CD8+) were investigated as potential predictive markers. These markers by itself, however, did not predict clinical benefit with atezolizumab plus nab-paclitaxel but only if the infiltrating immune cells were PD-L1 positive as well. Importantly, the efficacy of the combination treatment in PD-L1-positive patients was independent of their BRCA 1/2 mutation status [40].

Based on the study, atezolizumab received accelerated approval by the FDA and the EMA in combination with nab-paclitaxel for the treatment of patients with triple-negative MBC with PD-L1 positivity on tumor-infiltrating immune cells ($\geq$ 1 %).

6 Study Rationale

6.1 Rationale for a neoadjuvant treatment including smaller tumors

Neoadjuvant chemotherapy is as effective as adjuvant chemotherapy [41-43], therefore chemotherapy can be administered before or after surgery in early breast cancer patients, if chemotherapy is indicated. The St. Gallen 2017 panel recommended adjuvant chemotherapy and anti-HER2 therapy for HER2-positive stage pT1b pN0 and higher breast cancers. In the current version of the NCCN guidelines for breast cancer (version 3.2018) adjuvant chemotherapy is recommended in HER2-positive breast cancer patients with tumors ≥ 1cm or nodal involvement. For HER2-positive tumors of 0.6 to 1.0 cm without nodal involvement the NCCN guidelines recommend adjuvant chemotherapy plus trastuzumab if hormone receptor positive and recommend considering adjuvant chemotherapy and trastuzumab for hormone receptor negative patients.

Therefore, it is justifiable to include also patients with smaller tumors but ≥ 1cm into the ABCSG 52 trial.

In the GeparSepto trial, for example, cT1cN0 HER2-positive tumors were also included [44].

Without adequate treatment, patients with small HER2-positive breast cancers have an essential risk for recurrence. In a meta-analysis of randomized trials investigating the efficacy of adjuvant trastuzumab in HER2-positive breast cancers, patients with small (≤ 2cm) HER2-positive tumors and ≤ 1 positive lymph nodes had a cumulative incidence of recurrence at 8 years of 12.7 % (trastuzumab treated) vs 19.4 % (no trastuzumab) in the hormone receptor positive subgroup and a cumulative incidence of recurrence at 8 years of 20.4 % (trastuzumab treated) versus 26.3 % (no trastuzumab) in the hormone receptor negative subgroup [45]. In the APT trial, a non-randomized phase II trial, patients with small (≤ 3cm) node negative HER2-positive breast cancers were treated with adjuvant trastuzumab plus weekly paclitaxel [46]. In the APT trial a greater percentage of patients with hormone receptor positive disease (67 %) than in the adjuvant trastuzumab trials (51 % to 54 %) where included. Furthermore, 41.6 % of patients in the APT trial had tumors ≤ 1 cm compared with virtually no node-negative tumors ≤ 1 cm in the adjuvant trastuzumab trials [45] . Only 16 patients (9%) had tumors measuring 2.0 to 3.0 cm in the APT trial. Therefore, the risk of recurrence may be underestimated for tumors ≥ 1cm. According to the NCCN guidelines (version 3.2017) the APT regimen may be considered for patients with low-risk stage I HER2-positive tumors, particulary if they are not eligible for other standard adjuvant regimens due to comorbidities, but anthracycline and taxane based treatment or docetaxel in combination with carboplatin remain the preferred chemo regimen for the HER2-positive disease.

In the APT trial, a clinically significant asymptomatic decline in ejection fraction (LVEF decrease of 10 to 15 % from baseline, with the LVEF at least 1 % below the lower limit of the normal range; or a decrease of 16 % or more from baseline) occurred in 3.2 % (95 % CI, 1.7 to 5.4; 13 patients); in 2 of these patients, the ejection fraction did not normalize [46].

In the randomized phase II TRYPHAENA trial, cardiac safety of pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens was investigated in patients with HER2-positive early breast cancer [3]. During neoadjuvant treatment, 5.6 % in arm A (FEC + trastuzumab + pertuzumab × 3 → docetaxel + trastuzumab + pertuzumab ×3), 5.3% in arm B (FEC x 3 → docetaxel + trastuzumab + pertuzumab ×3), and 3.9 % in arm C (docetaxel + carboplatin + trastuzumab + pertuzumab ×6) experienced LVEF declines of ≥ 10 % from baseline to < 50 %. LVEF had improved to ≥ 50 % in all patients. During adjuvant treatment 5.9 % in arm A, 12.3 % in arm B, and 4.5 % in arm C had significant declines in LVEF; all of these declines had improved to ≥ 50 % at data cut-off. During follow-up, 4.3 % in arm A, 5.3 % in arm B, and 2.7 % in arm C experienced significant LVEF declines and LVEF values recovered to ≥ 50 % in all patients.

At our discretion, an epirubicin, trastuzumab and pertuzumab containing treatment is justifiable for patients with smaller node negative HER2-positive breast cancer, based on the former mentioned findings.

6.2 **Rationale for the Combination of chemotherapeutic Agents with Immunotherapy**

Conventional chemotherapeutic agents were thought to kill cancer cells by interfering with DNA synthesis and replication. Furthermore, chemotherapy was considered solely immunosuppressive by inducing neutropenia and/or lymphopenia. Today we know that chemotherapy agents harbor immunogenic properties beyond simple suppression of the host immune system. By inducing immunogenic cell death, chemotherapy can help to prime tumor-specific T cells through increased tumor antigen presentation, as well as by subverting immunosuppressive factors [58]. Therefore, an appropriate combination of chemotherapy and checkpoint inhibitors could augment the efficacy of PD-(L)1 blockade, particularly in less immunogenic, chemo-sensitive tumors. Indeed, two recent phase III trials in squamous and non-squamous non-small cell lung cancer (NSCLC) patients reported an improved overall survival (OS) with the PD-1 antibody pembrolizumab in combination with a carboplatin-based chemotherapy compared to chemotherapy alone in the first-line setting (KEYNOTE-189 and KEYNOTE-407) [59, 60]. Similarly, atezolizumab in combination with chemotherapy and bevacizumab has been shown to be superior to chemotherapy alone as first-line therapy in NSCLC (IMpower150) [61].

In metastatic triple-negative breast cancer (mTNBC), the combination of nab-paclitaxel and atezolizumab in first-line showed promising activity in a phase Ib trial with an overall response rate (ORR) of 70.8 % [62]. A corresponding phase III trial (IMpassion130) comparing atezolizumab plus nab-paclitaxel vs. placebo plus nab-paclitaxel showed a significantly longer PFS by the addition of atezolizumab in the intention-to-treat (ITT) population (median PFS 7.2 vs. 5.5 months; HR 0.80; 95 % CI 0.69 to 0.92; p=0.002). In patients with PD-L1 expression in at least 1 % of tumor-infiltrating immune cells (PD-L1-positive) the influence on PFS was more pronounced (median PFS 7.5 vs. 5.0 months; HR 0.62; 95 %CI 0.49 to 0.78; p<0.001) [39].

6.2.1 Rationale for the Combination of Atezolizumab with Epirubicin in the neoadjuvant Setting

Conventional chemotherapeutic agents are also known to harbour immunogenic properties. Doxorubicin was shown to enhance dendritic cell (DC) maturation [47], promote the antibody-presenting abilities of murine DCs [48], and induce the expression of heat shock proteins *in vitro* [49]. In another preclinical model, doxorubicin exposure resulted in the proliferation of tumor-specific CD8+ T-cells and promoted tumor infiltration of activated T-cells [50].

In an adaptive phase 2 trial, patients with metastatic triple negative breast cancer were randomized to nivolumab without an induction period, or a two-week induction treatment with irradiation, cyclophosphamide, cisplatin, or doxorubicin followed by nivolumab [51]. The overall response rate (ORR) in the overall group was 20%, and the highest ORR was observed in the doxorubicin induction group (ORR 35%).

Next to doxorubicin, also other anthracyclines (i.e. epirubicin, and idarubicin) can trigger immunogenic cell death, a regulated cell death that engages the adaptive immune system [52].

These data again suggest a sound rationale for the combination of an anthracyclin with immune-checkpoint modulators.

The clinical efficacy of epirubicin is similar to doxorubicin in the treatment of early or metastatic breast cancer, while epirubicin has a different toxicity profile particularly in regard to cardiotoxicity [53, 54].

As in Austria epirubicin is the most common applicated anthracycline for the treatment of breast cancer (personal communication with leading Austrian breast centers), and epirubicin was used in several prior ABCSG trials [55-57], epirubicin will be used within the ABCSG 52 trial.

6.3 Rationale for the Investigation of Biomarkers predicting Treatment Response

In immune-checkpoint-inhibitor combination trials in breast cancer patients, only a subset of patients had a benefit from the addition of a PD-1 or PD-L1 inhibitor.

In the phase 1b–2 clinical trial PANACEA, patients with trastuzumab resistant metastatic breast cancer were treated with trastuzumab in combination with the anti-PD1-antibody pembrolizumab [12]. PD-L1-positive patients achieved an objective response in 15 %, while no objective responders were seen among the PD-L1-negative patients.

In the phase III trial IMpassion130 the combination of atezolizumab and nab-paclitaxel was investigated as first-line treatment for metastatic triple negative breast cancer. For the PD-L1-negative subgroup, absolutely no benefit by the addition of atezolizumab to nab-paclitaxel was shown both regarding PFS and OS [40]. In PD-L1-positive patients median PFS was prolonged from 5.0 to 7.5 months; HR 0.62; 95 %CI 0.49 to 0.78; p<0.001) and an absolute survival difference between the two study arms of almost 10 months between the two study arms was observed in the (25.0 vs. 15.5 months; HR 0.62; 95 % CI 0.45 to 0.86) [39].

To identify patients who might benefit from the treatment regimen investigated in the ABCSG 52 trial, and to identify patients who do not benefit and for whom other treatment strategies should be investigated, a translational research project investigating predictive biomarkers will accompany the ABCSG 52 trial.

6.4 Rationale for the Evaluation of Safety and Tolerability and QoL

The evaluation of safety and tolerability of atezolizumab in combination with trastuzumab, pertuzumab and epirubicin as well as of QoL is an essential part of phase II trials and is in line with International Conference on Harmonization (ICH) and regulatory authorities (including EU Clinical Trials Directive). These endpoints are pivotal in order to establish the safety profile of this regimen.

The assessment of patient-reported outcomes (PROs) in clinical research provides important insights into how therapies affect the daily lives of patients. Patient reports regarding health-related QoL have proven to be more comprehensive than provider-collected data in breast cancer patients. Because atezolizumab is a new drug about which little is known regarding toxicity and impact on quality of life, questionnaires to assess overall quality of life, treatment satisfaction and tolerability symptoms in each of the two study arms will be used. In this study, patient-reported disease related symptoms and health-related quality of life (HRQoL) will be evaluated using the validated EORTC QLQ-C30 questionnaire and EORTC QLQ BR-45.

6.5 Risk–Benefit Assessment

The high rates of cardiac toxicity of a trastuzumab plus epirubicin combination in the metastatic setting has not been reproduced in neoadjuvant trials. In the phase III trial GeparSepto, HER2-positive patients were treated with 12 cycles of weekly nab-paclitaxel/paclitaxel followed by 4 cycles of EC (90 mg/m2 epirubicin plus 600 mg/m2 cyclophosphamid) q3w with concurrent trastuzumab and pertuzumab. LVEF decreases from baseline were observed in 7.6 % of patients. In 2.0 % of patients a LVEF decrease to < 50 % and a ≥ 10 % decrease from baseline was reported [64]. In the randomized phase II TRYPHAENA trial 5.6 % of patients in arm A (FEC + trastuzumab + pertuzumab × 3 → docetaxel + trastuzumab + pertuzumab ×3), 5.3 % in arm B (FEC x 3 → docetaxel + trastuzumab + pertuzumab ×3), and 3.9 % in arm C (docetaxel + carboplatin + trastuzumab + pertuzumab ×6) experienced LVEF declines of ≥ 10% from baseline to < 50 % during neoadjuvant treatment [3]. Based on these findings, the cardiac toxicity profile of doxorubicin in combination with pertuzumab and trastuzumab can be considered as acceptable.

To date, no toxicity data for a combination of an immune-checkpoint inhibitor plus doxorubicin, trastuzumab and pertuzumab are available. In one experimental arm of the I-SPY2 trial pembrolizumab in combination with weekly paclitaxel x 12 followed by doxorubicin in combination with cyclophosphamid was investigated in triple negative breast cancer patients. No myocarditis and no increased cardiac toxicities have been reported [63]. The authors mentioned that an experimental arm, where pembrolizumab will be continued for the anthracycline-based treatment sequence, will start enrolment soon. This new experimental arm has already been listed on clinicaltrials.gov (clinicaltrials.gov identifier NCT01042379, accessed on 12/27/2017).

Safety, i.e. the proportion of patients with at least one ≥ G3 toxicity according to NCI CTCAE Version 5.0 from study inclusion to surgery, is an important secondary endpoint of ABCSG 52. There is some uncertainty regarding potential toxicities of the triple antibody combination of atezolizumab, trastuzumab and pertuzumab alone as well as in combination with epirubicin. To address this uncertainty, we will rigorously implement a safety-monitoring program which allows to continuously monitor for excessive toxicity patterns beyond what is expected during the trial (refer to section 16.13).

7 Study Objectives

7.1 Primary Objective

- To evaluate the efficacy of a neoadjuvant immunochemotherapy regimen consisting of atezolizumab, trastuzumab, pertuzumab and epirubicin in regards to pathologic complete response (pCR = ypT0/is, ypN0) which is assessed in the overall study population at the time of surgery

7.2 Secondary Objectives

- To evaluate efficacy in regards to
  - Residual Cancer Burden (RCB)
  - Overall Response Rate (ORR)

  which are assessed in the overall study population at the time of surgery

7.3 Safety Objectives

- To evaluate the safety and tolerability of a neoadjuvant immunochemotherapy regimen consisting of atezolizumab, trastuzumab, pertuzumab and epirubicin which is assessed in the overall study population

7.4 Patient Reported Outcome (PRO) Objectives

- To evaluate Quality of Life (QoL) of a neoadjuvant immunochemotherapy regimen consisting of atezolizumab, trastuzumab, pertuzumab and epirubicin which is assessed in the overall study population at baseline, V3, the surgery visit and the EOSV

7.5 Exploratory Objectives

- To evaluate the endpoints radiographic complete response (rCR) and radiographic partial response (rPR) which are assessed in the overall study population at the time of surgery
- To evaluate the endpoints early rCR, rPR, mCR, and mPR at V3 which are assessed in the overall study population as well as between the two treatment arms
- To evaluate the rate of patients considered as not suitable for breast conserving surgery at baseline but finally performed breast conserving surgery assessed at the EOSV in the overall study population
- To evaluate surgery-associated and any other perioperative complications at the EOSV in the overall study population

7.6 Translational Objectives

- To explore signals of magnitude of association in regards to changes from baseline to V3 in immunological and genetic biomarkers which are assessed in the overall study population as well as between the two treatment arms

8 Study Endpoints

8.1 Primary Endpoint

- Proportion of patients with a pCR (=ypT0/is, ypN0) assessed in the overall study population at the time of surgery

8.2 Secondary Endpoints

- Two variables of treatment efficacy assessed in the overall study population at the time of surgery
    - Proportion of patients with RCB 0, RCB I, RCB II and RCB III (refer to section 23.6, Appendix VI)
    - Proportion of patients with ORR according to modified RECIST (refer to section 23.7, Appendix VII)

8.3 Safety Endpoints

- Patient incidence with toxicities ≥ grade 3 assessed in the overall study population according to CTCAE criteria Version 5.0 (refer to section 23.1, Appendix I)

8.4 Patient Reported Outcome (PRO) Endpoints

- QoL scores at baseline, V3, surgery visit and EOSV, as well as changes from baseline to V3, surgery visit and EOSV as measured using EORTC QLQ-C30 and EORTC QLQ-BR45 assessed in the overall study population

8.5 Exploratory Endpoints

- Proportion of patients with rCR and rPR defined by MRI according to modified RECIST (refer to section 23.7, Appendix VII) assessed in the overall study population at the time of surgery. In case novel methods/guidelines are in place at the time of analysis, these may additionally be used and analysed
- Proportion of patients with early rCR and rPR defined by MRI according to modified RECIST (refer to section 23.7, Appendix VII) as well as early mCR and mPR defined by PET according to modified PERCIST (refer to section 23.8, Appendix VIII) at V3 assessed in the overall study population as well as between the two treatment arms. In case novel methods/guidelines are in place at the time of analysis, these may additionally be used and analysed
- Proportion of patients considered as not suitable for breast conserving surgery at baseline but finally performed breast conserving surgery assessed at the EOSV in the overall study population.
- Patient incidence of surgery-associated and any other perioperative complications according to a validated classification described by Clavien and Dindo et al. (refer to section 23.5, Appendix V) at the EOSV assessed in the overall study population

8.6 Translational Endpoints

- Immunological and genetic biomarkers at baseline as well as changes from baseline to V3 assessed in the overall study population as well as between the two treatment arms. No pre-specification of the evaluated biomarkers is met at study inception due to scientific progress which may lead to the discovery of novel biomarkers during the conduct of the trial. Analysis will be done in total and separated for patients with/without pCR. Additionally, the overall study population as well as subgroups according to stratification factors will be considered:

- Baseline TILs: < 5 % vs. ≥ 5 %
- HR status: HR+ vs. HR-
- Prognostic stage: ≤ IIA vs. ≥ IIB (according to AJCC v.8.0 clinical prognostic stage groups, refer to section 23.3, Appendix III)

Analyses will be considered exploratory and no formal hypothesis testing will occur.

9 Patient Selection

9.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

Patient / Disease Specifics

(1) Signed informed consent obtained prior to any study specific assessments and procedures which are not performed as part of standard of care

(2) Female patients, age ≥ 18 years at the time of signing informed consent form (ICF)

(3) Histologically confirmed invasive, unilateral adenocarcinoma of the breast with the following characteristics:

- cT1c-4a-d, N0–3, M0 per AJCC (American Joint Committee on Cancer) Breast Cancer Staging version 8 (refer to section 23.3, Appendix III)
- In the case of a multifocal tumor (defined as the presence of two or more foci of cancer within the same breast quadrant), the largest lesion must be > 1 cm and designated as the “target” lesion for all subsequent tumor evaluations
- In the case of a multicentric tumor (defined as the presence of two or more foci of cancer within different quadrants), the largest lesion must be > 1 cm and designated as the “target” lesion for all subsequent tumor evaluations
- histologically confirmed HER2 positivity; HER2 measurement to be assessed locally as 3+ by immunohistochemistry or 2+ by immunohistochemistry with HER2 amplification by In Situ Hybridization (ISH) according to the ASCO/CAP guideline (refer to section 23.4, Appendix IV)
- If biopsies were taken from more than one focus, all histologically confirmed invasive breast cancer foci have to be HER2 positive. In case of a multicentric tumor, at least two foci in different breast quadrants have to be histologically confirmed HER2 positive breast cancer
- Hormone receptor positive or negative tumors

(4) Tumor tissue from FFPE core-needly biopsy of breast tumor measuring at least 3x1 mm must be transmitted to a central sample repository and feedback on central TIL assessment must be available prior to randomization

(5) Neoadjuvant chemotherapy indicated (at the discretion of the investigator)

(6) ECOG performance status 0-1

(7) In women of childbearing potential, urine or serum pregnancy test must be negative within 28 days prior to randomization. In postmenopausal women or hysterectomized patients, pregnancy tests do not need to be performed

Note: Women of childbearing potential must agree to remain abstinent or use adequate contraception that result in a failure rate < 1 % per year during the study treatment and for a period of 7 months following the last administration of study treatment. Adequate contraception is defined as one highly effective form (abstinence, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusion cap with spermicidal foam / gel / film / cream / suppository). Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

(8) Adequate left ventricular ejection fraction (LVEF) at baseline, defined as LVEF ≥ 55 % by either echocardiogram or MUGA

Adequate hematologic and end-organ function, defined by the following laboratory results:

Baseline body function specifics

(9) ANC ≥ 1.5 x 10^9/L (1500/µL) without granulocyte colony-stimulating factor support

(10) Lymphocyte count ≥ 0.5 x 10^9/L (500/µL)

(11) Platelet count ≥ 100 x 10^9/L (100,000/µL) without transfusion

(12) Hemoglobin ≥ 90 g/L (9 g/dL). Patients may be transfused to meet this criterion

(13) For patients not receiving therapeutic anticoagulation: INR or aPTT ≤ 1.5 x ULN. For patients receiving therapeutic anticoagulation: stable anticoagulant regimen.

(14) Aspartate amino transferase (AST), alanine amino transferase (ALT), and alkaline phosphatase (ALP) ≤ 2.5 x ULN

(15) Serum bilirubin ≤1.5 x ULN with the following exception: Patients with known Gilbert's syndrome: serum bilirubin level ≤ 3 x ULN

(16) Serum creatinine ≤ 1.5 x ULN AND creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula)

(17) Ability to understand and fill out PRO questionnaires

9.2 Exclusion Criteria

Patients who meet any of the following criteria must be excluded from study entry:

(1) Metastatic or locally advanced disease (without loco-regional treatment options with curative intention)

(2) Patient receiving any prior cancer therapy for invasive breast cancer and/or the same disease

(3) Bilateral invasive breast cancer

(4) Prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti- Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways

(5) History of other malignancy; patients who have been disease-free for 5 years or patients with a history of completely resected non-melanoma skin cancer or successfully treated in situ carcinoma are eligible

(6) Pregnant or lactating women

(7) Serious medical or psychiatric disorders that would interfere with the patient's safety or informed consent (at the discretion of the investigator)

(8) Clinically significant cardiovascular disease, requiring medication during the study and which might interfere with regularity of the study treatment, or not controlled by medication (at the discretion of the investigator)

(9) Clinically relevant, active bacterial, viral or fungal infection (at the discretion of the investigator)

(10) History of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, uncontrolled inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis. Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone are eligible. Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen are eligible as well

(11) Prior allogeneic stem cell or solid organ transplantation

(12) Concurrent participation in another clinical trial with the same primary endpoint and/or concurrent participation in another clinical trial with an investigational product

(13) Known hypersensitivity to the study drugs

(14) Active tuberculosis

(15) Patients receiving live, attenuated vaccine within 4 weeks prior to Cycle 1 Day 1 (= V1) AND not fit for study participation as per investigator's assessment.

Note: Patients may receive influenza vaccination if individual risk-benefit-assessment leads to investigator's decision that harmful effects would be otherwise anticipated during study participation.

(16) Treatment with therapeutic oral or iv antibiotics within 2 weeks prior to randomization

Note: Patients receiving prophylactic antibiotics (e.g. to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible

(17) Known uncontrolled HIV, HCV and HBV infection

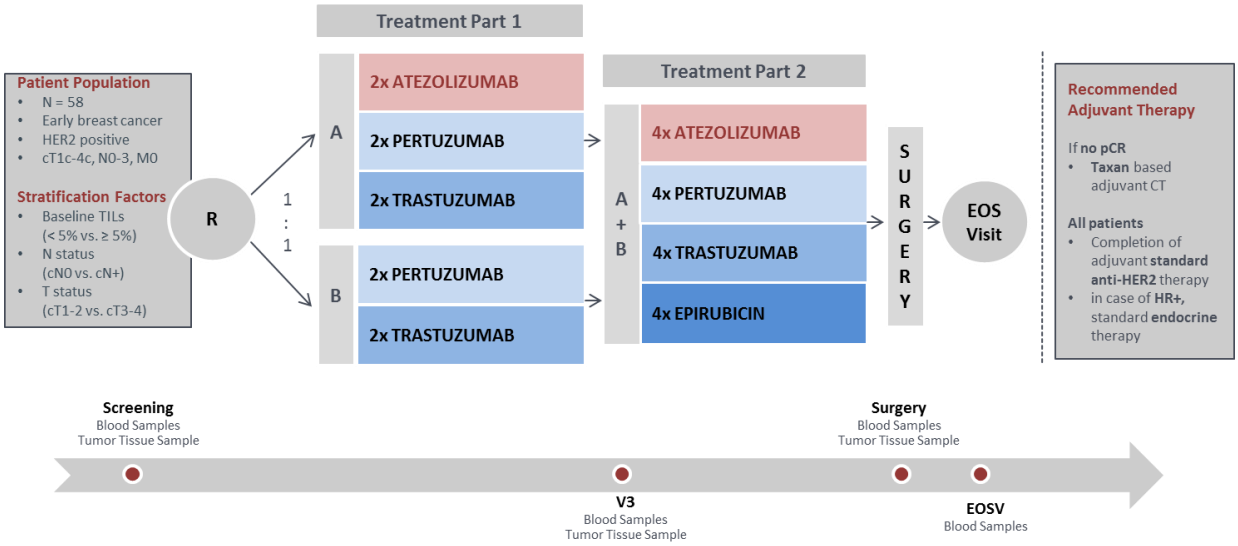
10 Study Design

10.1 Overall Description of Study Design

ABCSG 52 is an open-label, two-arm, randomized, single-stage phase II study of atezolizumab in combination with dual HER2 blockade (trastuzumab and pertuzumab) and epirubicin as neoadjuvant immunochemotherapy in patients with HER2-positive, HR positive/negative early breast cancer (please also refer to Figure 1).

Randomization between the two treatment arms is not performed for efficacy comparison purposes, but for investigating predictive biomarkers for atezolizumab induced biomarker changes.

Figure 1 Study Design



58 patients will be randomized at Austrian trial sites.

Patients will be randomized in a 1:1 ratio to receive either

- 2 cycles of atezolizumab q3w + 2 cycles of pertuzumab q3w and trastuzumab q3w (arm A)
- or 2 cycles of pertuzumab q3w and trastuzumab q3w (arm B)

in treatment part 1.

Treatment part 2 (consisting of 4 cycles of atezolizumab q3w, pertuzumab q3w, trastuzumab q3w and epirubicin q3w) will apply to all patients regardless of previous treatment assignment.

10.2 Study Timetable

Estimated recruitment period: approximately 18 months

Estimated study duration (per patient): approximately 6-8 months

Estimated study duration (overall): approximately 26 months

Estimated First Patient In: QIV 2019

Estimated Last Patient - Last Visit: QI 2022

10.3 Trial Sites

It is planned that approximately 8 Austrian trial sites will participate in this study.

10.4 Study Phases

The study consists of 4 different phases which apply to both arms A and B:

- Screening Phase
- Treatment Phase (comprising treatment part 1 and treatment part 2)
- Surgery Visit
- EOSV

10.5 **Screening Phase**

The screening phase is the time between the date a patient provides written informed consent and the time the patient completes randomization. Before any study specific assessments and procedures are performed, the investigator has to inform and obtain written informed consent from the patient. Procedures that are part of standard of care may occur before written informed consent is obtained.

After the patient has signed the informed consent form (ICF), a unique patient identifier is assigned when the patient is screened in the centralized web-based screening and randomization system. Further details on the process of the screening procedures will be provided in a study specific manual.

During the screening phase, only AEs deemed to be serious (SAEs) and related to protocol mandated, not routinely performed procedures, have to be reported.

Determination of patient eligibility will be performed during the screening phase. Mandatory data collection and procedures are outlined in section 11 (Study Assessments and Procedures) and section 21 (Schedule of Assessments).

In order to participate in the trial, a patient must fulfill all inclusion criteria and must not meet any of the exclusion criteria. Furthermore, a patient will need to consent for study participation and to the collection, storage and analysis of her blood, tumor tissue and stool samples for translational research as specified in section 13 (Translational Research Samples).

Prior to randomization, a representative tumor tissue block must be transmitted to a central sample repository and feedback of central TIL assessment must be available prior to randomization. Further details on the biosampling process will be provided in a study specific manual.

10.5.1 Re-Screening Procedures

Patients that initially screen-fail for the study may be permitted to re-screen one time under the following circumstances:

- Only in case the 28-day screening window (as well as applicable timelines within this window as outlined in the Schedule of Assessments, section 21) cannot be met for at least one of the given assessments and procedures
- Consent process should be repeated in case a new ICF version has been made available to the site in the meantime
- All screening procedures need to be available in the timeframe as outlined in section 21 (Schedule of Assessments) and might have to be repeated in case of re-screening
- Patients must meet all inclusion and none of the exclusion criteria at the time of re-screening in order to qualify for the study
- The initially assigned unique patient identifier will remain the same throughout the study participation (i.e. also for re-screening)

10.6 **Randomization Procedures**

Randomization will be done using a centralized web-based randomization system. Patients will be randomized 1:1 to either treatment arm based on a minimization algorithm including the three stratification criteria.

Patients will be stratified according to:

1. Baseline TILs: < 5 % vs. ≥ 5 %
2. HR status: HR+ vs. HR-
3. Prognostic stage: ≤ IIA vs. ≥ IIB (according to AJCC v.8.0 clinical prognostic stage groups, refer to section 23.3, Appendix III)

Note: Patients will not be replaced in case of patient withdrawals.

10.6.1 Procedures for Handling Patients Incorrectly Screened or Randomized or Initiated on Study Treatments

Patients who fail to meet the eligibility criteria should not, under any circumstances, be randomized or receive study treatment. There can be no exceptions to this rule.

In case a randomized patient does not meet the eligibility criteria and patient safety is concerned, the study sponsor has to be informed immediately, and a decision regarding actions to be taken with study treatment will be made in consultation with the responsible Medical Monitor (MM). For details refer to section 17.6 (Trial administrative structure).

10.7 **Treatment Phase**

The treatment phase is divided into treatment part 1 and treatment part 2.

For treatment part 1, the site will obtain the patient's treatment assignment (arm A or B) upon randomization via the centralized web-based screening and randomization system. Treatment part 2 will apply to all patients regardless of previous treatment assignment and no further action in the screening and randomization system is triggered.

As this is an open-label trial, treatment assignments will not be blinded. Initiation of study treatment on V1 is due within a maximum of 10 days after the day of randomization.

If screening assessments (excluding laboratory safety assessments) occur ≤ 7 days and screening laboratory safety assessments occur ≤ 3 days for laboratory (safety) assessment prior to V1, then they may serve as V1 assessments also and do not need to be repeated.

For details on the study treatments refer to section 12 (Study Treatments).

10.8 **End of Treatment (EOT)**

Date of last dose of neoadjuvant study treatment, irrespective if the patient completed study treatment or stopped study treatment earlier than scheduled. For details on permanent discontinuation of study treatment at an early stage of the trial refer to section 12.6 (Early Discontinuations of Study Treatments).

10.9 **Salvage Surgery**

Patients whose tumor assessment reveals disease progression at any point in time during the study should be treated according to investigator's decision and standard of care. In this case, salvage surgery can be an option and if performed should be documented in the eCRF. In case of salvage surgery, protocol specified timelines do not apply and the appropriate schedule is specified as per investigator's decision. However, EOSV has to be performed 7-42 days after salvage surgery, but at least 42 days after last dose of neoadjuvant study treatment and prior to start of adjuvant treatment.

Refer to section 10.9 (Appendix VII) for details on tumor size assessment as well as section 11.9 (Disease Monitoring) for details on the correct procedure in case of disease progresson.

Tumor surgery and lymph node dissection should be conducted according to institutional standards and international guidelines (St. Gallen, NCCN, ESMO, S3-Leitlinie Mammakarzinom).

10.10 Curative Surgery

Curative surgery has to be performed in all patients following completion of 6 cycles of neoadjuvant study treatment. Surgery should be performed within 28-49 days from last dose of neoadjuvant study treatment, unless an ongoing adverse event would require surgery to be delayed. In case of premature treatment discontinuation (eEOT), surgery should be performed within 28-49 days from last dose of study treatment.

After completion of neoadjuvant study treatment, breast tumor surgery and adequate lymph node surgery (sentinel biopsy or axillary dissection) should be conducted according to institutional standards and international guidelines (St. Gallen, NCCN, ESMO, S3-Leitlinie Mammakarzinom). Whether a patient is eligible for breast conserving surgery will be determined by the patient's surgeon.

Note: The date of the surgery visit correlates with the day of surgery.

10.11 End of Study Visit (EOSV)

All patients (regardless of premature discontinuation or end of treatment according to protocol) will complete the study after a last visit taking place within 7-42 days after curative (or if applicable salvage) surgery, but at least 42 days after last dose of neoadjuvant study treatment and prior to start of adjuvant treatment.

If no surgery is performed, for whatever reason, the EOSV will take place at least 49-91 days after the last dose of neoadjuvant study treatment. This applies also to any patient who discontinues neoadjuvant study treatment prematurely (eEOT). All study assessments to be performed during the EOSV should be completed as outlined in section 21 (Schedule of Assessments).

10.12 Overall End of Study

The end of study is reached after formal closure of all study sites and database closure.

10.13 Adjuvant Chemotherapy

Planned adjuvant treatment has to be documented in the eCRF at the EOSV and the decision on the choice of adjuvant treatment is at the discretion of the investigator. However, following treatment plans are recommended after completion of study treatment and following the EOSV:

- In case no pCR (ypT0/is, ypN0) was achieved, taxan-based adjuvant chemotherapy is recommended
- Completion of adjuvant standard anti-HER2 therapy and in case of hormone receptor positive patients, standard endocrine therapy is recommended

11 Study Assessments and Procedures

11.1 Informed Consent

Informed consent form (ICF) may be obtained greater than 28 days before randomization; it must, however be obtained prior to any protocol requested assessment and procedure (i.e. Screening Phase) which is not performed as part of standard of care.

Signed and dated ICFs for enrolled patients and for patients who are not subsequently screened or randomized will be maintained at the study site. All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before randomization.

11.2 Demographic Data and Medical History

Demographic data include age at randomization, gender at birth and at randomization, self reported race/ethnicity and menopausal status and will be collected during the screening phase (within 28 days prior to randomization).

Premenopausal (including perimenopausal) and postmenopausal women are included in this study. Patients may be considered postmenopausal in case one of the following criteria applies:

- prior bilateral ovariectomy/oophorectomy OR
- age ≥ 60 years OR
- age < 60 years with intact uterus and amenorrhoeic for ≥ 12 consecutive months OR
- age < 60 years hysterectomized and FSH and plasma oestradiol levels in the postmenopausal range according to local policies at the time of randomization

If none of the above mentioned criteria fully applies, the patient may be judged as premenopausal (including perimenopausal) according to local practice. However, in case of any doubts, investigator's judgement on menopausal status is pivotal and has to be documented in patient's notes.

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and smoking history and will be collected during the screening phase (within 28 days prior to randomization).

11.3 Vital Signs / Physical Examination / ECOG performance status

Assessment of **vital signs** at screening (within 28 days prior to randomization) and subsequent visits according to local practice has to be performed including at least diastolic and systolic blood pressure, body temperature and resting pulse rate. Vital signs should also be determined during and after the administrations, if clinically indicated.

Physical examination at screening (within 28 days prior to randomization) and subsequent visits according to local practice including height (only at screening) and body weight has to be performed. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Careful attention must be paid to the breast and the assessment of regional lymph nodes as well as cardiovascular symptoms. Any clinically significant abnormalities identified at screening have to be recorded as Medical History in the eCRF, any clinically significant new or worsened abnormalities assessed at subsequent visits have to be recorded as (S)AE in the respective Adverse Events eForms of the eCRF and reported via SAE reporting form if serious criteria are met.

Determination of **ECOG performance status** (refer to section 23.2, Appendix II) at screening (within 28 days prior to randomization) and subsequent visits is required.

11.4 **ECG**

A 12-lead ECG is required at screening (within 28 days prior to randomization) and for subsequent visits as clinically indicated. ECGs for each patient should be obtained from the same machine wherever possible. ECG recordings must be performed after the patient has been resting in a supine position for at least 5 minutes.

All ECGs deemed abnormal should be assessed by the investigator as to whether they are clinically significant. If there is a clinically significant abnormal finding, the investigator will record it as an AE on the respective eCRF. The original ECG traces must be stored in the patient medical record as source data. During the screening phase, clinically significant abnormal findings should be documented as part of the medical history.

11.5 **ECHO / MUGA**

ECHO and/or MUGA assessment is required at screening (within 28 days prior to randomization), at V3 (-7 days to 0 days) prior to study treatment administration and at the surgery visit (-14 to 0 days) prior to surgery. ECHO is the preferred method. Additional assessments to be performed as clinically indicated. At screening, patients with < 55 % LVEF are not eligible for study participation. During treatment, patients with < 50 % LVEF have to discontinue study treatment (eEOT).

11.6 **Laboratory (Safety) Assessment**

Screening laboratory assessments must be performed within 28 days prior to randomization and for subsequent visits prior to study treatment administration (-3 to 0 days) as well as prior to the surgery visit (-3 to 0 days).

Hematology assessments include hemoglobin, red blood cell (RBC) count, platelet count, hematocrit, white blood cell (WBC) count, absolute differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils and basophils) and should be performed at each visit (except for EOSV) and when clinically indicated.

Coagulation assessment via determination of activated partial thromboplastin time (aPTT) and international normalized ratio (INR) will be performed at screening and as clinically indicated at subsequent visits. Patients receiving therapeutic anticoagulation are eligible for study participation; however, coagulation assessments (INR and aPTT) are to be performed according to local practice.

Blood chemistry assessments include sodium, potassium, chloride, calcium, fasting glucose, blood urea nitrogen (BUN) or urea, creatinine and creatinine clearance, total bilirubin, alkaline phosphatase (ALP), alanine transaminase (ALT/GPT), aspartate transaminase (AST/GOT), gamma glutamyltransferase (GGT), lactic dehydrogenase (LDH), serum amylase and serum lipase at each visit (except for EOSV) and when clinically indicated.

Note: Prior to randomization, serum creatinine must be ≤ 1.5 x institutional ULN and creatinine clearance ≥ 50 mL/min (calculated using the Cockcroft-Gault formula).

TSH, (free T3 (or total T3), free T4)* have to be assessed at screening, V3 (-7 days) prior to study treatment administration and at the surgery visit (-14 days) prior to surgery.

***Note:** Free T3 (or total T3 for sites where free T3 is not assessed) and free T4 have to be assessed, only if abnormalities in TSH levels occur.

Urinalysis including pH, specific gravity, glucose, protein, ketones and blood to be performed at screening and as clinically indicated at subsequent visits.

Pro-brain natriuretic peptide (**Pro-BNP**) assessment should be performed at screening and at V3 (-3 to 0 days) prior to treatment administration.

11.7 Pregnancy Test

Pregnancy tests on blood or urine samples to be performed for women of childbearing potential within 28 days prior to randomization and on V1 (unless screening pregnancy test ist performed ≤ 7 days prior to study treatment start) of the study prior to commencing treatment. Afterwards, pregnancy tests will be performed on a regular schedule (e.g. on day 1 of each treatment cycle) but at least monthly. If results are positive the patient is ineligible/must be discontinued from study treatments. In the event of a suspected pregnancy during the study, the test should be repeated. In case of confirmed pregnancy, refer to section 16.10.

11.8 Tumor Assessments

Screening tumor assessments must be performed within 28 days prior to randomization.

Clinical tumor assessment (by palpation) will be performed at each visit (except for EOSV) according to standard of care.

Mammography will be performed at screening and as clinically indicated at subsequent visits according to standard of care. At screening, a bilateral mammography has to be performed.

Breast ultrasound and ultrasound of regional nodes will be performed at screening, at V3 (-7 to 0 days) prior to study treatment administration and at least 21 days after the last dose of neoadjuvant study treatment but prior to surgery according to modified RECIST (refer to section 23.7, Appendix VII). Breast ultrasound and ultrasound of regional nodes has to be performed according to standard of care.

MRI assessment will be performed at screening, at V3 (-7 to 0 days) prior to study treatment administration and at least 21 days after the last dose of neoadjuvant study treatment but prior to surgery according to modified RECIST (refer to section 23.7, Appendix VII). MRI field strength and sequence according to the I-SPY 2 trial [73] should be used: 1.5T or 3T MRI system using a fat-suppressed single-shot echo planar imaging sequence with b-values of 0 and 800 s/mm2 for diffusion-weighted imaging (DWI), followed by a T1-weighted sequence for dynamic contrast-enhanced MRI (DCE-MRI).

PET assessment will be performed at screening and at V3 (-7 to 0 days) prior to study treatment according to modified PERCIST (refer to section 23.8, Appendix VIII).

11.9 Disease Monitoring

Disease monitoring according to modified RECIST (refer to section 23.7, Appendix VII) will be performed at screening, at V3 (prior to study treatment administration) as well as at surgery visit.

Disease monitoring according modified PERCIST (refer to section 23.8, Appendix VIII) will be performed at screening, at V3 (prior to study treatment administration).

Please note the following in case of disease progression while on study treatment:

- In case of disease progression after 2 cycles of neoadjuvant study treatment (treatment part 1), patient may continue with neoadjuvant study treatment (treatment part 2) as per investigator's decision
- In case of disease progression during treatment part 1 (prior to administration of cycle 2 of study specific neoadjuvant treatment), patient may skip treatment part 1 and continue with treatment part 2 as per investigator's decision
- In case of disease progression during treatment part 2, patient has to be set eEOT
- In case salvage surgery is performed, patient has to be set eEOT

11.10 Translational Research Samples

Screening tumor tissue block must be transmitted to a central sample repository and feedback on central TIL assessment must be available prior to randomization. Additionally, tumor tissue will be collected at V3 (-7 to 0 days) prior to study treatment administration as well as at surgery. Tumor tissue from surgery has to be provided in case of curative or salvage surgery.

Further research blood samples (whole blood, plasma and serum) have to be obtained at screening (within 28 days prior to randomization), at V3 prior to study treatment administration, at the surgery visit prior to surgery and at the EOSV.

Stool sample has to be obtained at screening (within 28 days prior to randomization). In case stool sample has not been collected during screening, it has to be collected latest prior to first administration of neoadjuvant study treatment.

For further details on blood, stool and tissue sampling procedures, refer to section 13 (Translational Research Samples Procedures) as well as the study specific manual.

11.11 Patient Reported Outcomes (PROs)

For details regarding PRO assessments, refer to section 14 (Patient Reported Outcomes, PROs).

11.12 Surgical morbidity and mortality

Assessment of surgical morbidity, mortality and general complications according to Clavien Dindo (refer to section 23.5, Appendix V) should be documented at the EOSV. This is only applicable for patients who underwent surgery.

11.13 Surgical Data Collection

For details regarding the surgical data collection, refer to section 15 (Surgical Data Collection).

11.14 (Serious) Adverse Events

(S)AEs have to be reported after the patient has signed the informed consent until 42 days after the last dose of neoadjuvant study treatment.

Note: During the screening phase only SAEs deemed related to protocol mandated and not routinely performed procedures have to be reported. AEs fulfilling the criteria for expedited reporting have to be treated according to the reporting procedures described in section 16 (Safety Instructions and Monitoring) including a submission to the study sponsor within 24 hours of awareness.

For details regarding (Serious) Adverse Events reporting and definitions, refer to section 16 (Safety Instructions and Monitoring).

11.15 Restrictions during the Study

11.15.1 Contraception

Women of childbearing potential must agree to remain abstinent or use adequate contraception that result in a failure rate < 1 % per year during the study treatment and for a period of 7 months following the last administration of study drug. Adequate contraception is defined as one highly effective form (abstinence, (fe)male sterilization) OR two effective forms (e.g. non-hormonal IUD and condom / occlusion cap with spermicidal foam / gel / film / cream / suppository). Abstinence is only acceptable, if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

11.15.2 Concomitant Medications

Any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal medicines, nutritional supplements) and treatments (with the exception of surgery related medication e.g. anesthetics) will be recorded from 28 days prior to randomization up until the surgery visit. In case no surgery is performed, concomitant medication has to be recorded additionally at the EOSV.

The following medications are permitted on the study:

Permitted Medications

a) Therapeutic anticoagulation therapy is permitted. However, coagulation assessments (INR and aPTT) are to be performed according to local practice
b) Patients may receive live, attenuated influenza vaccination if individual risk-benefit-assessment leads to investigator's decision that harmful effects would be otherwise anticipated during study participation
c) Inhaled corticosteroids for chronic obstructive pulmonary disease
d) Mineralocorticoids (e.g., fludrocortisone)
e) Low-dose corticosteroids for patients with orthostatic hypotension or adrenocortical insufficiency
f) Bisphosphonates for the prevention of skeletal events
   Note: Patients who are receiving denosumab must be willing and able to receive a bisphosphonate instead while on study
g) Systemic corticosteroids and anti−TNF-α agents may also attenuate potential beneficial immunologic effects of treatment with atezolizumab but may be administered at the discretion of the investigator. If feasible, alternatives to these agents should be considered
h) In case of administration-related reactions (ARRs), symptoms may be treated with an analgesic/antipyretic such as meperidine or paracetamol, or an antihistamine such as diphenhydramine. Serious reactions may be treated with supportive therapy such as oxygen, beta-agonists and corticosteroids
i) Angiotensin converting enzyme inhibitor or angiotensin receptor blocker and beta-blocker for treatment of cardiac failure
j) Anti-diarrheal medication such as loperamid in case of diarrhea

Prohibited and Cautionary Medication

The following medications are prohibited on the study:

a) No other concurrent anti-cancer therapy (chemotherapy, hormonal therapy, immunotherapy, radiotherapy, biological therapy or other novel agent), including investigational agents is permitted during the course of the study treatment period for any patient
b) Investigational therapy other than the therpy investigated in this study is prohibited during the study
c) Patients must not receive live, attenuated vaccine within 4 weeks prior to Cycle 1 Day 1 (= V1) or at any time during the study and within 5 months after the last dose of study treatments
   Note: Patients may receive influenza vaccination if individual risk-benefit-assessment leads to investigator's decision that harmful effects would be otherwise anticipated during study participation
d) Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity
e) RANKL inhibitor (denosumab)
f) Immunomodulatory agents, including but not limited to interferons or IL-2, during the entire study; these agents could potentially increase the risk for autoimmune conditions when received in combination with atezolizumab

g) Immunosuppressive medications, including but not limited to cyclophosphamide, azathioprine, methotrexate, and thalidomide; these agents could potentially alter the activity and the safety of atezolizumab
h) Use of steroids to premedicate patients for whom CT scans with contrast are contraindicated (i.e., patients with contrast allergy or impaired renal clearance); in such patients, MRIs of the chest, abdomen, and pelvis with a non-contrast CT scan of the chest must be performed
i) In addition, patients should not receive other immunomodulatory agents for 10 weeks after atezolizumab discontinuation.
j) Metamizole (dipyrone) is prohibited in treating atezolizumab associated infusion-related reactions, due to its potential for causing agranulocytosis

Patients have to be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation of the investigator. Any medications, with the exceptions noted above, which are considered necessary for the patient's welfare, and which are believed not to interfere with study treatments, may be given at the discretion of the investigator. The medications, the doses, dates, relation to AE and indication for use should be recorded in the patient’s medical records and appropriate section of the eCRF.

12 Study Treatments

12.1 Treatment Schedule

IMP administered in this study is atezolizumab (treatment part 1 and part 2), pertuzumab (treatment part 1) and trastuzumab (treatment part 1).

Atezolizumab will be provided by Roche Austria GmbH free of charge for patients randomized to arm A and arm B for the entire treatment phase:

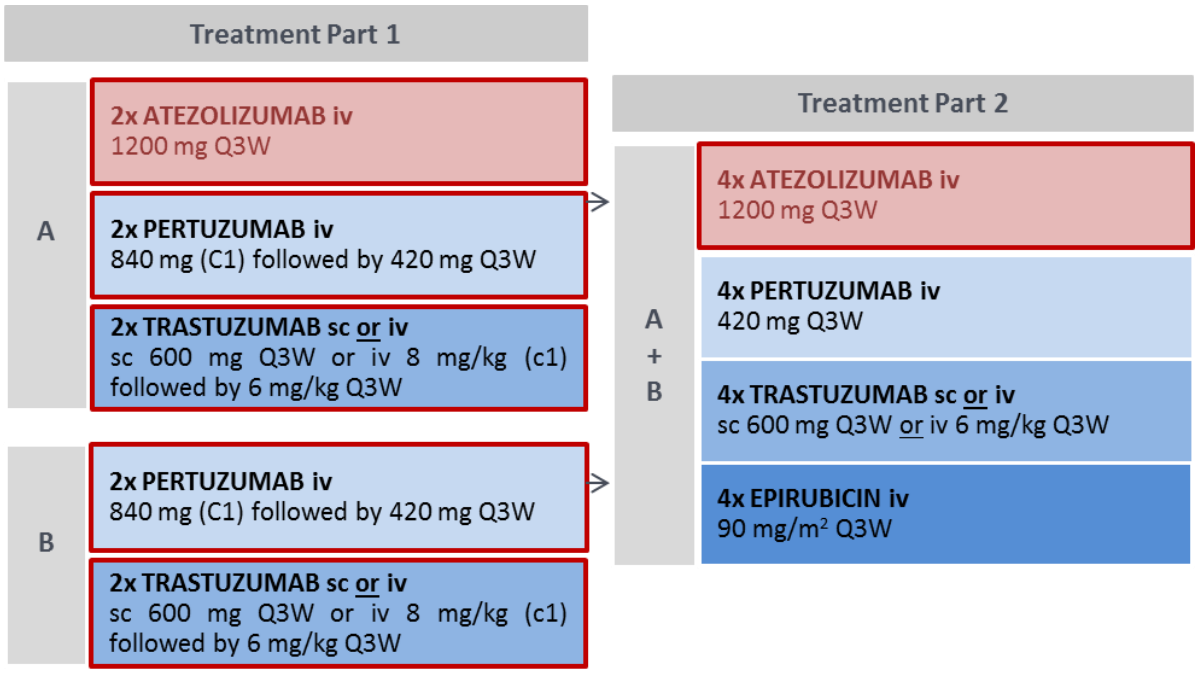
- only arm A patients receive atezolizumab for treatment part 1
- both arm A and arm B patients receive atezolizumab for treatment part 2

Furthermore, pertuzumab and trastuzumab for treatment part 1 for both arm A and arm B patients will be provided by Roche Austria GmbH free of charge.

Commercially available background treatments pertuzumab (treatment part 2), trastuzumab (treatment part 2) and epirubicin (treatment part 2) will be used.

Figure 2 Treatment Schedule

Note: red circled items are defined as IMPs. Others are defined as background treatments.



For treatment part 1 both arm A and arm B patients will receive 2 3-week cycles of pertuzumab (starting with 840 mg iv on cycle 1, followed by 420 mg iv for the subsequent cycle) and 2 3-week cycles of trastuzumab (starting with 600 mg sc or 8 mg/kg iv on cycle 1, followed by 600 mg sc or 6 mg/kg iv for the subsequent cycle). Arm A patients will additionally receive 2 3-week cycles of atezolizumab (1200 mg iv per cycle).

For treatment part 2, both arm A and arm B patients will receive 4 3-week cycles of atezolizumab (1200 mg iv per cycle), 4 3-week cycles pertuzumab (420 mg iv per cycle), 4 3-week cycles trastuzumab (600 mg sc or 6 mg/kg iv per cycle) as well as 4 3-week cycles of epirubicin (90 mg/m² per cycle).

Also refer to Figure 2 for an overview of the study treatments and dosing schedule and note that all study treatments of each cycle will be administered on the same day. If atezolizumab is administered (i.e. arm A patients in treatment part 1 and arm A as well as arm B patients in

treatment part 2), study treatment administration should start with atezolizumab. The further order of study treatment administration per cycle is to be performed according to standard of care.

Additionally, it is recommended that the initial dose of atezolizumab is delivered over 60 (± 15) minutes. Subsequent infusions will be delivered over 30 (± 10) minutes if the previous infusion was tolerated without infusion associated adverse events, or 60 (± 15) minutes if the patient experienced infusion associated adverse event with the previous infusion. It is further recommended to pause at least 30 minutes after the end of atezolizumab infusion to continue with further study treatment administration.

Infusion periods and pauses between administration of trastuzumab, pertuzumab and epirubicin should be performed according to current product information and standard of care.

12.2 **Investigational Medicinal Product (IMP)**

12.2.1 Atezolizumab (treatment part 1 and part 2)

Atezolizumab will be provided by Roche GmbH free of charge for the entire treatment phase (treatment part 1 and treatment part 2). Please refer to Figure 2 for a detailed dosing schedule.

12.2.1.1 Formulation, Packaging, Labeling and Storage

Atezolizumab will be made available as iv formulation.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels fulfill GMP Annex 13 requirements for labelling.

Atezolizumab should be kept at the study site in a locked, secure place under appropriate storage conditions. The labels and/or the current IB specify the appropriate storage conditions.

Atezolizumab should be prepared, stored and applied according to local standard and according to the information as provided in the current IB.

12.2.2 Pertuzumab (treatment part 1)

Pertuzumab will be provided by Roche GmbH free of charge for the entire treatment part 1. Please refer to Figure 2 for a detailed dosing schedule.

12.2.2.1 Formulation, Packaging, Labeling and Storage

Pertuzumab will be made available as iv formulation.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels fulfill GMP Annex 13 requirements for labelling.

Pertuzumab should be kept at the study site in a locked, secure place under appropriate storage conditions. The labels and/or the current product information specify the appropriate storage conditions.

Pertuzumab should be prepared, stored and applied according to local standard and according to the information as provided in the current product information.

12.2.3 Trastuzumab (treatment part 1)

Trastuzumab will be provided by Roche GmbH free of charge for the entire treatment part 1. Please refer to Figure 2 for a detailed dosing schedule.

12.2.3.1 Formulation, Packaging, Labeling and Storage

Trastuzumab will be made available as iv as well as sc formulation.

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels fulfill GMP Annex 13 requirements for labelling.

Trastuzumab should be kept at the study site in a locked, secure place under appropriate storage conditions. The labels and or and the current product information specify the appropriate storage conditions.

Trastuzumab should be prepared, stored and applied according to local standard and according to the information as provided in the current product information.

12.3 **Background Treatments**

12.3.1 Pertuzumab, trastuzumab and epirubicin (treatment part 2)

Commercially available pertuzumab, trastuzumab and epirubicin will be used for treatment part 2. Please refer to Figure 2 for a detailed dosing schedule.

12.3.1.1 Formulation, Packaging, Labeling and Storage

Background treatments should be prepared, stored and applied according to hospital standard and according to the information as provided in the current product information.

12.4 **Toxicity Management**

All study treatments of each cycle will be administered on the same day. If atezolizumab is administered (i.e. arm A patients in treatment part 1 and arm A as well as arm B patients in treatment part 2), study treatment administration should start with atezolizumab. The further order of study treatment administration per cycle is to be performed according to standard of care. Also refer to Figure 2. In case patients experience infusion-related reactions during the administration of any of the study treatments (IMP or background treatments), the continuation of the administration of the affected study treatment as well as any subsequent study treatment administrations of that same cycle may be delayed for a maximum of two days.

In case patients have to permanently discontinue any of the study treatments (IMPs and/or any of the background treatments) patients have to be set eEOT. Also refer to section 12.6 (Early Discontinuation of Study Treatments) for additional guidance in case of eEOT.

In case IMPs [ateozolizumab (treatment part 1 and 2), pertuzumab (treatment part 1), trastuzumab (treatement part1)] and/or any of the background treatments [pertuzumab (treatment part 2), trastuzumab (treatment part 2), epirubicin (treatment part 2)] have to be halted due to toxicitites, all other study treatments have to be halted as well until toxicities have been resolved. In general, the start of a cycle may be delayed for a maximum of ≤ 21 days. In case of a cycle delay of > 21 days, the patient has to be set eEOT. Cycles may be delayed but cannot be skipped.

Dose modifications for study treatment other than those recommended in this section are to be performed as per current product information/IB and according to standard clinical practice.

12.4.1 Atezolizumab (treatment part 1 and 2)

Dose reductions for atezolizumab are not permitted in this study. Patients may temporarily hold study treatment in case of adverse events that require a dose to be held as outlined below.

Toxicities associated or possibly associated with atezolizumab should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be

used to evaluate for a possible immunogenic etiology, if necessary. Although most immune-mediated AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab may not have an immediate therapeutic effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents. The investigator should consider the benefit-risk balance a given patient may be experiencing prior to further administration of atezolizumab.

12.4.1.1 Pulmonary Events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will also have CT scans of the chest performed as clinically indicated.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in Table 4.

Table 4 Management Guidelines for Pulmonary Events, including Pneumonitis

Event	Management
Pulmonary event, Grade 1	• Continue study treatment and monitor closely • Re-evaluate on serial imaging • Consider patient referral to pulmonary specialist
Pulmonary event, Grade 2	• Withhold study treatment • Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment • For recurrent events, treat as a Grade 3 or 4 event
Pulmonary event, Grade 3 or 4	• Permanently discontinue study treatment. • Bronchoscopy or BAL is recommended. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over 1 month.

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.2 Hepatic Events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and

hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in Table 5.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study treatment.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Table 5 Management Guidelines for Hepatic Events

Event	Management
Hepatic event, Grade 1	• Continue study treatment • Monitor LFTs until values resolve to within normal limits or to baseline values
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values **Events of > 5 days' duration:** • Withhold study treatment • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment
Hepatic event, Grade 3 or 4	• Permanently discontinue study treatment • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day oral prednisone • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.3 Gastrointestinal Events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in Table 6.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased CRP, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with 3 to 5 specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Table 6 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	• Continue study treatment • Initiate symptomatic treatment • Endoscopy is recommended if symptoms persist for > 7 days • Monitor closely
Diarrhea or colitis, Grade 2	• Withhold study treatment • Initiate symptomatic treatment • Patient referral to GI specialist is recommended • For recurrent events or events that persist > 5 days, initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day oral prednisone • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment
Diarrhea or colitis, Grade 3	• Withhold study treatment • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy • Initiate treatment with corticosteroids equivalent 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment
Diarrhea or colitis, Grade 4	• Permanently discontinue study treatment • Refer patient to gastrointestinal specialist for evaluation and confirmatory biopsy • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤1 0 mg/day oral prednisone before atezolizumab can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.4 Endocrine Events

Thyroid disorders, adrenal insufficiency, diabetes mellitus and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in Table 7.

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests

(e.g., TSH, growth hormone, luteinizing hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone [ACTH] levels and ACTH stimulation test) and magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 7 Management Guidelines for Endocrine Events

Event	Management
Asymptomatic hypothyroidism	• Continue study treatment • Initiate treatment with thyroid replacement hormone • Monitor TSH weekly
Symptomatic hypothyroidism	• Withhold study treatment • Initiate treatment with thyroid replacement hormone • Monitor TSH weekly • Consider patient referral to endocrinologist • Resume study treatment when symptoms are controlled and thyroid function is improving
Asymptomatic hyperthyroidism	TSH ≥ 0.1 mU/L and <0.5 mU/L: • Continue study treatment • Monitor TSH every 4 weeks TSH < 0.1 mU/L: • Follow guidelines for symptomatic hyperthyroidism
Symptomatic hyperthyroidism	• Withhold study treatment • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed • Consider patient referral to endocrinologist • Resume study treatment when symptoms are controlled and thyroid function is improving • Permanently discontinue study treatment
Symptomatic adrenal insufficiency, Grade 2-4	• Withhold study treatment • Refer patient to endocrinologist • Perform appropriate imaging • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab [a] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding study treatment, permanently discontinue study treatment
Hyperglycemia Grade 1 or 2	• Continue study treatment • Investigate for diabetes. If patient has type 1 diabetes, treat as Grade 3 event. If patient does not have type 1 diabetes, treat as per institutional guidelines

Event	Management
	• Monitor for glucose control
Hyperglycemia, Grade 3 or 4	• Withhold study treatment • Initiate treatment with insulin • Monitor for glucose control • Resume study treatment when symptoms resolve and glucose levels are stable
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold study treatment • Refer patient to endocrinologist • Perform brain MRI (pituitary protocol) • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • Initiate hormone replacement if clinically indicated • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment • For recurrent hypophysitis, treat as a Grade 4 event
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue study treatment • Refer patient to endocrinologist • Perform brain MRI (pituitary protocol) • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • Initiate hormone replacement therapy if clinically indicated

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before study treatment can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.5 Ocular Events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events). Management guidelines for ocular events are provided in Table 8.

Table 8 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	• Continue study treatment • Patient referral to ophthalmologist is strongly recommended • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy • If symptoms persist, treat as a Grade 2 event
Ocular event, Grade 2	• Withhold study treatment • Patient referral to ophthalmologist is strongly recommended • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy • If event resolves to Grade 1 or better, resume study treatment [a]

Event	Management
	• If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment
Ocular event, Grade 3 or 4	• Permanently discontinue study treatment • Refer patient to ophthalmologist • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone • If event resolves to Grade 1 or better, taper corticosteroids ≥ 1 month

[a] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.6 Immune-mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (e.g. BNP) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope.

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy.

All patients with possible myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an ECG, a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated. Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 9.

Table 9 Management Guidelines for Immune-mediated Myocarditis

Event	Management
Immune-mediated myocarditis, Grade 2	• Withhold study treatment • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment
Immune-mediated myocarditis, Grade 3-4	• Permanently discontinue study treatment • Refer patient to cardiologist • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv

Event	Management
	methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids ≥ 1 month

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone or equivalent before study treatment can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.7 Infusion-Related Reactions

No premedication is indicated for the administration of cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) with cycle 1 of atezolizumab may receive premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis. Guidelines for medical management of IRRs during cycle 1 are provided in Table 10. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 10 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	• Reduce infusion rate to half the rate being given at the time of event onset • After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate • If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate
IRR, Grade 2	• Interrupt atezolizumab infusion • Administer aggressive symptomatic treatment (e.g., oral or iv antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, iv fluids) • After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset **Note**: For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs
IRR, Grade 3 or 4	• Stop infusion • Administer aggressive symptomatic treatment (e.g., oral or iv antihistamine, anti-pyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, iv fluids) • Permanently discontinue study treatment

12.4.1.8 Pancreatic Events

Symptoms of abdominal pain associated with elevations of serum amylase and serum lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup

should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in Table 11.

Table 11 Management Guidelines for Pancreatic Events, including Pancreatitis

Event	Management
Amylase and/or lipase elevation, Grade 2	Serum amylase and/or serum lipase > 1.5-2.0 x ULN: • Continue study treatment • Monitor serum amylase and serum lipase weekly • For prolonged elevation (e.g., > 3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone Asymptomatic with serum amylase and/or serum lipase > 2.0-5.0 x ULN: • Treat as Grade 3 event
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold study treatment • Refer patient to gastrointestinal specialist • Monitor serum amylase and serum lipase every other day • If no improvement, consider treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment • For recurrent events, permanently discontinue study treatment
Immune-mediated pancreatitis, Grade 2 or 3	• Withhold study treatment • Refer patient to gastrointestinal specialist • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event resolves to Grade 1 or better, resume study treatment • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment • For recurrent events, permanently discontinue study treatment
Immune-mediated pancreatitis, Grade 4	• Permanently discontinue study treatment • Refer patient to gastrointestinal specialist • Initiate treatment with corticosteroid equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤ 10 mg/day oral prednisone before atezolizumab can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.9 Dermatologic Events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self limited, with or without pruritus. A dermatologist should evaluate

persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in Table 12.

Table 12 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	• Continue study treatment • Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines)
Dermatologic event, Grade 2	• Continue study treatment • Consider patient referral to dermatologist • Initiate treatment with topical corticosteroids • Consider treatment with higher-potency topical corticosteroids if event does not improve
Dermatologic event, Grade 3	• Withhold study treatment • Refer patient to dermatologist • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment
Dermatologic event, Grade 4	• Permanently discontinue study treatment

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤10 mg/day oral prednisone before study treatment can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.10 Neurologic Disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single-agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders are provided in Table 13.

Table 13 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	• Continue study treatment • Investigate etiology
Immune-mediated neuropathy, Grade 2	• Withhold study treatment • Investigate etiology • Initiate treatment as per institutional guidelines • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study

Event	Management
	treatment, permanently discontinue study treatment
Immune-mediated neuropathy, Grade 3 or 4	• Permanently discontinue study treatment • Initiate treatment as per institutional guidelines
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue study treatment • Refer patient to neurologist • Initiate treatment as per institutional guidelines • Consider initiation of corticosteroids equivalent to 1-2 mg/kg/day oral or iv prednisone

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.11 Immune-Related Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. Immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed and a neurologist should be consulted. Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 14.

Table 14 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	• Permanently discontinue study treatment • Refer patient to neurologist • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids ≥ 1 month

12.4.1.12 Renal Events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treateted for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a

renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment. Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in Table 15.

Table 15 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	• Continue study treatment • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values
Renal event, Grade 2	• Withhold study treatment • Refer patient to renal specialist • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment
Renal event, Grade 3 or 4	• Permanently discontinue study treatment • Refer patient to renal specialist and consider renal biopsy • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. But cycle may not be delayed for > 21 days.

12.4.1.13 Immune-mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in .

Event	Management
Immune-mediated myositis, Grade 1	• Continue study treatment • Refer patient to rheumatologist or neurologist • Initiate treatment as per standard of care
Immune-mediated myositis, Grade 2	• Withhold study treatment • Refer patient to rheumatologist or neurologist • Initiate treatment as per standard of care • Consider treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone and convert to 1-2 mg/kg/day oral prednisone or

Event	Management
	equivalent upon improvement • If cortocoisteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding immunosuppressive agent • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment
Immune-mediated myositis, Grade 3	• Withhold study treatment • Refer patient to rheumatologist or neurologist • Initiate treatment as per standard of care • Respiratory support may be required in more severe cases • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g. cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, resume study treatment [a] • If event does not resolve to Grade 1 or better while withholding study treatment, permanently discontinue study treatment • For recurrent events, treat as Grade 4 event
Immune-mediated myositis, Grade 4	• Permanently discontinue study treatment • Refer patient to rheumatologist or neurologist • Initiate treatment as per standard of care • Respiratory support may be required in more severe cases • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day iv methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g. cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); convert to 1-2 mg/kg/day oral prednisone or equivalent upon improvement • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent • If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month

[a] If corticosteroids have been initiated, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab can be resumed. But cycle may not be delayed for > 21 days.

12.4.2 Pertuzumab (treatment part 1)

Dose reductions for toxicity are not permitted. Pertuzumab doses may be delayed due to toxicities. Please note, that in case of a cycle delay of > 21 days, the patient has to permanently discontinue entire study treatment and has to be set eEOT.

12.4.2.1 Infusion-related reactions, hypersensitivity reactions and anaphylaxis

Pertuzumab has been associated with infusion reactions. Close observation of the patient during and for 60 minutes after the first infusion and during and for 30 minutes following subsequent

infusions of pertuzumab is recommended. If a significant infusion reaction occurs, the infusion should be slowed down or interrupted and appropriate medical therapies should be administered as per local practice. Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be considered in patients with severe infusion reactions. This clinical assessment should be based on the severity of the preceding reaction and response to administered treatment for the adverse reaction.

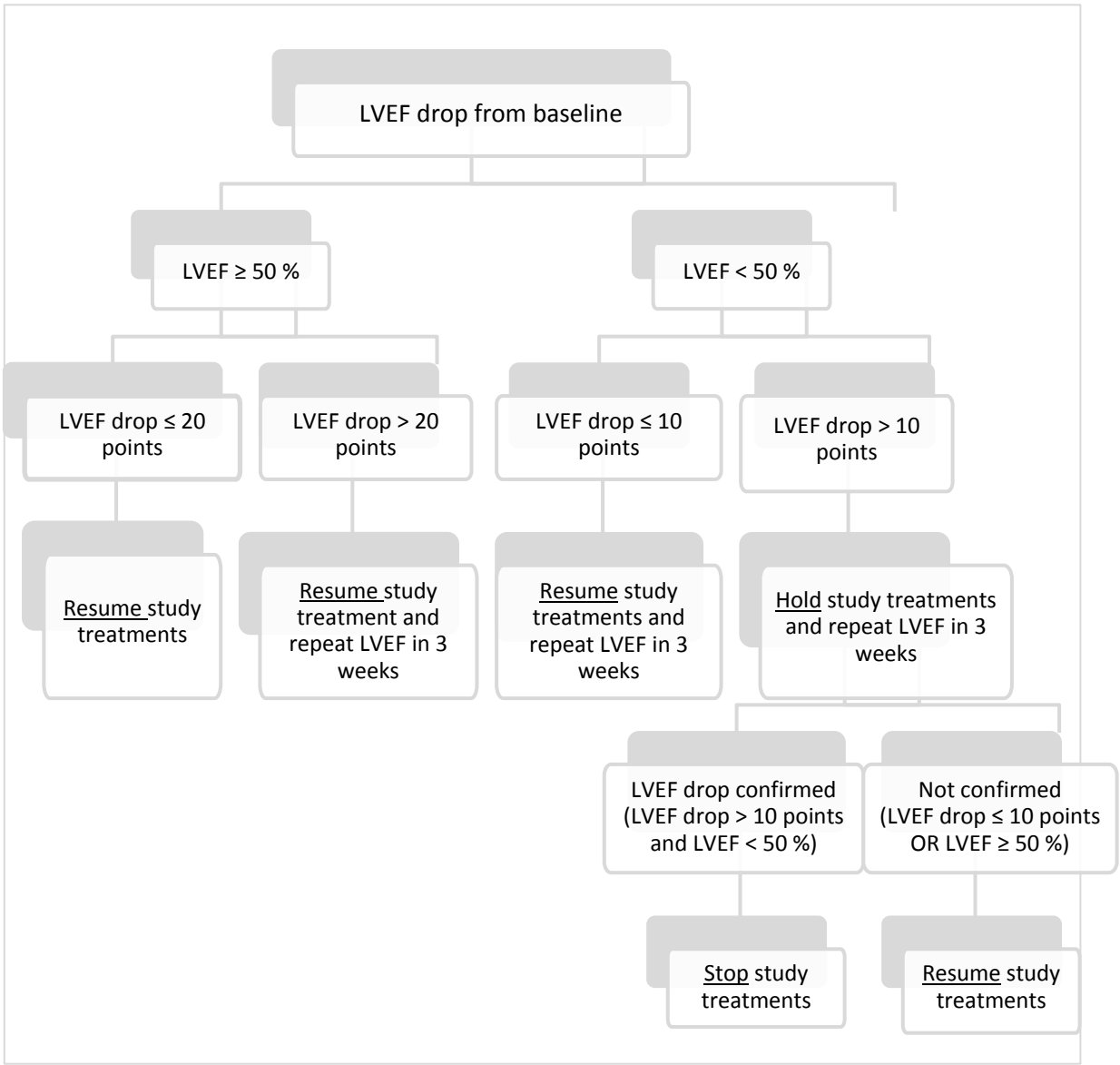
Patients should be observed closely for hypersensitivity reactions. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. Pertuzumab is contraindicated in patients with known hypersensitivity to pertuzumab or to any of its excipients.

12.4.2.2 Left ventricular dysfunction

Cardiac exclusion criteria are specified in this study protocol and have to be closely followed. Additionally, LVEF is assessed prior to first administration of pertzumab and at regular intervals during study treatment (refer to section 21, Schedule of Assessments) to ensure that LVEF is within the institution's normal limits.

For further guidance on the monitoring of cardiac events, refer to Figure 3.

Figure 3 Asymptomatic decline in LVEF: algorithm for continuation and discontinuation of study treatments



12.4.3 Trastuzumab (treatment part 1)

Dose reductions for toxicity are not permitted. Trastuzumab doses may be delayed due to toxicities. Please note, that in case of a cycle delay of > 21 days, the patient has to permanently discontinue entire study treatment and has to be set eEOT.

12.4.3.1 Infusion/Administration-related reactions (ARRs) and hypersensitivity

ARRs are defined as systemic 'infusion-related reactions' associated with iv administration of trastuzumab and systemic reactions associated with sc administration. Local injection site reactions are excluded from this definition.

Infusion/ARRs and hypersensitivity are known to occur with the administration of trastuzumab. Pre-medication may be used to reduce risk of occurrence of ARRs. ARRs include all systemic reactions related to the administration of trastuzumab (both iv and sc).

ARRs may be clinically difficult to distinguish from hypersensitivity reactions. Serious ARRs to trastuzumab including dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation and respiratory distress, supraventricular tachyarrhythmia and urticaria have been reported. Patients should be observed for ARRs. Interruption of an iv infusion may help to control such symptoms and the infusion may be resumed when symptoms abate. Refer to section 11.15.2 (Concomittant Medications) for details on the symptomatic treatment of ARRs.

12.4.3.2 Cardiac dysfunction

Patients treated with trastuzumab are at increased risk of developing CHF NYHA Class II-IV or asymptomatic cardiac dysfunction. In addition, caution should be exercised in treating patients with increased cardiac risk (e.g., hypertension, documented coronary artery disease, CHF, diastolic dysfunction, older age). Patients who receive anthracycline after stopping trastuzumab may also be at increased risk of cardiac dysfunction. Cardiac exclusion criteria are specified in this study protocol and have to be closely followed and additional cardiac monitoring is to be performed as per the Schedule of Assessments (refer to section 21) and as clinically indicated .

Refer to Figure 3 for the management of asymptomatic cardiac dysfunction. Patients who develop asymptomatic cardiac dysfunction may benefit from more frequent monitoring (e.g. every 6-8 weeks). If patients have a continued decrease in left ventricular function, but remain asymptomatic, the physician should consider discontinuing therapy if no clinical benefit of trastuzumab therapy can be detected.

If symptomatic cardiac failure develops during trastuzumab therapy, it should be treated with standard medications for heart failure (refer to section 11.15.2, Concomitant Medication).

12.4.3.3 Pulmonary adverse drug reactions

Severe pulmonary events have been reported with the use of trastuzumab (iv formulation) in the post-marketing setting. These events have occasionally resulted in fatal outcome and may occur as part of an IRR/ARR or with a delayed onset. In addition, cases of interstitial lung disease including lung infiltrates acute respiratory distress syndrome, pneumonia, pneumonitis, pleural effusion, respiratory distress, acute pulmonary oedema and respiratory insufficiency have been reported. Risk factors associated with interstitial lung disease include prior or concomitant therapy with other anti-neoplastic therapies known to be associated with it such as taxanes, gemcitabine, vinorelbine and radiation therapy.

12.4.3.4 Benzyl alcohol

When administering trastuzumab to a patient with a known hypersensitivity to benzyl alcohol, trastuzumab should be reconstituted with water for injection. In this case, only one dose per

trastuzumab vial should be used. The reconstituted solution should be used immediately. Any unused portion must be discarded.

12.4.4 Background Treatments

Toxicity Management of background treatments trastuzumab (treatment part 2), pertuzumab (treatment part 2) and epirubicin (treatment part 2) has to be performed according to the current product information and/or institutional standard.

12.5 **Treatment Compliance**

The administration of IMP atezolizumab (treatment part 1 and part 2), pertuzumab (treatment part 1) and trastuzumab (treatment part 1) as well as background treatments trastuzumab (treatment part 2), pertuzumab (treatment part 2) and epirubicin (treatment part 2) have to be recorded in the appropriate sections of the eCRF.

12.5.1 IMP Drug Accountability

A drug accountability form (inventory and dispensing log) for atezolizumab (treatment part 1 and part 2), pertuzumab (treatment part 1) and trastuzumab (treatment part 1) will be provided by the study sponsor, and must be kept accurate and current by the study site. Following content is mandatory:

- Dates and quantities of atezolizumab/pertuzumab/trastuzumab received
- Date, quantity (number/ lot nb. of preparation) and patient identification number for administered atezolizumab/pertuzumab/trastuzumab
- Initials of the person dispensing atezolizumab/pertuzumab/trastuzumab to the patient

Periodically throughout and at the end of the study, responsible study sponsor staff will conduct an inventory check of all atezolizumab/pertuzumab/trastuzumab supplies. At the end of the study, a final drug accountability review at study site will be conducted.

IMPs must not be used outside the context of this study protocol.

IMPs must not be destroyed or returned prior to completion of monitoring activities in relation to drug accountability. Handover for destruction at the study site has to be adequately documented and confirmed by the investigator/delegate with the respective signature.

Investigator/delegated site staff will be responsible for handling IMPs and completion of associated drug accountability forms. However, the investigator/delegate will be responsible for correct, accurate and complete accountability of all used and unused clinical trial supplies.

12.5.1.1 Background Treatments Drug Accountability

Background treatments for treatment part 2 (pertuzumab, trastuzumab and epirubicin) will be administered at the clinical trial site and commercially available products will be used. Therefore, drug accountability for background treatments of treatment part 2 will not be performed.

12.6 **Early Discontinuations of Study Treatments**

Incorrectly randomized patients may have to discontinue treatment after evaluation of any potential safety concern by the Medical Monitor. Also refer to section 17.6 (Trial Administrative Structure). Continued study assessments according to the protocol (e.g. for surgery visit, EOSV) should be performed even if the study treatment is discontinued.

Patients may be discontinued from study treatment early in the following situations:

- Patient decision
- AE (and e.g., life threatening or other unacceptable toxicity, the discovery of an

unexpected, significant, or unacceptable risk to the patient randomized in the study as per investigator's decision
- Contralateral invasive breast cancer
- Second primary non-breast malignancy
- Severe non-compliance to protocol as judged by the investigator and/ or study sponsor
- In case disease progression leads to salvage surgery (for details also refer to section 11.9, Disease Monitoring)
- The investigator believes that patient is no longer deriving clinical benefit
- Pregnancy
- Informed consent withdrawal
- Death
- Termination of the study by the study sponsor
- In case patients have to permanently discontinue any of the study treatments (IMPs and/or any of the background treatments)

Note: In case patient discontinues study treatment early and proceeds treatment with an alternate, non-study specific neoadjuvant treatment as per investigator's decision, this alternate neoadjuvant treatment as well as subsequent surgery (if performed), should be documented in the eCRF. In case patient not only withdraws from study treatment but withdraws from study participation entirely, such data will not be documented in the eCRF from the point of withdrawal onwards.

12.6.1 Procedures for Discontinuation of a Patient from Study Treatments

Upon discontinuation of a patient from the study treatments, the patient's tumor status should be assessed and, if indicated, disease progression should be confirmed by appropriate assessment and documented at the next patient visit. After discontinuation of study treatments, the investigator should perform the best possible observation(s), test(s) and evaluation(s) as well as give appropriate medication and all possible measures for the safety of the patient. In addition, the main reason and treatment plan at the time of discontinuation should be recorded in the eCRF. Patients will be requested to perform the study visits (surgery visit, EOSV) and study assessments as outlined in the protocol and in section 21 (Schedule of Assessments).

After discontinuation of study treatment at any point in the study, all ongoing AEs or SAEs should be followed until resolution unless, in the investigator's opinion the condition is unlikely to resolve, or the patient has ended the study. .

If an investigator becomes aware of any SAEs, including death, at any time after a patient has completed the study, considering there is a reasonable possibility that the event is causally related to the study treatment, the investigator should notify the study sponsor.

12.7 **Withdrawal from Study / End of Study (EOS)**

At any time, patients are free to discontinue study treatment or withdraw from the study without prejudice to further clinical care. Withdrawal of consent for all study participation will end patient activity in the study.

Reasons for early withdrawal from the study:

- Withdrawal of informed consent
- Patient lost to follow-up
- Death
- Termination of study by study sponsor

If the study is terminated early regardless of the reason for early termination, all applicable data available for the patient on study at the time of termination must be recorded in the eCRF. In terminating the study, the study sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

13 Translational Research Samples

Additional biological sample collection is required for the translational research objective/endpoint as defined in the present study protocol. Please find below a list of samples to be collected per patient during the study.

Sample collections at the respective visits are detailed in section 21, Schedule of Assessments. The samples will be collected, stored and shipped according to procedures provided in a separate study specific manual.

13.1 Blood Sampling

Blood samples for translational research include whole blood, serum and plasma samples. No pre-specification of the evaluated biomarkers is met at study inception due to scientific progress which may lead to the discovery of novel biomarkers during the conduct of the trial.

The blood draw will be performed at 4 time points during the study:

- Screening
- V3 (prior to study drug administration)
- Surgery visit (prior to surgery)
- EOSV

13.2 Tumor Tissue Sampling

Tumor Tissue from FFPE core-needle biopsy of breast tumor measuring at least 3x1 mm must be transmitted to a central sample repository for central TIL assessment once the patient is screened in the web-based screening and randomization system. Feedback on central TIL assessment must be available **prior to randomization**.

Sample shipment to the respective central sample laboratory may only be performed following patient consent and allocation of the study specific patient identification number.

Tumor Tissue will be collected at 3 time points during the study:

- Screening
- V3 (within 7 days prior to visit)
- Surgery visit (tumor tissue from curative or salvage surgery, as applicable)

Note: In case additional tumor tissue material is available, it is encouraged to collect and transmit it to the central biorepository.

13.3 Stool Sampling

A single stool sample per patient has to be collected during screening. If stool sample has not been collected during screening, it has to be collected prior to first administration of neoadjuvant study treatment at the latest.

13.4 Chain of Custody of Biological Samples

A full chain of custody is maintained for all biological samples throughout their lifecycle. The Principal Investigator at each site keeps full traceability of collected biological samples from the patients while in storage at the site until shipment. The sample receiver keeps full traceability and documentation (e.g. receipt of arrival) of the samples while in storage and during use until used up or disposed of or until further shipment. The study sponsor keeps principle oversight of the entire life cycle e.g. through internal procedures, monitoring of study sites and auditing of external laboratory providers.

14 Patient Reported Outcomes (PROs)

The assessment of patient reported outcomes (PROs) in clinical research provides important insights into how therapies affect the daily lives of patients. Patient reports regarding health-related QoL have proven more comprehensive than provider-collected data in breast cancer patients [68].

Because atezolizumab is a new drug with little knowledge of toxicity and impact on quality of life, questionnaires to assess overall quality of life, treatment satisfaction and tolerability symptoms in each of the two study arms will be used.

14.1 EORTC QLQ-C30 and EORTC QLQ-BR45

In this study, patient-reported disease related symptoms and health-related quality of life (HRQoL) will be evaluated using the validated EORTC QLQ-C30 questionnaire and EORTC QLQ BR-45.

The EORTC QLQ-C30 consists of 30 items measuring global health/QoL scale, functioning scales (physical, role, emotional, cognitive, and social functioning scale) and symptom scales/items (fatigue, nausea and emesis, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties). All scales and single items range from 0 to 100. High scores for functioning and global health/QoL scales indicate high/healthy levels of functioning/high QoL, whereas high scores for symptom scales/items indicate a high level of symptoms/problems [69].

The EORTC measurement strategy is to supplement the generic EORTC QLQ-C30 with disease-specific modules. In line with this strategy, all patients should additionally complete the EORTC QLQ-BR45.

The 45-item EORTC QLQ BR45 contains seven multi-item scales to assess body image, sexual functioning, systemic therapy side effects, arm symptoms, breast symptoms, target symptom scale and satisfaction scale and single items to assess sexual enjoyment, future perspective and upset by hair loss. The target symptom scale can be further divided into 3 subscales: endocrine therapy scale, endocrine sexual scale and skin/mucosis scale. All scales and single items range from 0 to 100. A high score for all functioning scales indicates high/healthy level of functioning/high QoL, whereas a high score for symptom scales/items indicates a high level of symptoms/problems [77].

14.2 Administration of PRO Questionnaires

Paper-based EORTC QLQ-C30 and EORTC QLQ-BR45 will be administered at screening (within 28 days prior to randomization), at V3 (prior to administration of study treatments), at the surgery visit (prior to surgery) and at EOSV.

Each trial site should, if possible, allocate the responsibility for the administration of the questionnaires to a specific individual (e.g., a research nurse, study coordinator) and if possible assign a back-up person to cover if that individual is absent. The significance and relevance of the data need to be explained carefully to participating patients so that they are motivated to comply with data collection.

The instructions for completion of the PRO questionnaires are as follows:

- The EORTC QLQ-C30 should be completed before the EORTC QLQ-BR45
- Both questionnaires must be completed prior to any other study procedures (following informed consent) and before discussion of disease progress, if applicable, to avoid biasing the patient's responses to the questions. They must be completed in private by the patient
- The patient should be given sufficient time to complete at their own speed
- Upon completion of the questionnaires, they should be handed back to the person responsible for questionnaires, who should check for completeness and document the information in the eCRF

15 Surgical Data Collection

Following surgery related data have to be collected and documented in the eCRF.

Breast related

1. Patient considered suitable for breast conserving surgery, as assessed at baseline (prior to start of neoadjuvant study treatment)
2. Patient considered suitable for breast conserving surgery, as assessed at the surgery visit (prior to surgery)
3. Planned surgery as assessed at the surgery visit (prior to surgery)
    a. Planned primary surgical treatment (breast conserving surgery/mastectomy)
4. Primary surgery (breast conserving surgery/mastectomy)
    a. Primary surgery performed in new tumor boundaries
    b. Resection status
5. Additional surgery(ies)/ (breast conserving surgery/mastectomy)
    a. Resection status

Axilla related

6. Clinical status of axilla prior to neoadjuvant study treatment (positive/negative)
7. Clinical status of axilla after completion of neoadjuvant study treatment (positive/negative)
8. Sentinel biopsy
9. Sentinel detected
10. Axilla dissection performed

Please note, that these questions will be documented in the respective eCRF sections according to the course of the trial.

16 Safety Instructions and Safety Monitoring

The following safety instruction and guidance for this study is designed to ensure patient safety and will include specific eligibility criteria, safety reporting obligations and monitoring assessments as detailed below. The Principal Investigator is responsible for ensuring that all delegated staff involved in the study is familiar with the content of this section.

16.1 Definition of Adverse Events (AEs)

According to the ICH guideline for Good Clinical Practice (GCP), an AE is any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product regardless of causal attribution. An AE can therefore be any of the following:

a. Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
b. Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in section 16.9.3
c. Recurrence of an intermittent medical condition (e.g., headache) not present at baseline.
d. Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms, requires additional diagnostic testing or medical/ surgical intervention, leads to a change in study treatment or concomitant treatment or discontinuation from study drug or is considered to be an AE by the investigator
e. AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment

The term AE is used to include both serious and non-serious AEs.

For each AE the investigator will make an assessment of seriousness (see section 16.2 for serious criteria), severity (see section 16.5) and causality (see section 16.6).

16.2 Definition of Serious Adverse Events (SAEs)

An SAE is any AE that meets any of the following criteria:

- Results in death
- Is immediately life-threatening (i.e., the AE, in the view of the investigator, places the patient at immediate risk of death. This does not include any AE that had it occurred in a more severe form or was allowed to continue might have caused death.)
- Requires in-patient hospitalization or prolongation of existing hospitalization (at least one overnight stay)
- Results in persistent or significant disability or incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Is a congenital abnormality or birth defect in a neonate/ infant born to a mother exposed to the study treatment
- Is an important medical event in the investigator´s judgement (i.e. may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above)

The following hospitalization scenarios are not considered to be AEs:

- Hospitalizations for protocol mandated procedures (e.g., hospitalization for chemotherapy administration)
- Hospitalization for respite care
- Hospitalization for a preexisting condition provided that all of the following criteria are met:
  - The hospitalization was planned prior to study participation
  - The patient has not suffered an AE
- Hospitalization due solely to progression or recurrence of the underlying cancer

- Hospitalization for outpatient care outside of normal clinic operating hours that is required per protocol or per standard of care

16.3 Definition of Adverse Event of Special Interest (AESI)

AESIs defined for atezolizumab for this study are as follows:

- Autoimmune hemolytic anemia
- Grade ≥ 2 cardiac disorders (e.g., atrial fibrillation, myocarditis, pericarditis)
- Events suggestive of hypersensitivitiy, infusion-related reactions, cytokine-release syndrome, influenza-like illness, systemic inflammatory response syndrome and systemic immune activation
- Immune-related adrenal insufficiency
- Immune-related colitis
- Immune-related endocrinopathies: immune-related diabetes mellitus, immune-related pancreatitis, immune-related hyperthyroidism and immune-related hypophysitis
- Immune-related neurological disorders: immune-related Guillain-Barré syndrome, immune-related myasthenic syndrome or myasthenia gravis and immune-related meningoencephalitis
- Immune-related hepatitis including AST or ALT > 10 × ULN
- Immune-related myositis
- Immune-related nephritis
- Immune-related ocular inflammatory toxicity
- Immune-related pneumonitis
- Immune-related severe cutaneous reaction
- immune-related vasculitis
- Rhabdomyolysis
- Systemic lupus erythematosus

AESI defined for pertuzumab:

- Left ventricular dysfunction

AESI defined for trastuzumab:

- Congestive heart failure

16.4 Reporting Period for (Serious) Adverse Events

(S)AE reporting is mandatory from the date of informed consent form signature (i.e., screening phase) until 42 days after the last dose of neoadjuvant study treatment.

- **Screening phase**: During the screening phase, only AEs deemed to be serious (SAEs) **and** related to protocol mandated and not routinely performed procedures have to be reported.
- **SAEs occurred after the end of the reporting period:** If an investigator learns of any SAE, including death, at any time after the end of the reporting period, and considers there is a reasonable possibility that the event is causally related to the IMP, the Investigator has to notify the study sponsor.

16.5 Assessment of Severity

Severity of AEs will be graded according to the NCI's Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 on a five-point scale (grade 1 to 5).

For those events not specifically listed in the NCI CTCAE, Table 16 will be used for assessing severity.

Table 16 AE Severity Grading Scale

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living[a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living[b,c]
4	Life-threatening consequences or urgent intervention indicated[d]
5	Death related to AE[d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events

Note: Based on the most recent version of NCI CTCAE (v 5.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding one's self, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a SAE (see section 16.8 for reporting instructions), per the definition of SAE in section 16.2.

[d] Grade 4 (only if immediately life threatening) and 5 events must be reported as SAEs (see section 16.8 for reporting instructions), per the definition of SAE in section 16.2.

16.6 Assessment of Causality to Study Treatments

The causality of AEs (their relationship to all study treatment/ procedures) will be assessed by the investigator(s) and communicated to the study sponsor.
The following guidance should be taken into consideration to determine whether or not an AE is considered to be related to the IMP or background treatments, indicating “yes” or “no” accordingly.

- Temporal relationship of event onset to the initiation of study drug
- Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)
- Known association of the event with the study drug or with similar treatments
- Known association of the event with the disease under study
- Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event
- Presence of non treatment-related factors that are known to be associated with the occurrence of the event

Table 17 Causality of AEs to study treatments

Is the AE suspected to be caused by the study treatment on the basis of facts, evidence, science-based rationales, and clinical judgment?	
YES	There is a plausible temporal relationship between the onset of the AE and administration of the study treatment, and the AE cannot be readily explained by the patient’s clinical state, intercurrent illness, or concomitant therapies; and/ or the AE follows a known pattern of response to the study treatment; and/ or the AE abates or resolves upon discontinuation

	of the study treatment or dose reduction and, if applicable, reappears upon re-challenge.
NO	AEs will be considered related, unless they fulfill the criteria as specified below. Evidence exists that the AE has an etiology other than the study treatment (e.g. pre-existing medical condition, underlying disease, intercurrent illness, or concomitant medication); and/ or the AE has no plausible temporal relationship to administration of the study treatment (e.g., cancer diagnosed 2 days after first dose of study treatment).

16.7 Routine Adverse Event Reporting

(S)AEs will be collected in a routine manner at scheduled times according to the schedule of assessments (see section 21) throughout the clinical trial until 42 days after the last dose of neoadjuvant study treatment. All AEs newly occurring or preexisting AEs worsening during the AE Reporting Period have to be recorded in the AE section of the eCRF.
All unresolved AEs have to be followed up until resolution to baseline grade or better, until the event is assessed as stable by the investigator, the patient is lost to follow-up or withdraws consent.
The prompt recording of AEs in the eCRF is the responsibility of each investigator engaged in clinical research, as required by applicable regulations.

16.8 Expedited Adverse Event Reporting

Investigators must report any SAE and AESI (as defined in section 16.3) to the study sponsor immediately after awareness (i.e. within 24 hours), if the event is fatal or life-threatening on the same business day. It is the responsibility of the investigator to compile all necessary information and ensure that the study sponsor receives a report according to the reporting requirements.
All relevant follow-up information must also be provided to the study sponsor within the above mentioned timelines

Either of the ABCSG Safety Reporting Contacts to be used:

- **Email address: sae-reporting@abcsg.at or**
- **Fax number: +43 1 908 90 51**

All SAEs and AESIs have to be reported to the study sponsor using the study specific SAE reporting form, whether or not considered causally related to the study treatment. All SAEs will additionally be documented in the respective eCRF.

16.9 Special Considerations for Adverse Events

16.9.1 Adverse Events based on Signs and Symptoms

When collecting AEs, the recording of diagnoses is preferred (whenever possible) to recording of signs or symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

16.9.2 Adverse Events based on Examinations and Tests

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting investigator should use the clinical, rather than the laboratory term (e.g., anemia versus low haemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE. Any new or aggravated clinically relevant abnormal medical

finding at a physical examination as compared with the baseline assessment will be reported as an AE.

16.9.3 Disease Progression

Disease progression can be considered as an increase in tumor size attributable to the disease for which the IMP(s) is/are being studied. Progressive disease or hospitalization due to progressive disease (local or distant metastasis to the primary cancer under study, refer to section 23.7 (Appendix VII) should be considered as disease progression and not as AE/SAE. Events, which are unequivocally due to disease progression, should not be reported as an AE/SAE during the study.

16.9.4 New Cancers

The development of a new primary cancer should be regarded as an AE/ SAE and will in the majority of cases meet at least one of the serious criteria (see section 16.2). New primary cancers are those that are not the primary reason for the administration of the study treatment and have developed after the inclusion of the patient into the study. They do not include metastases of the original breast cancer. Metastases of the original breast cancer or their symptoms should not be reported as an AE/SAE, as they are considered to be disease progression.

16.9.5 Lack of Efficacy

When there is deterioration in the condition for which the study treatment is being used there may be uncertainty as to whether this is lack of efficacy or an AE. In such cases, unless the study sponsor or the reporting physician considers that the study treatment contributed to the deterioration of the condition, or local regulations state to the contrary, the deterioration should be considered to be a lack of efficacy and not an AE.

16.9.6 Deaths

All deaths that occur during the study, from signing the ICF until the last visit (=EOSV), must be reported as follows:

- Death clearly the result of disease progression should be documented in the eCRF on the respective death eForm, but should not be reported as an SAE
- Where death is not due (or not clearly due) to progression of the disease under study, the medical condition causing the death must be reported to the study sponsor as an SAE within **24 hours of awareness, but anyway on the same business day** (see section 16.8 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death. This information should be captured in the eCRF
- Deaths with an unknown cause should always be reported as an SAE. A postmortem assessment (i.e. autopsy) may be helpful in the assessment of the cause of death, and if performed a pseudonymized copy of the postmortem results should be forwarded to the ABCSG Safety Reporting Contact as soon as possible

16.9.7 Overdose

Atezolizumab is supplied in vials containing the fixed 1200 mg dose of drug substance, which minimizes the chance of overdose. Because the dose per patient is not based on weight or body surface area, and no dose calculation is required, the risk of overdose due to medication errors is minimal. The data available to date suggest that the potential for harm from overdose is very low.

There is no experience with overdosage of pertuzumab in human clinical trials. Single doses higher than 25 mg/kg (1727 mg) have not been tested.

There is no experience with overdosage in trastuzumab (iv formulation) in human clinical trials. Single doses higher than 10 mg/kg have not been tested.

For trastuzumab (sc formulation) single doses of up to 960 mg have been administered with no reported untoward effect.

Study treatments must only be used in accordance with the dosing recommendations in this protocol. Any dose or frequency of dosing that exceeds the dosing regimen specified in this protocol should be considered as an overdose.

Adverse reactions associated with overdose should be treated symptomatically and should be managed appropriately.

16.10 **Pregnancy**

All pregnancies and their outcomes should be reported to ABCSG Safety Reporting Contact (see section 16.8) using the study specific Pregnancy Reporting Form within 24h of awareness.

16.10.1 Maternal Exposure

If a patient becomes pregnant during the course of the study, all study treatment should be discontinued immediately.

The outcome of any conception occurring from the date of the first dose of neoadjuvant study treatment until 3 months after the last dose should be followed up and reported.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study treatments under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was withdrawn from the study treatment.

16.11 **Product Complaints**

All product complaints (with or without AE) should be reported to ABCSG Safety Reporting Contact (see section 16.8) within 15 calendar days of the awareness date.

Product complaints without AE should be sent via email including the following minimal information:

- Detailed description of product complaint
- Date
- Product name (incl. dosage, dosage form, package size)
- Batch number
- Contact (name. adress, telephone number, email)

Product complaints with AE should be reported via the study specific SAE reporting form.

16.12 **Special Situation Reports**

The following events are considered as Special Situations for safety reporting in the absence of an AE. Special Situation Reports shall be reported to ABCSG Safety Reporting Contact (see section 16.8) within 30 calendar days of the awareness date. These have to be reported using the study specific SAE reporting form.

Special Situation Reports	Definition	Exchange without an AE?
Abuse	This corresponds to the persistent or sporadic, intentional excessive use of study treatment, which is accompanied by harmful physical or psychological effects.	Yes
Intercepted medication error	This refers to situations where a study medication error occurred, and an intervention caused a break in the chain of events in the treatment process before reaching the patient. The intervention has prevented actual harm being caused to the patient.	Yes
Medication error	A medication error is an unintended failure in the study treatment process that leads to, or has the potential to lead to, harm to the patient (including potential medication errors or intercepted medication errors).	Yes
Misuse	This refers to situations where the study treatment is intentionally and inappropriately used not in accordance with the the terms of the Marketing Authorization.	Yes
Overdose	This refers to the administration of a quantity of a study treatment given per administration or cumulatively, which is above the maximum recommended dose according to the authorized product information. Clinical judgement should always be applied.	Yes
Potential medication error	This refers to the recognition of circumstances that could lead to a study medication error, and may or may not involve a patient. It refers to all possible mistakes in the prescribing, storing, dispensing, preparation for administration or administration of study medication by all persons who are involved in the study treatment process.	Yes

16.13 Safety Monitoring Program – Rule for excessive Toxicity

Safety, i.e. the proportion of patients with at least one ≥ G3 toxicity (i.e.immune-related and/or cardiac toxicities) according to CTCAE Version 5.0 from study treatment start until 42 days after the last dose of neoadjuvant study treatment, is an important endpoint of ABCSG 52. In this study a

safety monitoring program is established which allows to continuously monitor for excessive toxicity patterns beyond what is expected during the trial. In detail, a pre-specified Pocock-type boundary for toxicity monitoring [70] is implemented (refer to Table 18). Details regarding the calculation of the boundaries can be found in the Statistical Analysis Plan.

Table 18 Pocock-boundary stopping rule for ≥ G3 toxicity

Number of patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	4	4	5	5	5	6	6	7	7	7	8	8	8	8	9	9	9
Number of patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	10	10	10	11	11	11	11	12	12	12	13	13	13	13	14	14	14	15	15	15
Number of patients, n	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58		
Boundary, b_n	15	16	16	16	16	17	17	17	18	18	18	18	19	19	19	19	20	20		

In case the number of patients with at least one ≥ G3 toxicity is ≥ the boundary b_n out of n patients (e.g. awareness of 12 or more patients with at least ≥ G3 toxicities out of 30 patients), the study will be halted for recruitment and sites will be informed accordingly. Only the first onset of a G3 toxicity per patient will be considered.

In case the study is halted, the DMC and MM will meet to investigate these toxicities and give a recommendation on whether the study should be continued or terminated for safety concerns. Patients already randomized into the study will continue to receive study treatment and/or continue with their visit schedule according to section 21 (Schedule of Assessments) up until a decision by the DMC and MM has been reached. Sites will be informed after decision by the DMC and MM has been reached.

Note: Further details will be provided via a study specific manual.

17 Study Management

17.1 Training of Study Site Personnel

Training of the investigational staff at the study site will be conducted according to SOPs and procedures implemented by the study sponsor. The Principal Investigator will ensure that appropriate training relevant to the study is given to the delegated staff, and that any new information relevant to the performance of this study is forwarded to the staff involved. The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

17.2 Data Acquisition/Documentation and Archiving

As set forth in the ICH Guidelines for GCP, the investigator has to acquire, record and report the data correctly according to source data, and shall handle the coded data assigned to the patients and their documentation with the greatest possible care. All observations and evaluations have to be completely transparent.

Source documents are original documents, data and records from which the patient's eCRF (electronic case report form) data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence. The Principal Investigator and delegated study site staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from applicable national or international regulatory authorities. If required by national legislation, all original source documents supporting entries in the eCRF must be maintained and be readily available.

ECOG-PS, CTCAE-Grade, weight, body height and body temperature can be entered directly in the eCRF, without additional supporting source data ("Direct entry"). Further direct entries may be defined.

The Principal Investigator or delegated study site staff must complete requested information in the eCRF in a timely manner, usually within 10 working days after the patient visit. Any raised data queries ("raised data clarification request") need to be responded by the Principal Investigator or dedicated study site staff in a timely manner of issuing the data query (also within 2 weeks after generation). For the purpose of source data verification, the Principal Investigator ensures sufficient time for monitoring visits and appropriate access of CRAs (Clinical Research Associate) to all relevant patient records.

The Principle Investigator should maintain a list of appropriately qualified persons to whom study duties are delegated. All persons authorized to make entries and/or corrections in the eCRF will be included on the respective form.

Any records and documents relating to the conduct of this study and the distribution of IP, including ICFs, laboratory test results, and medication inventory records, etc. must be retained by the Principal Investigator for a minimum of 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer.

At the end of the study, the study sponsor will provide documented site data on an electronic storage device for archiving purposes.

17.3 Data Collection

The study site will be supplied by the study sponsor with an adequate data collection tool i.e. a web browser address for the Electronic Data Capture (EDC) system MACRO, Interface TRIALDATAPORT, which has been fully validated and complies with 21 CFR Part 11 and the Guidance for Industry on

Computerized Systems Used in Clinical Trials requirements. MACRO enables the study site staff to perform a web-based online data documentation in the eCRF.

MACRO provides communication tools which will help users to manage discrepancies electronically, to conduct source data verification and to improve communication within the study team.

The trained Principal Investigator and designated study site staff will enter the data required according to the protocol from source documents (e.g. medical records etc.) into the EDC system. All information in the eCRF must be traceable to these source documents. Data recorded directly in the eCRF are outlined in section 17.2 (Data Acquisition/Documentation and Archiving) or will be additionally defined before study start. A CRA will review the data entered in the eCRF by study site staff for completeness and accuracy according to respective Trial Monitoring Plan (TMP).

Automatic validation programs and manual checks for data discrepancies in the eCRF may result in data queries generated for resolution by the study site staff. Designated study site staff is required to respond to these data queries and perform any necessary changes to the data.

Adverse Events as well as Medical History will be coded by the study sponsor using the MedDRA dictionary.

Audits for quality assurance of the documentation in the eCRF may be performed according to the relevant SOPs of the study sponsor.

17.4 **On-Site Quality Control**

The study will be monitored in accordance with ICH/GCP and all other relevant study specific and legal provisions by the responsible and adequately trained CRA in order to ensure patient well-being and data integrity. The ABCSG CRA will contact and visit the study sites as defined in the study specific TMP. During the visit, the CRA will be permitted to inspect the Investigator File and the various records of the study patients (e.g. source documents) on request, provided that the patient confidentiality is maintained in accordance with local regulations. If applicable, CRAs will visit other site facilities (e.g., pharmacy, drug storage areas, laboratories) in order to review additional study-related records/processes and to evaluate and ensure appropriate study conduct and compliance with the protocol, ICH GCP, and applicable study specific and regulatory requirements.

CRAs will review documented data in the eCRFs for completeness and accuracy according to the study specific TMP, subsequently flag all reviewed pages with a specific mark (“SDV done”) and potentially raise data queries (“data clarification request”) in case of missing source data or incorrect data entries. Immediately after electronic issuance of the queries, they become visible to the Principal Investigator/delegates, the clinical data managers and the study sponsor’s clinical safety staff (“raised data clarification request”). CRAs and/or clinical data managers and/or ABCSG’s clinical safety staff will follow up with trial site personnel in terms of any necessary corrections or additions until final data query resolution.

CRAs will summarize the on-site activities by drafting a Monitoring Visit Report to the study sponsor, including significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

By signing the site agreement, the Principal Investigator or designee agrees to cooperate with the CRA to ensure resolution of problems and other issues identified during study monitoring.

For information regarding audits and inspections, please refer to section 18.6 (Audit and Inspections).

17.5 **Study Oversight**

To ensure the quality of clinical data across all patients and sites, data entered in the EDC system will be checked as described in the respective Data Management Plan. During this process(es),

patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management process(es), data queries and/or site notifications will be raised via EDC for site completion.

The Principal Investigator or designee will sign the Confirmation Form i.e. sign and date the indicated places in the eCRF. These signature(s) will indicate that the Principal Investigator or designee inspected/reviewed the data entered in the eCRF, the data queries, and the site notifications, and agrees with the content at the time all data cleaning procedures are completed.

17.6 **Trial administrative structure**

In the present study a study specific steering committee (SC), data monitoring committee (DMC) and Medical Monitor (MM) will be established/nominated. Details on the responsibilities are outlined below.

17.6.1 Steering Committee (SC)

The study will be performed under the supervision of a Steering Committee consisting of representatives of the sponsor ABCSG, dedicated investigators and other experts (defined as the ABCSG board). The Steering Committee will provide academic leadership and guidance, will periodically review the progress of the study and take decisions on DMC recommendations and study conduct.

17.6.2 Data Monitoring Committee (DMC)

A DMC will be established by the study sponsor. The responsibilities of the DMC include but are not limited to the following:

- Advisory function for all responsibilities as listed for MM. DMC acts as a consultant for the MM, where required.
- Deputy contact for MM responsibilities, in case MM is not available and decision is urgently required
- A safety monitoring program has been introduced in this study, where DMC (alongside MM) assessment might be required. For details refer to section 16.13 (Safety Monitoring Program – Rule for excessive Toxicity)
- Participation in regular DMC meetings to review and discuss aggregated study data

17.6.3 Medical Monitor (MM)

A Medical Monitor will be nominated by the study sponsor. The responsibilities of the MM include but are not limited to the following:

- Evaluation of important protocol deviations (IPDs)
  Note: IPDs include all deviations endangering the basal medical concept of the study, e.g. not protocol-conform patient or study treatment administration, which may jeopardize the safety of the patient or the data integrity.
- Primary contact for assessment of study related medical questions (e.g. toxicity management of study treatments, eligibility questions) and decisions whether or not a patient should be discontinued from study treatment (e.g. in case randomized patient does not meet the eligibility criteria and patient safety is concerned)
- A safety monitoring program has been introduced in this study, where MM (alongside DMC) assessment might be required. For details refer to section 16.13 (Safety Monitoring Program – Rule for excessive Toxicity)

18 Ethical and Regulatory Requirements

18.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH-GCP, and applicable regulatory requirements.

By signing the study protocol, the Principal Investigator agrees to comply with the instructions and procedures described therein and thus to adhere to the principles of Good Clinical Practice which these instructions and procedures reflect.

The provision of individual genotype results to patients, any insurance company, any employer, their family members, general physician or any other third party, is not permitted as part of the National Genetic Law ("Gentechnikgesetz"). Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the patient.

18.2 Patient Data Protection and Confidentiality

Patient medical information, both associated with biologic specimens or not, is confidential and may only be disclosed to third parties as permitted by the patient information sheet and informed consent form (or separate authorization for use and disclosure of personal health information) which has been signed by the patient, unless permitted or required by law.

The investigator must ensure that the patient's confidentiality is maintained. On the case report forms or other documents submitted to the study sponsor, patients should be identified by the patient study number only. Documents that are not for submission to the study sponsor (e.g., signed informed consent forms) should be kept in strict confidence by the investigator.

In compliance with local regulatory requirements and ICH GCP guidelines, it is required that the investigator and institution permit authorized representatives of study sponsor, of the regulatory agency(s), and of the Ethics Committee(s) (EC) direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to her study-related records without violating the confidentiality of the patient.

18.3 Ethics Committee and Regulatory Review

According to National Standards, an EC must approve the final study protocol, including the final version of the patient information sheet(s) and informed consent form(s) and any other written information and/or materials to be provided to the patients. Submission of the final study protocol and related documentation will be done according to national standards.

The study sponsor will ensure the distribution of these documents to the applicable EC, and the investigator/delegate to the study site staff. The opinion of the EC will be given in writing. Before screening of any patient into the study, the final study protocol must be approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations. The study sponsor will provide Regulatory Authority, EC and Principal Investigators with safety updates/ reports according to local requirements.

The study sponsor is responsible for providing the EC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IMP. The study sponsor is responsible for providing SUSARs to the participating investigators.

18.4 Protocol amendments, other changes and study termination

Study procedures will not be changed without the mutual agreement of the Coordinating

Investigators and the study sponsor.

Any modifications to the study protocol or the patient information sheet and informed consent form which may impact on the conduct of the study, potential benefit of the study, or may affect patient safety, 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 will be released by the study sponsor, agreed by the investigator(s) and approved by the EC and national authority or a notification to the national regulatory authority is done, according to local regulations, prior to implementation. A written statement that the study protocol, any subsequent relevant amended documents and the patient information sheet and informed consent form have been approved by the EC must be provided to the study sponsor before the amended documents are initiated. The study sponsor will distribute any subsequent amendments and new versions of the protocol to each Principal Investigator.

Administrative changes of the study protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the study sponsor, agreed by the investigator(s) and notified to the EC and national regulatory authority according to local regulations.

Each change in the study protocol should be reported to (Roche GmbH) prior to submission to the involved ECs and national regulatory authority, as contractually agreed.

The study sponsor and the Principal Investigator (at the respective study site) reserve the right to terminate the study according to the study contract. The study sponsor should notify the EC and national regulatory authority in writing of the study's completion or early termination and send a copy of the notification to the investigator(s), if applicable.

18.5 **Informed Consent**

It is the responsibility of the Prinicipal Investigator, or an investigator designated by the Prinicipal Investigator, to obtain written informed consent from each patient prior to participating in this study, after adequate explanation (in oral and written form) of the aims, methods, anticipated benefits, and potential hazards of the study. This information must be provided to the patient prior to undertaking any trial-related procedure which is not part of the routine clinical management of the patient (i.e. would not be indicated outside the study).

For patients not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where the patient and/or his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient or the legally acceptable representative has orally consented to participation in the trial, the witness' signature on the form will attest that the information in the patient information sheet and informed consent form was accurately explained and understood. The investigator or designee must also explain that the patients are completely free to refuse, to enter the study or to withdraw from it at any time, for any reason. The entire procedure must be documented in the records/charts for every single patient.

The patient (or the patient's legally acceptable representative) should be provided ample time and opportunity to inquire about details of the trial and to decide whether or not to participate. All questions about the trial should be answered to the satisfaction of the patient or the patient's legally acceptable representative.

Furthermore, it is the investigator's responsibility to obtain the signed informed consent including a signature from the person conducting the informed consent discussion, prior to undertaking any trial-related procedure. The proposed informed consent must comply with the ICH GCP guideline and regulatory requirements.

The eCRF for this study contains a section for documenting patient informed consent and must be completed appropriately.

If new safety information results in significant changes in the risk/benefit assessment, the patient information sheet and informed consent form should be reviewed, updated and approved by the EC, if necessary. All patients on study (including those already being treated) should be informed of the new information in written form and give their written consent to continue in the study according to the procedure described above.

18.6 **Audit and Inspections**

Authorized representatives of the study sponsor or a regulatory authority may perform audits or inspections at the trial site, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, ICH-GCP, and any applicable regulatory requirements. Direct access to all trial-related records therefore should be made available upon request of the auditor/inspector. Additionally, the Investigator will inform the study sponsor if contacted by a regulatory agency about an inspection at the trial site.

19 Statistical Methods and Considerations

Details on the planned statistical methods and analyses can be found in the Statistical Analysis Plan. Translational endpoints and according analyses will be included in a separate Analysis Plan.

19.1 Description of Analysis Populations

Three analysis populations are considered:

- Intention-to-Treat (ITT) population: consists of all patients who were randomized
- Safety (SAF) population: consists of all patients who were randomized and received at least one dose of study treatments
- Efficacy assessment (EA) population: consists of all patients who were randomized, were treated with at least two cycles of study treatment (hence, received two doses of trastuzumab and pertuzumab or trastuzumab, pertuzumab and atezolizumab, respectively, during treatment part 1, with a maximum time difference of 4 weeks between the two doses), and were assessable for pCR status (hence, for whom surgery was performed)

19.2 Types and time points of analyses

No interim analysis is planned.

The primary analysis will take place after all patients completed the study. It will include the analysis of efficacy (primary and secondary), safety, PRO and exploratory endpoints.

19.3 Methods of Statistical Analyses

The hypothesis for the primary endpoint is that at least 40 % of the patients achieve a pCR. In this case the study result will be considered positive.

For efficacy (primary and secondary) and exploratory endpoints, estimates and 95 % confidence intervals will be given based on the ITT population. A sensitivity analysis for primary, secondary and exploratory endpoints will be repeated based on the EA population. Additionally, the influence of possible predictors will be analysed by uni- and multivariate logistic regression for the primary endpoint.

The safety endpoint will be presented as absolute counts (percentages) in total and separated for patients who did or did not achieve a pCR based on the SAF population.

PRO endpoints will be analysed based on the ITT population. The EORTC QLQ-C30 and EORTC QLQ B23 scales and single items will be linearly transformed to 0-100 and analysed according to the recommendations of the EORTC QoL Group. Differences of at least 10 points on the scales/items were defined as the threshold for minimum of clinically significant difference.

19.4 Sample Size, Accrual Time and Study Duration

The following sample size calculation was performed for the primary endpoint, the pCR proportion in the overall study population, and yielded a required sample size of n=58. Based on clinical data from the NeoSphere trial [23]) and statistical and medical expert opinion, a pCR proportion of 40 % in the overall study population is assumed. Aim of the study is to estimate the true population pCR proportion with a given level of precision. The following formula was considered for this sample size estimation:

$$n \geq \left(\frac{z}{m}\right)^2 \times \hat{p}(1 - \hat{p})$$

, where n is the required sample size, z is the Z-score (i.e. the boundary for the area of $\frac{\alpha}{2}$ in the standard normal distribution), m is the desired margin of error, and $\hat{p}$ is the estimated sample pCR proportion.

Regarding the parameters of this formula, the following assumptions were made by the investigators:

- z=1.96 by normal approximation to the binomial distribution
- $\hat{p}$ (pCR proportion in the overall study population)=0.4
- m (Level of precision / Margin of error (i.e. half the 95 % confidence interval width)): 13 %

With these assumptions, we would need to recruit n=55 patients into ABCSG 52.

19.4.1 Sensitivity analysis for the sample size calculation

Due to the relationship between $\hat{p}$ and $\hat{p}(1-\hat{p})$, the 95 % confidence interval would be widest in the case ABCSG 52 would yield a pCR proportion of 0.5 (“scenario of widest confidence interval”). Otherwise (i.e. if the estimated pCR proportion is 0.3 or 0.6), the confidence interval would be narrower. We therefore re-estimated the sample size under the “scenario of the widest confidence interval”, i.e. at $\hat{p}$ = 0.5. In this scenario, we would need a sample size of n=57 patients. The investigators believe that a pCR proportion of 0.5 is at least clinically plausible, and we therefore decided to select this sample size estimate for planning the study. As 57 is an uneven number and randomization will be performed 1:1, our final sample size estimate for ABCSG 52 is n=58 patients with assessable pCR status.

20 **Publication Policy**

The Coordinating Investigators and study sponsor will comply with recognized ethical standards concerning publications and authorship, including Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors (ICMJE). Furthermore, publications and oral presentations of any results from the study shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the ABCSG publication SOP, the terms concerning publications in the Site Agreement and, if applicable, any specific policy developed for the study.

21 Schedule of Assessments

	Screening[a]		Treatment[b]			Surgery Visit[c]	EOS Visit[d]
			Treatment Part 1 1:1 randomization	Treatment Part 2 All patients			
Time window (visits)	Days -28 to 0		Day 1 of each 3 week cycle (± 3 days)	Day 1 of each 3 week cycle (± 3 days)		Within 28-49 days from last dose of neoadjuvant study treatment[e]	Within 7-42 days after surgery, but at least 42 days after last dose of neoadjuvant study treatment[f]
Time window (assessments)	Days -28 to 0		Assessments to be performed on day of visit, if not otherwise indicated				
Patient Visit	**0**		**V1[g]-V2**	**V3**	**V4-V6**	**V7**	**V8**
Informed Consent	X[h]	**Randomization**					
Inclusion/Exclusion Criteria	X						
Demographic Data[i]	X						
Medical History[j]	X						
Vital Signs, Physical Examination, ECOG performance status[k]	X		X	X	X	X	X
Clinical Tumor Assessment (by palpation)[l]	X		X	X	X	X	
ECG (12-lead)	X		as clinically indicated				

	Screening[a]		Treatment[b]			Surgery Visit[c]	EOS Visit[d]
			Treatment Part 1 1:1 randomization	Treatment Part 2 All patients			
Time window (visits)	Days -28 to 0		Day 1 of each 3 week cycle (± 3 days)	Day 1 of each 3 week cycle (± 3 days)		Within 28-49 days from last dose of neoadjuvant study treatment[e]	Within 7-42 days after surgery, but at least 42 days after last dose of neoadjuvant study treatment[f]
Time window (assessments)	Days -28 to 0		Assessments to be performed on day of visit, if not otherwise indicated				
Patient Visit	**0**		**V1[g]-V2**	**V3**	**V4-V6**	**V7**	**V8**
ECHO or MUGA scan[m]	X		as clinically indicated	X (-7 to 0 days)	as clinically indicated	X (-14 to 0 days)	as clinically indicated
Hematology[n]	X		X (-3 to 0 days)	X (-3 to 0 days)	X (-3 to 0 days)	X (-3 to 0 days)	
Coagulation (INR, aPTT)[o]	X		as clinically indicated				
Blood Chemistry[p]	X		X (-3 to 0 days)	X (-3 to 0 days)	X (-3 to 0 days)	X (-3 to 0 days)	
TSH, (free T3 (or total T3), free T4)[q]	X			X (-3 to 0 days)		X (-3 to 0 days)	
Pro-BNP	X			X (-3 to 0 days)			
Serum/Urine Pregnancy Test[r]	X		X (-7 to 0 days)	X	X	X	X
Urinalysis[s]	X		as clinically indicated				

	Screening[a]		Treatment[b]			Surgery Visit[c]	EOS Visit[d]
			Treatment Part 1 1:1 randomization	Treatment Part 2 All patients			
Time window (visits)	Days -28 to 0		Day 1 of each 3 week cycle (± 3 days)	Day 1 of each 3 week cycle (± 3 days)		Within 28-49 days from last dose of neoadjuvant study treatment[e]	Within 7-42 days after surgery, but at least 42 days after last dose of neoadjuvant study treatment[f]
Time window (assessments)	Days -28 to 0		Assessments to be performed on day of visit, if not otherwise indicated				
Patient Visit	**0**		**V1[g]-V2**	**V3**	**V4-V6**	**V7**	**V8**
Mammography[t]	X[u]		as clinically indicated				
MRI assessment, breast ultrasound[t] and ultrasound of regional nodes[t] according to modified RECIST[v]	X			X (-7 to 0 days)		X (at least 21 days after the last dose of neoadjuvant study treatment but prior to surgery)	
PET assessment according to modified PERCIST[v]	X			X (-7 to 0 days)			
Tumor Tissue	X[w]			X[w] (-7 to 0 days)		X[x]	
Whole blood, plasma and serum samples for Translational Research	X			X		X	X
Stool sample	X		(X)[y]				
Study treatment administration[z]			X	X	X		

	Screening[a]	Treatment[b]			Surgery Visit[c]	EOS Visit[d]
		Treatment Part 1 1:1 randomization	Treatment Part 2 All patients			
Time window (visits)	Days -28 to 0	Day 1 of each 3 week cycle (± 3 days)	Day 1 of each 3 week cycle (± 3 days)		Within 28-49 days from last dose of neoadjuvant study treatment[e]	Within 7-42 days after surgery, but at least 42 days after last dose of neoadjuvant study treatment[f]
Time window (assessments)	Days -28 to 0	Assessments to be performed on day of visit, if not otherwise indicated				
Patient Visit	**0**	**V1[g]-V2**	**V3**	**V4-V6**	**V7**	**V8**
PRO / Quality of Life assessment[aa]	X		X		X	X
Concomitant medications[bb]	X	X				(X)[cc]
Surgical morbidity and mortality[dd]						X
Surgical data[ee]	X				X	(X)
SAEs/AEs[ff]	X	X				

a) Screening Phase: All screening evaluations must be completed and reviewed to confirm that patients meet all inclusion criteria and do not meet any of the exclusion criteria before randomization.

b) Treatment Phase: Cycle 1/Day 1 (= V1) due within a maximum of 10 days after the day of randomization. All assessments to be performed prior to study drug administration, unless otherwise indicated. If screening assessments excluding laboratory assessments occur ≤ 7 days and screening laboratory safety assessments occur ≤ 3 days prior to V1, then they may serve as V1 assessments and do not need to be repeated.

c) Surgery Visit: The date of the surgery visit correlates with the day of surgery. Surgery should be performed wthin 28-49 days from last dose of neoadjuvant study treatment, unless an ongoing adverse event would require surgery to be delayed. All assessments of the surgery visit should be performed prior to surgery, unless otherwise indicated.

d) EOS Visit: Visit to be performed prior to start of adjuvant treatment. Planned adjuvant treatment to be documented in eCRF.

e) In case of salvage surgery, protocol specified timelines do not apply and the appropriate schedule is specified as per investigator's decision. However, EOSV has to be performed 7-42 days after salvage surgery, but at least 42 days after last dose of neoadjuvant study treatment and prior to start of adjuvant treatment.

f) In case no surgery was performed, EOSV should be scheduled within 49-91 days after last dose of neoadjuvant study treatment.

g) Results of standard-of-care examinations performed prior to written patient consent and within 28 days prior to V1 may be used. It is not required to repeat such examinations for screening.

h) Informed consent form may be obtained greater than 28 days before randomization; it must, however, be obtained prior to any protocol required assessment (i.e., Screening Phase) which is not performed as part of standard of care.

i) Demographic Data include age at randomization, gender at birth and at randomization, self reported race/ethnicity and menopausal status.

j) Medical History includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures) and smoking history.

k) Assessment of vital signs according to local practice has to be performed including at least diastolic and systolic blood pressure, body temperature and resting pulse rate. Vital signs should also be determined during and after the administrations, if clinically indicated.
Physical examination according to local practice including height (only at screening) and body weight has to be performed. A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems. Careful attention must be paid to the breast and the assessment of regional lymph nodes as well as cardiovascular symptoms. Any clinically significant abnormalities identified at screening have to be recorded as Medical History in the eCRF, any clinically significant new or worsened abnormalities assessed at subsequent visits have to be recorded as (S)AE in the respective Adverse Events eForms and reported via SAE reporting form if serious criteria are met.

l) Clinical Tumor Assessment (by palpation) according to standard of care.

m) ECHO is the preferred method.

n) Hematology parameters include hemoglobin, red blood cell (RBC) count, platelet count, hematocrit, white blood cell (WBC) count and absolute differential WBC count (neutrophils, lymphocytes, monocytes, eosinophils and basophils).

o) Patients receiving therapeutic anticoagulation are eligible for study participation; however, coagulation assessments (INR and aPTT) are to be performed according to local practice.

p) Blood chemistry parameters include sodium, potassium, chloride, calcium, fasting glucose, BUN or urea, creatinine and creatinine clearance, total bilirubin, ALP, ALT/GPT, AST/GOT, GGT, LDH, serum amylase and serum lipase.

q) Free T3 (or total T3 for sites where free T3 is not assessed) and free T4 to be assessed, only if abnormalities in TSH levels occur.

r) Pregnancy tests on blood or urine samples will be performed for women of childbearing potential within 28 days prior to randomization and on V1 (unless screening pregnancy test is performed ≤ 7 days prior study treatment start) of the study prior to commencing treatment. Afterwards, pregnancy tests will be performed on a regular schedule (e.g. on day 1 of each treatment cycle) but at least once monthly.

s) At screening, urinalysis including pH, specific gravity, glucose, protein, ketones and blood is to be performed and afterwards only if clinically indicated.

t) Mammography, breast ultrasound and ultrasound of regional nodes according to standard of care.

u) At screening bilateral mammography is to be performed.

v) In case of disease progression, salvage surgery may be performed and should be documented in the clinical database.

w) Representative tumor tissue FFPE block from diagnostic core biopsy for screening and V3 measuring at least 3x1 mm. Screening tumor tissue FFPE block must be transmitted to a central sample repository and feedback of central TIL assessment must be available prior to randomization. Tissue banking will be required for translational endpoint analyses.

x) Tumor tissue from surgery has to be provided in case of curative or salvage surgery.

y) If stool sample has not been collected during screening, it has to be collected prior to first administration of neodjuvant study treatment at the latest.

z) For detailed information on administration of study treatments, refer to respective product information/IB as well as section 12. Atezolizumab administration during the treatment part 1 for Arm A patients only.

aa) PRO includes 2 questionnaires (EORTC QLQ-C30 and EORTC QLQ BR-45) and will be collected at the time points as indicated in the schedule. Questionnaires should be completed prior to any other study assessments are performed on that day.

bb) Any concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal medicines, nutritional supplements) and treatments (with the exception of surgery related medication e.g. anesthetics) will be recorded from 28 days prior to randomization up until the surgery visit.

cc) Only in case no surgery is performed, concomitant medication has to be recorded additionally at the EOSV.

dd) Assessment of surgical morbidity, mortality and general compolications according to Clavien Dindo. Only applicable for patients who underwent surgery.

ee) Refer to section 15 (Surgical Data Collection) for details.

ff) S(AE)s have to be reported after the patient has signed the informed consent until 42 days after the last dose of neoadjuvant study treatment.

Note: during the screening phase only SAEs deemed related to protocol mandated and not routinely performed procedures have to be reported. AEs fulfilling the criteria for expedited reporting have to be treated according to the reporting procedures described in section 16 including a submission to the study sponsor within 24 hours of awareness.

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23 Appendices

23.1 Appendix I: NCI Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0

A copy of the NCI CTCAE version 5.0 can be downloaded from the CTEP web site:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

23.2 **Appendix II: ECOG Performance Status**

Description	Grade
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, i.e. light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50 % of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

23.3 **Appendix III: AJCC Cancer Staging (8th edition)**

from Amin MB, Edge S, Greene F, Byrd DR, Brookland RK, Washington MK, Gershenwald JE, Compton CC, Hess KR, et al. (Eds.). *AJCC Cancer Staging Manual (8th edition)*. Springer International Publishing: American Joint Commission on Cancer; 2017.

23.3.1 Definition of Primary Tumor (T) – Clinical and Pathological

T Category	T Criteria
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis (DCIS)*	Ductal carcinoma *in situ*

T Category	T Criteria
Tis (Paget)	Paget disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension (round any measurement >1.0-1.9 mm to 2 mm)
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or macroscopic nodules); invasion of the dermis alone does not qualifiy as T4
T4a	Extension to the chest wall; invasion or adherence to pectoralis muscle in absence of invasion of chest wall structures does not qualify as T4
T4b	Ulceration and/or ipsilateral macroscopic satellite nodules and/or edema (including peau d'orange) of the skin that does not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b are present
T4d	Inflammatory carcinoma

* *Note:* Lobular carcinoma *in situ* (LCIS) is a benign entity and is removed from TNM staging in the *AJCC Cancer Staging Manual, 8th Edition*

23.3.2 Definition of Regional Lymph Nodes - Clinical (cN)

cN Category	cN Criteria
cNX*	Regional lymph nodes cannot be assessed (e.g. previously removed)
cN0	No regional lymph node metastases (by imaging or clinical examination)
cN1	Metastases to movable ipsilateral Level I, II axilliary lymph node(s)
cN1mi**	Micrometastases (approximately 200 cells, larger than 0.2 mm, but no

cN Category	cN Criteria
	larger than 2.0 mm)
cN2	Metastases in ipsilateral Level I, II axilliary lymph nodes that are clinically fixed or matted;
	or in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN2a	Metastases in ipsilateral Level I, II axilliary lymph nodes fixed to one another (matted) or to other structures
cN2b	Metastases only in ipsilateral internal mammary nodes in the absence of axillary lymph node metastases
cN3	Metastases in ipsilateral infraclavicular (Level III axillary) lymph node(s) with or without Level I, II axillary lymph node involvement;
	or in ipsilateral internal mammary lymph node(s) with Level I, II axillary lymph node metastases;
	or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
cN3a	Metastases in ipsilateral infraclavicular lymph node(s)
cN3b	Metastases in ipsilateral internal mammary lymph node(s) in axillary lymph node(s)
cN3c	Metastases in ipsilateral supraclavicular lymph node(s)

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or fine needle aspiration/core needle biopsy respectively

**The cNX category is used sparingly in cases where regional lymph nodes have previously been surgically removed or where there is no documentation of physical examniation of the axilla*

***cN1mi is rarely used but may be appropriate in cases where sentinel node biopsy is performed before tumor resection, most likely to occur in cases treated with neoadjuvant therapy*

23.3.3 Definition of Regional Lymph Nodes - Pathological (pN)

pN Category	**pN Criteria**
pNX	Regional lymph nodes cannot be assessed (e.g. not removed for pathological study or previously removed)
pN0	No regional lymph node metastasis identified or ITCs only
pN0(i+)	ITCs only (malignant cell clusters no larger than 0.2 mm) in regional lymph node(s)
pN0(mol+)	Positive molecular findings by reverse transcriptase polymerase chain reaction (PT-PCR); no ITCs detected
pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or clinically negative internal mammary nodes with micrometastases or macrometastases by sentinel lymph node biopsy
pN1mi	Micrometastases (approximately 200 cells, larger than 0.2 mm, but none larger than 2.0 mm)
pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis larger than 2.0 mm
pN1b	Metastases in ipsilateral internal mammary sentinel nodes, excluding ITCs
pN1c	pN1a and pN1b combined
pN2	Metastases in 4-9 axillary lymph nodes; or positive ipsilateral internal mammary lymph nodes by imaging in the absence of axillary lymph node metastases
pN2a	Metastases in 4-9 axillary lymph nodes (at least one tumor deposit larger than 2.0 mm)
pN2b	Metastases in clinically detected internal mammary lymph nodes with or without microscopic confirmation; with pathologically negative axillary nodes
pN3	Metastases in 10 or more axillary lymph nodes;
	or in infraclavicular (Level III axillary) lymph nodes;
	or positive ipsilateral internal mammary lymph nodes by imaging in the presence of one or more positive Level I, II axillary lymph nodes;
	or in more than three axillay lymph nodes and micrometastases or macrometastases by sentinel lymph node biopsy in clinically negative ipsilateral internal mammary lymph nodes;
	or in ipsilateral supraclavicular lymph nodes

pN Category	pN Criteria
pN3a	Metastases in 10 or more axillary lymph nodes (at least one tumor deposit larger than 2.0 mm);
	or metastases to the infraclavicular (Level III axillary lymph) nodes
pN3b	pN1a or pN2a in the presence of cN2b (positive internal mammary nodes by imaging);
	or pN2a in the presence of pN1b
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Note: (sn) and (f) suffixes should be added to the N category to denote confirmation of metastasis by sentinel node biopsy or FNA/core needle biopsy respectively, with NO further resection nodes

23.3.4 Clinical Prognostic Stage

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G2	Positive	Positive	Positive	IB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N2 M0	G1	Positive	Positive	Positive	IIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G2	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Any T Any N M1	Any	Any	Any	Any	IV

**T1 includes T1mi*

***N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status*

**** N1 includes N1mi, T2, T3 and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3 N1 and T4 N1, respectively*

Notes:

1. *Because N2mi categorization requires evaluation of the entire node, and cannot be assigned on the basis of an FNA or core biopsy, N1mi can only be used with Clinical Prognostic Staging when clinical staging is based on a resected lymph node in the absence of resection of the primary cancer, such as the situation where sentinel node biopsy is performed prior to receipt of neoadjuvant chemotherapy or endocrine therapy.*
2. *For cases, with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma in situ (e.g. Tis N1, etc) the grade, HER2, ER, and PR information from the tumor in the lymph node should be used for assigning stage group*
3. *For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the Clinical Progonostic Stage Group table [76]*
4. *The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemetic chemotherapy (including anti-HER2 therapy)*

Pathological Prognostic Stage

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0 T0 N1mi M0 T1* N1mi M0	G1	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
				Negative	IA
	G2	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
	G3	Positive	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N1** M0 T1* N1** M0 T2 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
	G2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
	G3	Positive	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA
		Negative	Positive	Positive	IB
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T2 N1*** M0 T3 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G2	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
	G3	Positive	Positive	Positive	IB
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIB
		Negative	Positive	Positive	IIA
				Negative	IIB
			Negative	Positive	IIB
				Negative	IIIA

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status ist…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T0 N2 M0 T1* N2 M0 T2 N2 M0 T3 N1*** M0 T3 N2 M0	G1	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
	G2	Positive	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIB
	G3	Positive	Positive	Positive	IIA
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIA
		Negative	Positive	Positive	IIB
				Negative	IIIA
			Negative	Positive	IIIA
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
T4 N0 M0 T4 N1*** M0 T4 N2 M0 Any T N3 M0	G1	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
	G2	Positive	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIA
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIC
	G3	Positive	Positive	Positive	IIIB
				Negative	IIIB
			Negative	Positive	IIIB
				Negative	IIIB
		Negative	Positive	Positive	IIIB
				Negative	IIIC
			Negative	Positive	IIIC
				Negative	IIIC

When TNM is…	And Grade is…	And HER2 Status is…	And ER Status is…	And PR Status is…	Then the Clinical Prognostic Stage Group is…
Any T Any N M1	Any	Any	Any	Any	IV

**T1 includes T1mi*

***N1 does not include N1mi. T1 N1mi M0 and T0 N1mi M0 cancers are included for prognostic staging with T1 N0 M0 cancers of the same prognostic factor status*

****N1 includes N1mi. T2, T3, and T4 cancers and N1mi are included for prognostic staging with T2 N1, T3, N1 and T4 N1, respectively*

Notes:

1. *For cases, with lymph node involvement with no evidence of primary tumor (e.g. T0 N1, etc.) or with breast ductal carcinoma in situ (e.g. Tis N1, etc.) the grade, HER2, ER, and PR information form the tumor in the lymph node should be used for assigning stage group*
2. *For cases where HER2 is determined to be "equivocal" by ISH (FISH or CISH) testing under 2013 ASCO/CAP HER2 testing guidelines, the HER2 "negative" category should be used for staging in the Pathological Progonostic Stage Group Table [76]*
3. *The prognostic value of these Prognostic Stage Groups is based on populations of persons with breast cancer that have been offered and mostly treated with appropriate endocrine and/or systemic chemotherapy (including anti-HER2 therapy)*

23.4 **Appendix IV: ASCO/CAP guideline**

http://ascopubs.org/doi/abs/10.1200/JCO.2018.77.8738

23.5 **Appendix V: Clavien Dindo classification of surgical complications**

Full Scale		**Contracted Form**	
Grades	Definition	Grades	Definition
Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic and radiological interventions.	**Grade I**	Same as for Full Scale
	Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics and electrolytes and physiotherapy. This grade also includes wound infections opened at the bedside.		
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications. Blood transfusions and total parenteral nutrition are also included.	**Grade II**	Same as for Full Scale
Grade III	Requiring surgical, endoscopic or radiological intervention	**Grade III**	Grades III-a & III-b
Grade III-a	Intervention not under general anesthesia		
Grade III-b	Intervention under general anesthesia		
Grade IV	Life-threatening complication (including CNS complications)[1] requiring IC/ICU-management	**Grade IV**	Grades IV-a & IV-b
Grade IV-a	Single organ dysfunction (including dialysis)		
Grade IV-b	Multi organ dysfunction		
Grade V	Death of a patient	**Grade V**	Same as for Full Scale

Full Scale		Contracted Form	
Grades	Definition	Grades	Definition
Suffix 'd'	If the patient suffers from a complication at the time of discharge, the suffix “d” (for ‘disability’) is added to the respective grade of complication. This label indicates the need for a follow-up to fully evaluate the complication.		

[1] brain hemorrhage, ischemic stroke, subarrachnoidal bleeding,but excluding transient ischemic attack (TIA);IC: Intermediate care; ICU: Intensive care unit

Reference: Dindo D., Demartines N., Clavien P.A.; Ann Surg. 2004; 244: 931-937

23.6 **Appendix VI: Measurement of Residual Cancer Burden (RCB)**

Measurement of RCB according to Symmans W.F., et al., *Measurement of residual breast cancer burden to predict survival after neoadjuvant chemotherapy.* J Clin Oncol. 2007 Oct 1;25(28):4414-22.

23.7 **Appendix VII: Modified Response Criteria in Solid Tumors (RECIST): modified excerpt from original publication**

Selected sections from the Response Criteria in Solid Tumors (RECIST), version 1.1 [71] are presented below, with slight modifications and the addition of explanatory text as required for clarity.

	RECIST v1.1	**Modified RECIST**
Method of assessments	CT as primary modality, ultrasound not recommended	Primary assessment by MRI and ultrasound
Target lesions	Up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ)	1 target lesion in the breast. Unifocal: the largest measurable diameter defines the target lesion Multifocal/multicentric: the largest lesion must be > 1 cm and designated as target lesion for all subsequent tumor evaluations
Lymph nodes	May be considered target lesions based on size criteria (≥ 15 mm in SAD)	Pathologic axillary lymph nodes are not to be designated as target lesions and should be considered as non-target lesions.
Possibility of having only non-target disease	Allowed	Not allowed

23.7.1 Measurability of tumor at baseline

23.7.1.1 Measurable lesions

Tumor lesions measured in at least one dimension (longest diameter in the plane measurement is to be recorded) with a minimum size of:

- 10 mm by MRI scan (MRI scan slice thickness no greater than 5 mm)

Malignant lymph nodes

- ≥ 15 mm in short axis on MRI scan (MRI scan slice thickness no greater than 5 mm) or by ultrasound
- At baseline and in follow-up, only the short axis will be measured and followed

23.7.1.2 Non-measurable Lesions:

All other lesions, including small lesions

- Longest diameter ≤ 10 mm, or
- pathological lymph nodes with ≥ 10 to < 15 mm short axis

23.7.2 Method of assessment

As breast MRI is the most accurate modality for anatomicalassessing the extent of residual disease following neoadjuvant chemotherapy, MRI is the preferred modality to follow breast lesions in a neoadjuvant setting [72] Therefore, primary assessment in this study is performed by MRI.

MRI field strength and sequence according to the I-SPY 2 trial [73] should be used: 1.5T or 3T MRI system using a fat-suppressed single-shot echo planar imaging sequence with b-values of 0 and 800 s/mm2 for diffusion-weighted imaging (DWI), followed by a T1-weighted sequence for dynamic contrast-enhanced MRI (DCE-MRI).

23.7.3 Tumor response evaluation

To assess objective response for future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study.

23.7.3.1 Target lesion

Target lesion should be selected on the basis of its size (lesion with the longest diameter) and should lend itself to reproducible repeated measurement. One target lesion in the breast has to be determined during baseline and documented accordingly.

In case of a unifocal tumor lesion in the breast, the largest measurable diameter defines the target lesion. In case of multifocal tumor lesions in the breast (defined as the presence of two or more foci of cancer within the same breast quadrant), or a multicentric tumor (defined as the presence of two or more foci of cancer within different quadrants), the largest lesion must be > 1 cm and designated as target lesion for all subsequent tumor evaluations,

Pathologic axillary lymph nodes are not to be designated as target lesions and should be considered as non-target lesions.

23.7.3.2 Non-target lesions

Non-target lesions include any other measurable breast lesions not identified as target lesion or pathologic axillary lymph nodes.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging event if not involved by tumor.

23.7.4 Response criteria

23.7.4.1 Evaluation of target lesions

This section provides the definitions of the criteria used to determine objective tumor response for target breast lesion:

- **rCR**: disappearance of target lesion
- **rPR:** at least a 30% decrease of the largest diameter of the target lesion, taking as reference the baseline diameter.
- **Radiographic progressive disease (rPD)**: at least a 20 % increase of the largest diameter of the target lesion, taking as reference the smallest measurement of the largest diameter of the target lesion on study (this includes the screening diameter, if it is the smallest on study)
  Note: the appearance of one ore more new lesions is also considered progression

- **Radiographic stable disease (rSD)**: neither sufficient shrinkage to qualify for rPR nor sufficient increase to qualify for PD, taking as reference the smallest measurement of the largest diameter of the target lesion on study.
- **Not evaluable (NE)**

Special notes on the assessment of target lesions

Target lesions that become "too small to measure"

While on study, lesion recorded at baseline should have its actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions which are recorded as target lesion at baseline become so faint on MRI scan that the radiologist may not feel comfortable assigning an exact measure and may report it as being too small to measure. When this occurs it is important that a value is recorded in the eCRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared: measurement should be reported as 0 mm
- If lesion is believed to be present and is faintly seen but too small to measure: default value of 5 mm should be assigned
  Note: To reiterate, however, if the radiologist is able to provide an actual measure, this should be recorded, even if it is below 5 mm

Lesions that split or coalesce on treatment

In case a lesion "fragments", the longest diameter of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion".

23.7.4.2 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they do not need to be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **rCR**: disappearance of all non-target lesions
  - All lymph nodes must be non-pathologic in size (< 10 mm short axis)
- **Non-rCR/Non-rPD**: persistence of one or more non-target lesion(s)
- **rPD**: unequivocal progression (see comments below) of existing non-target lesion
  Note: the appearance of one or more new lesions is also considered progression
- **NE**

Special notes on the assessment of non-target lesions

To achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of rSD or rPR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of study treatment. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of rSD or rPR of target disease will therefore be extremely rare.

23.7.4.3 New lesions

The appearance of new malignant lesions indicates disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, i.e. not attributable to differences in scanning technique, change in imaging modality of findings thought to represent something other than tumor. This is particularly important when the patient's baseline lesions show partial or complete response.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal i.e., because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat assessments confirm there is definitely a new lesion, then progression should be documentedusing the date of the initial assessment.

23.7.5 Evaluation of response

23.7.5.1 Timepoint response

Table 19 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

Table 19 Time point response: patients with target (+/- non-target) disease

Target lesion	Non-target lesions	New lesions	Overall response
rCR	rCR	No	rCR
rCR	Non-rCR/non-rPD	No	rPR
rCR	NE	No	rPR
rPR	Non-rPD or NE	No	rPR
rSD	Non-rPD or NE	No	rSD
NE	Non-rPD	No	NE
rPD	Any	Yes or No	rPD
Any	rPD	Yes or No	rPD
Any	Any	Yes	rPD

23.7.5.2 Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that

the contribution of the individual messing lesion(s) would not change the assigned time point response.

If target lesion was not assessed either because scan was not done or scan could not be assessed due to poor image quality or obstructed view, the response for target lesion should be NE. Similarly, in case one or more non-target lesions are not assessed, the response for non-target lesions should be NE except where there is clear progression in non-target lesions that are assessed.

Special notes on response assessment

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as symptomatic deterioration. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study treatment. The objective response status is to be determined by evaluation of target and non-target disease as shown in Table 19.

For equivocal findings of progression (e.g. very small and uncertain new lesions, cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

23.8 Appendix VIII: Modified PET Response Criteria in Solid Tumors (PERCIST): modified excerpt from original publication

Selected sections from the PET Response Criteria in Solid Tumors (PERCIST), Version 1.0 [74] are presented below, with slight modifications and the addition of explanatory text as required for clarity.

Throughout the study the same PET scanner should be used per patient. It is further recommended to follow the reconstruction criteria according to EARL 1.0 [75].

23.8.1 Required parameters for baseline fluorine 18 fluorodeoxyglucose (FDG) PET

- Measurement of "hottest" single tumor and background area on images (usually of the liver) required at baseline
- A single target lesion is selected as the primary parameter
  Note: the most metabolically active tumor focus corresponds to the most aggressive portion of the tumor, which is the most clinically important area
- The peak standardized uptake value corrected for lean body mass (SUL_{peak}) is chosen

23.8.2 Background activity

- A 3-cm diameter spherical volume of interest (VOI) is placed in the right side of liver, midway between the dome and inferior margin (excl. central ducts and vessels) for background activity
- SUL and standard deviation (SD) of SUL in the spherical VOI are measured (to 2 significant digits)
- There are different methods of computing the lean body mass. Currently, it is suggested to use the equation by James:

For women:

$$LBW = [1.07 \times W] - 148 \times [\frac{W^2}{H^2}]$$

[where *LBW* is lean body weight, *W* is weight in kilograms and *H* is height]

- Measurement of background liver activity is compromised if a patient has a metastatic disease and a 3-cm-diameter spherical VOI cannot be drawn without including obvious metastatic tumor
- If the liver is deceased, the mean background SUL and SD can be measured in a cylindrical VOI with a diameter of 1 cm and a long axis (parallel to descending aorta) of 2 cm in the center of the descending thoracic aorta (excl. aorta wall)

23.8.3 Target lesion at baseline

- SULpeak is measured as the single hottest tumor. A 1-mL spherical VOI is placed at the focus of the hottest tumor. The 1-mL sphere with the highest mean SUL value can be computed automatically or manually.
  - Visual inspection of PET images is typically required
  - Normal FDG-containing structures (e.g. renal pelvis) should not be quantified
  - SUL_{peak} can be identified manually by moving a fixed 1-mL spherical VOI iteratively over tumor foci with visually increased FDG uptake and finding the focus that gives the highest mean SUL value
- It is recommended to record the imaging plane and coordinates of the lesion and that an image of the lesion with the VOI placed be saved

- Software that supports voxel subsampling is recommended, although adequate approximation of the 1-mL VOI usually can be achieved with simple VOI tools
- For a tumor to be **measurable** (at baseline): SULpeak must be ≥ 1.5x the mean SUL in the 3-cm diameter spherical VOI + 2xSD
- The tumor is considered **not measurable** (at baseline): when the SULpeak is lower than this threshold
  Note: If the target lesion is not measurable at baseline, it should be noted that the measurement of the lesion is below the minimum threshold for evaluation
- When the activity in the descending thoracic aorta is measured (instead of the liver), the minimum threshold for evaluation is 2x mean SUL of the thoracic aorta in a tubular VOI + 2x SD
- In case of a new lesion of **unequivocal progression** during the study (V3): response of progression can be designated even if the target lesion at baseline does not meet the minimum threshold for evaluation
  Note: Threshold for evaluability of the target lesion only applies to baseline

23.8.4 Required parameters for FDG PET during the study (V3)

- The follow-up imaging (=V3) and all available clinical information should be considered fully in the selection of the target lesion
- Known areas of iatrogenic or benign FDG uptake should not be selected as target lesion
- It is required to select the hottest tumor at each time point
  Note: Selected baseline target lesion may not be the hottest tumor at V3

23.8.5 Assessable FDG PET study and measurable target lesion

- Mean SL + imaging conditions of the liver must be stable to be assessable
- To be assessable, differences between baseline and during the study (V3) SUL in the liver must be
  - ≤ 20% of the larger of the 2 liver measurements and
  - ≤ 0.3 SUL units
- The imaging condition that allow for comparison are as follows
  - Difference between the injection-to-imaging time of baseline and to that of during the study (V3) should be ≤ 15 minutes
  - Injection-to-imaging start time for both baseline and during the study (V3) should be ≥ 50 minutes and ≤ 70 minutes
  - Same imager should be used at the same site
  - Same acquisition and reconstruction protocol and software version should be used
  - Difference between injected dose of FDG for the baseline study as well as during the study (V3) study should be ≤ 20%
  - Patients should fast for at least 4 hours prior to administration of FDG. Serum glucose levels must be < 200 mg/dL

  Note: If imaging conditions are not met, it should be noted in the report.

23.8.6 Objective response

- It is encouraged to record the percentage of change in tumor metabolism as a continuous variable with notation of the number of weeks since treatment start
- The percentage of change in target lesions is computed as:

$$100 \times [FTL_{SULpeak} - \frac{BTL_{SULpeak}}{BTL_{SULpeak}}]$$

[where $FTL_{SULpeak}$ is the *SULpeak* of the V3 target lesion and $BTL_{SULpeak}$ is the SUL_{peak} of the baseline target lesion]

- The PERCIST categories for response to treatment are mCR, mPR, metabolic stable disease (mSD) and metabolic progressive disease (mPD)

23.8.7 PERCIST categories for response to treatment

- For **complete metabolic response**, a target lesion must show complete resolution of FDG uptake
  - FDG uptake < mean SUL of the liver and indistinguishable from the surrounding background
  - This requires data for all other lesions to return to background levels and that no new FDG-avid lesions in a pattern typical of cancer appear
  - In case no FDG-avid tumor is visible, the mean SULpeak of the anatomic location situated as close as possible to the site of the original tumor should be measured
  - Normal structure with high FDG uptake (e.g. bowel loop that occupies site of the original target lesion) should be avoided in the measurement of results during the study (V3)
  - Complete metabolic response does not require the SUL_{peak} to decrease to zero
- For **partial metabolic response** a decrease of ≥ 30% and at least 0.8 SUL units must be shown between the most intense evaluable lesion at baseline and the most intense lesion at V3
  - A decrease in SUL_{peak} ≥ 0.8 SUL unites in the target lesion
  - No new lesion in a pattern typical of cancer
  - No identifiable increase in size > 30% in a non-target lesion
- For **stable metabolic disease**, an increase or decrease in SUL_{peak} of < 30% is required
- For **progressive metabolic disease**, lesions must show
  - an increase of ≥ 30% and
  - increase of at least 0.8 SUL units in a target lesion or
  - development of a new lesion or
  - > 1 new lesions
- The response (% of change in SUL_{peak} and time in weeks after treatment start) should be included
  - For progressive metabolic disease, whether new lesions are present or absent, the number of weeks into therapy + number of new lesions should be reported. If a non-target lesion behaves differently from baseline target lesion, further consideration is required.
- Duration of overall response is calculated as the date of the best response to the date when recurrent or progressive disease was first noted

Table 20 Scenarios for target and non-target lesions showing different responses during the study (V3) and overall response synthesis

Original target response	Original non-target response	Overall response
mCR	mPR	mPR
mCR	mSD	mPR or mSD
mCR	mPD	mPD

Original target response	Original non-target response	Overall response
mPR	mCR	mPR
mPR	mSD	mPR or mSD*
mPR	mPD	mPD
mSD	mCR	mSD
mSD	mPR	mSD
mSD	mPD	mPD
mPD	mCR	mPD
mPD	mPR	mPD
mPD	mSD	mPD

*the choice between mPR and mSD depends on the difference between the percentage in change in SUL an absolute SUL. If the decrease from baseline to follow-up (=V3) is sufficient the response is mPR. If the decrease is < 30 % or 0.8 SUL units, the response is mSD.

23.8.8 Unresolved and partly resolved issues

- Multiple aspects of PET response assessment have not been fully addressed in PERCIST due to lack of sufficient data. Please refer to the full PERCIST criteria for additionally information

23.8.9 Recommended exploratory data to consider for collection and documentation

Please note that these data will not be documented in the eCRF, but should be included on the medical report, if performed and available.

Table 21 PET metrics for collection of optional exploratory data

SUL_{peak} of up to the 5 hottest tumors	Mean SUL in 1-mL spherical VOIs is calculated
	5 hottest assessable SUL_{peak} values at baseline are included
	Up to two lesions per organ are evaluated
	To calculate percentage of change in SUL of 5 lesions, date from each lesion is summed before and after treatment [1]
Maximum SUL	
Mean SUL at 50% and 70% of SUL_{peak} or maximum SUL	
PET-derived metabolic tumor volume [2]	> 50 % of SUL_{peak}
	> mean SUL + 2SD of liver
	> mean SUL + 3SD of liver
	> 1.5 x mean SUL + 2SD of liver
	Liver mean SUL and SD from 3-cm spherical VOI: for all tumor foci, 5 lesions with the highest SUL, or one lesion with highest SUL

Total lesion glycolysis [3]	Total lesion glycolysis = mean SUL of total tumor times total metabolic tumor volume in mL
	Total lesion glycolysis increase ≥ 75 % categorized as mPD
	Total lesion glycolysis decrease ≥ 45 % categorzed as mPR
Nonassessable tumors	Tumors with FDG uptake < 1.5 x (mean SUL) + 2SD
	Note and measure disappearance, or obvious progression, segregating the data

[1] Change in data required for categorization as mPR and mPD with more than one target lesion is yet undefined.

[2] FDG uptake of tumor lower than the threshold for metabolic tumor volume could be zero at follow up (=V3), even when SUL_{peak} does not show mCR.

[3] Threshold percentage for response assessment of total lesion glycolysis is undefined.