



**A randomized open-label phase II study of
letrozole plus afatinib versus letrozole alone
in first-line treatment of advanced ER+, HER2-
postmenopausal breast cancer with low ER expression**

CLINICAL TRIAL PROTOCOL TRIO-020

Protocol version / Date	Version 5.0 / 31 July 2018
Sponsor	Translational Research In Oncology (TRIO)
EUDRACT #	2013-002192-18
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LIST OF ABBREVIATIONS

ABC	Advanced Breast Cancer
ALT	Alanine Aminotransferase / GPT
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase / GOT
BC	Breast Cancer
BI	Boehringer Ingelheim
BUN	Blood Urea Nitrogen
°C	Degrees Celsius
CAP	Chest Abdomen Pelvis
CBR	Clinical Benefit Response
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTA	Clinical Trial Application
CTCAE	Common Terminology Criteria of Adverse Events
CV	Coefficient of Variation
DCF	Data Clarification
DDI	Drug-Drug interaction
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic Acid
DSUR	Developmental Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture System
ER	Estrogen Receptor
°F	Degrees Fahrenheit
FISH	Fluorescent In Situ Hybridization
Fmol	Fentomole
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practices
HDPE	High Density Polyethylene
HER2	Human Epidermal Growth Factor Receptor 2
HR	Hormone Receptors
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
INN	International Nonproprietary Name
IRB	Institutional Review Board
ITT	Intent-To-Treat
IWRS	Interactive Web Recognition System
LDH	Lactate dehydrogenase
LFT	Liver Function test

LPLV	Last Patient Last Visit
μL	Microliter
μM	Micromolar
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
mL	Milliliter
mos	months
MRI	Magnetic Resonance Imaging
Msec	Milliseconds
NCBI	National Center for Biotechnology Information
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non Small Cell Lung Cancer
OR	Objective Response
OS	Overall Survival
PFS	Progression-Free Survival
P-gp	P-glycoprotein
PICF	Patient informed Consent From
PK	Pharmacokinetic(s)
PR	Partial Response
PS	Performance Status
RECIST	Response Evaluation Criteria In Solid Tumors
RH	Relative Humidity
RNA	Ribonucleic Acid
SAP	Statistical Analysis Plan
SD	Stable Disease
SNP	Single Nucleotide Polymorphism
SoC	Standard Of Care
SoD	Sum of Diameters
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TRIO	Translational Research In Oncology
TTP	Time To Progression
Txt	Treatment
UCLA	University of California Los Angeles
UK	United Kingdom
UNL	Upper Normal Limit
WBC	White Blood Cells

PROTOCOL SYNOPSIS

Protocol Title	A randomized open-label Phase II study of letrozole plus afatinib (BIBW2992) versus letrozole alone in the first-line treatment of advanced ER+, HER2-postmenopausal breast cancer with low ER expression.
Protocol #	TRIO-020
Trial Duration	Accrual = 18 months Total time = 44 months
Participating Investigator Sites	This is a TRIO-sponsored trial with Dr Richard FINN, as Trial chair 26 sites worldwide.
Background and Rationale	<p>The challenges in novel drug development in cancer medicine are clear: while many molecular targets have been identified, predicting which patients will gain benefit from inhibiting those targets remains critical. One of the great challenges in breast cancer research has been the integration of HER-family inhibitors into clinical practice outside of HER2 amplification (Alvarez RH, 2010). Clearly, HER2 amplification is a well-validated predictive marker for response to the small molecule dual EGFR/ HER2 inhibitor lapatinib (Geyer CE, 2006) and the humanized monoclonal antibody trastuzumab (Slamon DJ, 2011). However, outside of HER2 amplification, the role of the epidermal growth factor receptor (EGFR/ HER1), its ligands, and co-receptors in clinical breast cancer has been elusive. Of the other HER-family members, EGFR has been aggressively pursued in breast cancer with both small molecules (erlotinib, gefitinib, lapatinib) and monoclonal antibodies (cetuximab) with disappointing efficacy (Alvarez RH 2010). These results contribute to the following hypotheses: (1) EGFR is not an important therapeutic target in breast cancer, (2) the available inhibitors are insufficient at blocking EGFR signaling in breast cancer tissue, or (3) the population of breast cancer patients with EGFR <i>driven</i> disease is smaller than expected and a combination of biomarkers for patient selection is required.</p> <p>The interplay between steroid hormone signaling and peptide growth factor signaling through the HER-family is well described in breast cancer (Arpino G, 2008). Both expression of EGFR and HER2 amplification have been shown to mediate resistance to anti-estrogen therapy in laboratory models and clinical studies (Massarweh S, 2008) (Osborne CK, 2005) (Rimawi MF, 2010). These data have been the rationale for pursuing the combination of HER family inhibition and anti-estrogen therapy. In patients with HER2 amplification, studies with both trastuzumab and lapatinib have shown an improvement in progression-free survival with the addition of anti-HER2 therapy in combination with anastrozole or letrozole respectively (Kaufman B, 2009) (Johnston S, 2009). The latter trial, EGF30008, was a randomized, placebo-controlled, phase III trial of over 1200 post-menopausal women with HR-positive disease. Two hundred and nineteen women were enrolled with confirmed HER2 amplification. Patients were randomized to receive either letrozole and placebo or letrozole and lapatinib. Primary endpoint of the trial was PFS. The HER2 amplified cohort had a significant improvement in progression-free survival (PFS) with the addition of lapatinib (hazard ratio [HR] = 0.71; 95% CI, 0.53 to 0.96; p=0.019); median PFS was 8.2 vs 3.0 months, respectively. However, in subjects with centrally confirmed, HR-</p>

	<p>positive, HER2 negative tumors (n=952) there was no improvement in PFS. A pre-planned Cox regression analysis to try to enrich for an EGFR-dependent clinical phenotype, identified prior anti-estrogen therapy as a significant factor in the HER2 negative population. A non-significant trend toward prolonged PFS for lapatinib in combination with letrozole was seen in patients who experienced relapse less than 6 months after their prior tamoxifen discontinuation (HR = 0.78; 95% CI, 0.57 to 1.07; $p=0.117$). While this trend is of interest, the identification of a molecular marker for response to lapatinib and letrozole in HER2 negative women would be of potential great value.</p> <p>Previous biomarker work by Dr Richard Finn's group identified a correlation between quantitative hormone receptor measurements and response to lapatinib and paclitaxel in a HER2 negative cohort of women with advanced breast cancer (Finn RS, 2009). In addition other studies have suggested a relationship between peptide growth factor signaling and hormone receptor status (Arpino G W. H., 2005), specifically, that progesterone receptor (PR) loss in estrogen receptor (ER) positive disease is associated with higher expression of EGFR and/or HER2. In addition, a pre-surgical trial demonstrated cell-cycle inhibition in ER-positive and PR-weak or PR-negative patients with breast cancer who were exposed to a short course of the EGFR inhibitor gefitinib (Finn RS, 2006).</p> <p>Recently, the standard treatment of patients with ER-positive, HER2-negative ABC have dramatically changed with the introduction into clinical practice of cyclin-dependent kinase (CDK) 4/6 inhibitors. Palbociclib, abemaciclib and ribociclib FDA-approved CDK4/6 inhibitors for the treatment of women with ER-positive, HER2-negative ABC.</p> <p>The benefit of CDK4/6 inhibitors in combination with aromatase inhibitors as an effective first-line option was first demonstrated in the phase 2 clinical trial PALOMA-1 and was later confirmed in the phase 3 trial PALOMA-2. This trial randomized a total of 666 postmenopausal women in a 2:1 fashion to receive palbociclib plus letrozole or placebo plus letrozole. The median progression-free survival reported was 24.8 months (95% CI, 22.1 to not estimable) in the palbociclib-letrozole group, as compared with 14.5 months (95% CI, 12.9 to 17.1) in the placebo-letrozole group (hazard ratio for progression or death, 0.58; 95% CI, 0.46 to 0.72; $P<0.001$). Palociclib and later ribociclib and abemaciclib trials helped to reshape the standard approaches in ER-positive, HER2-negative ABC.</p> <p>To further test the hypothesis that semi-quantitative ER and PR measurements are molecular markers for EGFR dependence, we performed a blinded, retrospective analysis of ER and PR in HER2 negative breast cancer in the EGF30008 cohort (Finn RS, 2009). In this analysis that compared the activity of letrozole versus letrozole and lapatinib in ER+ women, it was determined that those women with low ER expression (defined as the lowest quartile based on semi-quantitative IHC, H-score) had a significant improvement in PFS with the combination vs letrozole alone (13.6 mos vs 6.6 mos, HR= 0.65; 95% CI 0.47 to 0.9, $p<0.005$). This finding was of particular significance as the overall HER2 negative population did not show any significant benefit from the addition of lapatinib. Only when a specific criterion was applied to isolate patients with low ER expression, was a subpopulation of breast cancers with HER dependence identified. Also, to note, is that the low ER expressing patients had a very poor natural history with letrozole alone, with a PFS of 6.6 mos. This is much less than</p>
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	<p>the overall population and higher ER expressing patients whose PFS was approximately 14 mos.</p> <p>The proposed trial with afatinib was designed to test the hypothesis that low ER expression as determined by semi-quantitative immuno-histochemistry (IHC) is a biomarker for HER-dependence in women with HER2 negative breast cancer</p> <p>Protocol amendment 4.0 was released on 09 May 2016 and its main change was the enrollment closure due to insufficient efficacy data to pursue development of afatinib in breast cancer and low recruitment in the trial. As of the date of release of this new protocol amendment, there are 6 patients still on treatment in the trial and among those, only 2 patients are treated with the combination of letrozole and afatinib (Arm B). Due to the limited number of patients still on treatment, and especially in Arm B, TRIO and BI agreed to release this amendment to discontinue the trial, allowing patients receiving afatinib to continue with this treatment outside of the TRIO-020 trial.</p>
<p>Objectives / Endpoints</p>	<p>The planned objectives were</p> <p>Primary Objective :</p> <ul style="list-style-type: none"> To assess the effect of letrozole plus afatinib and of letrozole alone on progression-free survival (PFS) in the first line treatment of ER+, HER2 negative postmenopausal ABC women with low ER expression. <p>The Primary endpoint was PFS.</p> <p>Secondary Objectives :</p> <ul style="list-style-type: none"> To assess secondary measures of efficacy of afatinib administered in combination with letrozole and of letrozole alone. <p>Endpoints: Overall survival (OS), Objective Response rate (OR) and Time to tumor progression (TTP)</p> <ul style="list-style-type: none"> To assess the safety and tolerability of afatinib administered in combination with letrozole and of letrozole alone. <p>Endpoint: overall safety profile</p> <p>The enrollment was closed prematurely on 05 MAR 2016 due to the small number of patients randomized compared to what was initially planned as per the statistical analysis. The data collected for all patients will be described per arm but no statistical comparison will be made. Therefore the primary and secondary objectives are not applicable.</p>
<p>Population</p>	<p>Inclusion Criteria</p> <p>Signed and dated informed consent.</p> <p>Postmenopausal females, 18 years of age or older.</p> <p>Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease.</p> <p>HER2 negative breast cancer.</p> <p>ER positive breast cancer. Central testing (required for all patients) must demonstrate that the tumor is ER+ with low expression (H-score [1-159]).</p> <p>Paraffin-embedded tumor block(s) or 15 to 20 unstained slides available for</p>

	<p>centralized assessment of ER, PR, and HER2.</p> <p>Measurable disease according to RECIST 1.1 or bone-only non measurable disease.</p> <p>ECOG Performance status 0 or 1.</p> <p>Adequate hematological, hepatic and renal functions.</p> <p>Baseline LVEF \geq 50%.</p> <p>Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.</p> <p>Exclusion Criteria</p> <p>Brain metastases, spinal cord compression, carcinomatous meningitis, or leptomeningeal disease.</p> <p>Prior treatment with any type of systemic therapy for advanced disease.</p> <p>Prior treatment with letrozole in (neo)adjuvant setting with disease-free interval \leq 12 months from completion of treatment until randomization.</p> <p>Prior treatment with any anti HER-family targeted therapy in (neo)adjuvant setting.</p> <p>Any concurrent or previous malignancy within 5 years prior to randomization, except for adequately and radically treated basal or squamous skin cancer, or carcinoma in situ of the cervix, or other non-invasive/in-situ neoplasm.</p> <p>Non-measurable disease according to RECIST 1.1, with the exception of bone-only non-measurable disease.</p> <p>Known pre-existing interstitial lung disease.</p> <p>Significant or recent acute gastrointestinal disorders with diarrhea as a major symptom.</p> <p>History or presence of clinically relevant cardiovascular abnormalities as per investigator assessment.</p> <p>Any other concomitant serious illness or organ system dysfunction as per investigator assessment</p> <p>Any contraindication to oral agents.</p> <p>Active hepatitis B infection (defined as presence of HepB sAg and/ or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) or known HIV carrier.</p> <p>Known or suspected active drug or alcohol abuse.</p> <p>Known hypersensitivity to afatinib or letrozole or the excipients of any of the trial drugs.</p> <p>Concomitant treatment with strong inhibitor of P-gp (see section 5.5.2).</p> <p>Any ongoing acute clinically significant toxic effect of prior anticancer therapy or any persisting complication of prior surgery.</p> <p>Patients with known history of keratitis, ulcerative keratitis or severe dry eye.</p>
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	Participation in the active phase of other clinical trials of investigational agents in which last trial treatment was administered within 2 weeks prior to randomization.
Trial Design	<p>This is an open-label, multicenter, international, randomized, Phase II clinical trial that aimed to assess the efficacy and safety of letrozole in combination with afatinib(oral EGFR inhibitor) versus letrozole monotherapy for the first-line treatment of postmenopausal women with ER+, HER2 negative advanced breast cancer with low ER expression.</p> <p>In order to assess the level of ER expression we used a semi-quantitative scoring system (McClelland RA 1990) defined as:</p> <p>H-score = (% of cells stained at intensity category 1x1) + (% of cells stained at intensity category 2x2) + (% of cells stained at intensity category 3x3).</p> <p>This formula results in an H-score in the range of 0-300 where 300 equals 100% of tumor cells stained strongly (i.e., 3+). Low ER expression was defined as tumor sample with H-score below 160 (Finn RS, 2009).</p> <p>All patients consented on the trial submitted a tumor sample to the designated central laboratory for central confirmation of ER/PR and HER2 statuses and determination of the H-score. This was assessed prior to randomization.</p> <p>Patients with HER2 negative, ER+ advanced breast cancer with low ER expression defined as H-score between 1 and 159 entered screening phase and performed the required screening assessments.</p> <p>Eligible patients were randomly assigned in a 1:1 ratio and stratified according to sites of disease (bone only disease vs. other) and prior administration of hormonal therapy in neo/adjuvant setting (Yes vs. No) to either :</p> <p>Arm A: Continuous regimen of oral letrozole 2.5 mg until progression of disease or any other trial treatment discontinuation criteria.</p> <p>or</p> <p>Arm B: Continuous regimen of oral letrozole 2.5 mg daily plus oral afatinib 30 mg daily until progression of disease or any other trial treatment discontinuation criteria.</p> <p>IN ADDITION the following applies whichever comes first:</p> <ul style="list-style-type: none"> • If the patients treated with the combination of afatinib and letrozole (arm B) discontinue the trial treatment (whatever the reason) before 30 November 2018, the patients from the other arm (arm A, letrozole alone) still on treatment will also be discontinued from the trial at the same time. They may continue receiving letrozole using commercial drug as standard of care according to their treating physician discretion. • If the patients treated with afatinib and letrozole (arm B) have not discontinued the trial treatment by 30 November 2018, all patients currently on treatment in the trial (including the ones only treated by letrozole alone (arm A)) will be discontinued from the trial at that time. They may continue receiving their treatment if in alignment with their treating physician judgment as follows: <ul style="list-style-type: none"> ○ Patients in arm A: may continue receiving letrozole using commercial drug as standard of care according to their treating physician discretion.

	<ul style="list-style-type: none"> ○ Patients in arm B: may continue receiving afatinib in the context of alternative drug supply outside the clinical trial as appropriate according to local legislation. Additionally, they may continue receiving letrozole using commercial drug as standard of care according to their treating physician discretion. ● Note: In case no alternative drug supply outside the clinical trial as appropriate according to local legislation can be put in place and the 2 patients in Arm B are still on treatment on 30 November 2018, the protocol and PICF will need to be revised again. <p>Once the patient is discontinued from trial treatment and has undergone the End of Treatment Visit, she will be permanently discontinued from the trial and treated as per local clinical practice.</p> <p>This trial also includes an optional exploratory research component. This optional portion of the trial is a molecular profiling assay aimed to assess the relationship of antitumor activity with the expression of a few cell cycle-related proteins and other markers that may be identified in the future. Patients may participate in this trial even if they choose not to participate in the sample banking component.</p>
<p>Protocol Treatment</p>	<p>Arm A: Continuous regimen of oral letrozole 2.5 mg until progression of disease or any other trial treatment discontinuation criteria.</p> <p>or</p> <p>Arm B: Continuous regimen of oral letrozole 2.5 mg daily plus oral afatinib 30 mg daily until progression of disease or any other trial treatment discontinuation criteria.</p> <p>According to the decision to discontinue the patients from the trial by 30 November 2018, the active patients will not receive their treatment in the scope of the trial, but as commercial drug for letrozole and in the frame of alternative drug supply outside the clinical trial as appropriate according to local legislation for afatinib after that date.</p> <p>Note: In case no alternative drug supply outside the clinical trial as appropriate according to local legislation can be put in place and the 2 patients in Arm B are still on treatment on 30 November 2018, the protocol and PICF will need to be revised again.</p>
<p>Efficacy Assessments</p>	<p>Disease assessments every 12 weeks until documentation of progressive disease.</p> <p>This is applicable until 30 November 2018. After that date, the patients will be followed by their physician as per standard of care and the efficacy assessments will be performed as per local practice.</p>
<p>Safety Assessments</p>	<p>Physical examination, blood tests (hematology and blood chemistry) before each visit (every month) during the treatment period.</p> <p>LVEF every 12 weeks during the treatment period.</p> <p>This is applicable until 30 November 2018. After that date, the patients will be</p>

	followed by their physician as per standard of care and the safety assessments will be performed as per local practice.
Additional Assessments	None
Statistical Methods and Sample Size	N/A Due to the small number of patients enrolled in the trial, only a descriptive analysis will be conducted.

1. BACKGROUND AND RATIONALE

1.1 Disease Overview

Breast cancer (BC) is the most common invasive cancer in women, with more than one million cases and nearly 600,000 deaths occurring worldwide annually. Although age-adjusted mortality from breast cancer has been decreasing since 1990, the median survival for patients with metastatic disease is still approximately 18 to 24 months (Ferlay J, 2010) and the medical need remains very high. In 2010, an estimated 209,060 newly diagnosed cases of breast cancer and 40,230 breast cancer-related deaths occurred in the United States (Jemal A, 2010). Corresponding estimates in Europe for 2008 are 420,800 new cases and 129,300 deaths (Ferlay J, 2010). Although chemotherapy has improved outcomes, the marginal benefits achieved with cytotoxic agents seem to have reached a plateau, which has led to a recent, rapid increase in the development of molecular targeted therapeutics in breast cancer. This increase has been aided by technological advances in the characterization of the molecular heterogeneity of breast cancer. Consequently, breast cancer has been classified based on gene expression patterns into several different subtypes, including luminal A and B, HER2-positive, basal-like, and normal-like, although there can be some overlap in characteristics among the subtypes. Importantly, each of these molecular subtypes is associated with distinct prognoses (Sorlie T, 2001). The current trial focuses on addressing those women with ER+ breast cancer. Perhaps the greatest impact in the treatment of ER+ breast cancer has been the use of anti-estrogen agents in the adjuvant setting. However, there is still a number of women that relapse during or after adjuvant therapy and develop some degree of hormone independence. For these women, cytotoxic chemotherapy extends survival but is not curative. Certainly, any new agent that could improve survival and slow the progression to chemotherapy initiation would be of clinical importance.

1.2 Current Treatment Overview

Approximately two thirds of breast cancers express estrogen receptor ER (Harvey JM, 1999) and a role for estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormone receptor-positive advanced breast cancer (ABC), particularly for those with slowly progressive disease and limited tumor-related symptoms (Hurvitz SA, 2008). Conversion of androgens to estrogens via aromatase enzyme action represents the main source of estrogens in postmenopausal women. Letrozole (Femara®) is an oral non-steroidal aromatase inhibitor that is approved worldwide for the first line treatment of postmenopausal women with hormone receptor-positive ABC. In a multicenter Phase 3 trial (Mouridsen H, 2003), 916 patients with hormone receptor positive or hormone receptor unknown ABC were randomized to receive either letrozole or tamoxifen up to disease progression. Most of the patients (91%) had received no prior treatment for their advanced disease. Letrozole was superior to tamoxifen for time to progression TTP (median, 9.4 vs 6.0 months, $p < 0.0001$), time to treatment failure TTF (median, 9 vs 5.7 months, $p < 0.0001$), overall objective response rate ORR (32% vs 21%, $p = 0.0002$), and overall clinical benefit (50% vs 38%, $p = 0.0004$). Median overall survival (OS) was slightly prolonged for the randomized letrozole arm (34 vs 30 months), however approximately 50% of the patients in the tamoxifen arm crossed over to letrozole at disease progression.

Besides letrozole or other aromatase inhibitors there are other anti-estrogen therapies available including direct estrogen receptor down-regulators such as fulvestrant (Faslodex) (Hurvitz SA, 2008).

Recently, the standard treatment of patients with ER-positive, HER2-negative ABC have dramatically changed with the introduction into clinical practice of cyclin-dependent kinase (CDK) 4/6 inhibitors. Palbociclib, abemaciclib and ribociclib FDA-approved CDK4/6 inhibitors for the treatment of women with ER-positive, HER2-negative ABC.

1.3 The benefit of CDK4/6 inhibitors in combination with aromatase inhibitors as an effective first-line option was first demonstrated in the phase 2 clinical trial PALOMA-1 and was later confirmed in the phase 3 trial PALOMA-2. This trial randomized a total of 666 postmenopausal women in a 2:1 fashion to receive palbociclib plus letrozole or placebo plus letrozole. The median progression-free survival reported was 24.8 months (95% CI, 22.1 to not estimable) in the palbociclib-letrozole group, as compared with 14.5 months (95% CI, 12.9 to 17.1) in the placebo-letrozole group (hazard ratio for progression or death, 0.58; 95% CI, 0.46 to 0.72; P<0.001). Palociclib and later ribociclib and abemaciclib trials helped to reshape the standard approaches in ER-positive, HER2-negative ABC.

Investigational Medicinal Product Overview

Afatinib is a highly potent, irreversible ErbB family blocker that displays anti-tumour efficacy both in vitro and in vivo. Afatinib has shown efficacy signals in clinical trials and thus may represent an excellent drug candidate for the treatment of a variety of cancers.

Afatinib covalently binds to and irreversibly blocks signaling from all homo- and heterodimers formed by the ErbB family members: Epidermal growth factor receptor (EGFR, ErbB1), HER2 (ErbB2), ErbB3 and ErbB4. Objective responses to treatment have been observed in afatinib Phase I monotherapy and combination therapy trials in patients with solid tumors, including NSCLC, HNSCC, urothelial carcinoma, breast cancer, esophageal cancer and cholangiocarcinoma. Clinical activity has been observed in Phase II trials in patients with NSCLC, HER2-positive trastuzumab-refractory breast cancer and urothelial carcinoma (UC). Superiority of afatinib monotherapy has been demonstrated in two pivotal randomized Phase III trials in patients with EGFR mutation positive NSCLC over standard platinum based chemotherapy, in a Phase IIb trial comparing head to head afatinib monotherapy to first generation EGFR TKI gefitinib, and in a randomised Phase III trial in patients with SCC of the lung, extending PFS progression-free survival and overall survival compared to erlotinib as second-line treatment. Afatinib monotherapy was also shown to be superior to methotrexate, in a Phase III trial in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (HNSCC), extending PFS as second line treatment.

Afatinib is approved for use:

- as monotherapy in patients with advanced EGFR mutation positive NSCLC in more than 70 countries including the EU and US.
- for the treatment of NSCLC of squamous histology after platinum based chemotherapy in more than 40 countries including the EU and US.

Afatinib is currently in development in the following indications: recurrent and/or metastatic HNSCC; urothelial carcinoma and ErbB alteration; pediatric patients with recurrent/refractory

neuroectodermal tumors, rhabdomyosarcoma and/or other solid tumors with known ErbB pathway deregulation regardless of tumor histology; advanced NSCLC harboring HER2 mutations, previously treated with chemotherapy; and in combination with pembrolizumab in the second line treatment of patients with locally advanced or metastatic squamous cell carcinoma of the lung.

1.3.1 Preclinical pharmacology and toxicology

In mice, afatinib reaches efficacious plasma exposure with once-daily dosing throughout the treatment period. afatinib displays antitumor activity, including tumor regression, against established subcutaneous xenografts in nude mice either as a single agent or in combination with a cytotoxic agent like docetaxel. The necessary maximum plasma concentrations were between 80 to 285 nM for single agent activity. The absolute bioavailability was medium-high in rats (45%). The median t_{max} after oral administration was 4 hours and the terminal half-life was 4.5 hours. The terminal half-life of the radiolabelled compound was considerably longer indicating persistence of metabolites in the system. The exposure was dose proportional without gender-related effects. Some accumulation in the 13-week and 26-week toxicology trial appeared more pronounced in males. In minipigs there was a slight tendency towards supra-proportional increases in AUC_{0-24h} with increasing doses, which was considered to be of minor relevance. A consistent effect on accumulation was not seen.

In the whole body autoradiography in rats, afatinib was distributed in all organs with the exception of the CNS after oral administration. The highest concentrations were found in the kidney, liver, lung, and spleen. In general, a slow elimination of radioactivity was seen. The major excretion pathway is via faeces (91%). Afatinib covalently binds to plasma proteins. Whether such protein haptens are immunogenic and capable of inducing allergic reactions is unknown.

Afatinib did not show relevant inhibition or induction of cytochrome P450 isoenzymes, and it appears unlikely that drug-drug interactions as based on this mechanism will occur. In vivo, afatinib was metabolized only to a minor extent and the metabolism was governed by adduct formation to proteins or nucleophilic small molecules. It was found that metabolism is of subordinate role for afatinib and that enzyme-catalyzed metabolic reactions play a negligible role for the metabolism of afatinib in vivo. Only approximately 2% of the dose were metabolized by FMO3 in vivo. The CYP3A4-dependent N-demethylation was even too low to be quantitatively detected in human volunteers. Therefore, intrinsic (e.g. genetic predisposition) or extrinsic (e.g. by comedications) effects on the activity of FMO3 or CYP3A4 in vivo are expected to be of little, if any, relevance for the pharmacokinetics of afatinib.

In vitro, afatinib was found to be a P-gp substrate (estimated K_m 10-30 μ M) and a moderate to weak inhibitor of P-gp (estimated K_i of 3.4 μ M). It cannot be excluded that concomitant treatment with other P-gp substrates or P-gp inhibitors may alter the plasma concentrations of afatinib. Since $1/K_i$ of afatinib is resulting in values considerably below 0.1 which would be the defined "cut off" value for considerable drug-drug interactions based on P-gp (afatinib acting as a P-gp inhibitor) it is unlikely that afatinib may alter the plasma concentrations of other P-gp substrates.

Safety pharmacology studies (GLP) in rats indicate no adverse effects on behavior or respiratory function. Afatinib in the doses tested was essentially devoid of effects on the CNS and pulmonary system. Lack of organ specific toxicity was also true for the cardiovascular system with the exception of reduced contractility at higher intravenous doses.

An effect on renal and liver function was seen with a very high oral dose of 300 mg/kg in rats. Furthermore, a dose dependent effect on gastrointestinal function was seen, leading to a substantial inhibition at the highest dose. *In vitro* data, together with the lack of effect on the ECG in pigs and minipigs, do not indicate a risk for QT prolongation related arrhythmias.

A variety of single and repeated dose studies were conducted with afatinib. The main target organs were the skin (rat), the gastrointestinal tract (both species) and the kidneys (rat). The severity of the findings resulted in premature sacrifices and mortality of rats at high dose groups in repeat dose studies.

In the gastrointestinal tract, increasing systemic exposure was associated with dose dependent atrophy of the epithelium and concomitant focal erosions/ulcerations in the stomachs of rats and minipigs. Clinically, this was characterized by diarrhea in both species and fecal occult blood in a single minipig. Other organs affected by the epithelial atrophy in the rat were the skin, prostate, uterus, and vagina. In minipigs, the upper respiratory tract, seminal vesicles, and the corneal epithelium were affected by epithelial atrophy. In the gastrointestinal and respiratory tract, atrophy of the mucinous glands, e.g. salivary glands, was also found. These atrophic changes were minimal to slight and fully reversible during the recovery periods and are most likely related to the pharmacodynamic mechanism of afatinib.

Findings in rat kidneys include papillary necrosis and dilated tubules. The kidney as a target organ in animals is also described for the EGFR-inhibitors gefitinib (Iressa™) and erlotinib (Tarceva™).

Afatinib is not irritating to intact skin. Afatinib is slightly mutagenic in a single bacteria strain, but it did not show genotoxic potential *in vivo* when tested up to overt toxic/lethal doses. Because of the pharmacodynamic mechanism, afatinib is probably embryo-/fetotoxic.

Based on these toxicological findings and the experience with other EGFR- and HER2-inhibitors, the risks of anti-EGFR and anti-HER2 therapy with afatinib might primarily consist of gastrointestinal effects (including diarrhea) and skin rash.

1.3.2 Clinical pharmacokinetic and safety

PK data available from clinical trials until now indicate that afatinib was moderately fast absorbed after oral administration, with median t_{max} values mainly between 2 and 5 hours. For afatinib there was no deviation from dose-proportionality detectable. However, moderate to high inter- and intra-individual differences in plasma concentrations were seen. Afatinib was highly distributed out of the blood and had a moderate to high clearance. The gMean terminal half-life was mainly in the range of 13-57 h. Steady state was reached no later than 8 days after the first administration. The major route of elimination of afatinib was via the faeces. After food intake, a decreased systemic exposure was observed compared to administration of afatinib under fasted conditions. Typically, an accumulation ratio based on AUC values between 1.8 and 4.0 has been observed. At doses of 40 mg and above individual $C_{max,ss}$ and $AUC_{t,ss}$ values were mainly in the same range as those found to demonstrate anti-tumor activity in nude mouse tumor xenograft models.

Adverse events observed with afatinib are consistent with those reported for other EGFR- and dual EGFR/HER2-inhibitors. These include predominantly gastrointestinal (GI) and dermatological adverse events which are dose-dependent. Diarrhea, including severe diarrhea, has been reported during treatment with afatinib. Diarrhea may result in dehydration with or without renal impairment, which in rare cases has resulted in fatal outcomes. Diarrhea usually occurred within the first 2 weeks of treatment. Patients of low body weight, females, and patients with low

baseline renal function appear to be at higher risk for the development of higher grades of diarrhea. Up to 5-7% of patients experienced dehydration and pre renal insufficiency, most likely secondary to gastrointestinal toxicities, particularly diarrhea. Other gastrointestinal adverse events include mucositis/stomatitis, nausea, and vomiting. Dermatological adverse events include rash, acne, paronychia, pruritus, dry skin, eczema, and folliculitis. Rash/acne occurred at a high frequency and half of the cases begin within 4 weeks of exposure to afatinib. Grade 3 rash is observed in about 17-18% of patients and those at higher risk for Grade 3 rash/acne appear to be the patients of low body weight/body surface area and patients with low baseline renal function. A higher incidence of CTCAE Grade 3 adverse events (especially diarrhea) have been observed in phase II trials at 50 mg.

Interstitial lung disease (ILD) is reported in approximately 1% of patients and is a serious (potentially fatal) adverse event. One related case of fatal interstitial lung disease (ILD) was reported in a NSCLC patient. Considering reports of suspected cases of ILD on afatinib, trials exclude patients with known pre-existing ILD from treatment with afatinib and careful monitoring of pulmonary symptoms with sudden onset is warranted in all clinical trial protocols. For further details and regular updates on listed adverse events please refer to the current IB.

Afatinib is metabolized only to a minor extent therefore PK-response correlations were performed only for the parent compound afatinib. There was no clear trend observed between afatinib trough plasma concentrations and objective response. A correlation was observed between trough plasma concentration and severity of diarrhea and rash/acne as measured by the CTCAE grades for these adverse events. Severity of diarrhea and rash/acne increased with increasing trough plasma concentration of afatinib.

The safety profile of afatinib is characterized by a significant incidence of dose-dependent gastrointestinal and skin adverse events. Early, proactive, and effective management of these adverse events is mandated in ongoing and forthcoming clinical trials with early intervention to manage diarrhoea and skin toxicities.

1.4 Rationale

The challenges in novel drug development in cancer medicine are clear: while many molecular targets have been identified, predicting which patients will gain benefit from inhibiting those targets remains critical. One of the great challenges in breast cancer research has been the integration of HER-family inhibitors into clinical practice outside of HER2 amplification (Alvarez RH, 2010). Clearly, HER2 amplification is a well-validated predictive marker for response to the small molecule dual EGFR/ HER2 inhibitor lapatinib (Geyer CE, 2006) and the humanized monoclonal antibody trastuzumab (Slamon DJ, 2011). However, outside of HER2 amplification, the role of the epidermal growth factor receptor (EGFR/ HER1), its ligands, and co-receptors in clinical breast cancer has been elusive. Of the other HER-family members, EGFR has been aggressively pursued in breast cancer with both small molecules (erlotinib, gefitinib, lapatinib) and monoclonal antibodies (cetuximab) with disappointing efficacy (Alvarez RH 2010). These results contribute to the following hypotheses: (1) EGFR is not an important therapeutic target in breast cancer, (2) the available inhibitors are insufficient at blocking EGFR signaling in breast cancer tissue, or (3) the population of breast cancer patients with EGFR *driven* disease is smaller than expected and a combination of biomarkers for patient selection is required.

The interplay between steroid hormone signaling and peptide growth factor signaling through the HER-family is well described in breast cancer (Arpino G, 2008). Both expression of EGFR and HER2

amplification have been shown to mediate resistance to anti-estrogen therapy in laboratory models and clinical studies (Massarweh S, 2008) (Osborne CK, 2005) (Rimawi MF, 2010). These data have been the rationale for pursuing the combination of HER family inhibition and anti-estrogen therapy. In patients with HER2 amplification, studies with both trastuzumab and lapatinib have shown an improvement in progression-free survival with the addition of anti-HER2 therapy in combination with anastrozole or letrozole respectively (Kaufman B, 2009) (Johnston S, 2009). The latter trial, EGF30008, was a randomized, placebo-controlled, phase III trial of over 1200 post-menopausal women with HR-positive disease. Two hundred and nineteen women were enrolled with confirmed HER2 amplification. Patients were randomized to receive either letrozole and placebo or letrozole and lapatinib. Primary endpoint of the trial was PFS. The HER2 amplified cohort had a significant improvement in progression-free survival (PFS) with the addition of lapatinib (hazard ratio [HR] = 0.71; 95% CI, 0.53 to 0.96; $p=0.019$); median PFS was 8.2 vs 3.0 months, respectively. However, in patients with centrally confirmed, HR-positive, HER2 negative tumors ($n=952$) there was no improvement in PFS. A pre-planned Cox regression analysis to try to enrich for an EGFR-dependent clinical phenotype, identified prior anti-estrogen therapy as a significant factor in the HER2 negative population. A non-significant trend toward prolonged PFS for lapatinib in combination with letrozole was seen in patients who experienced relapse less than 6 months after their prior tamoxifen discontinuation (HR = 0.78; 95% CI, 0.57 to 1.07; $p=0.117$). While this trend is of interest, the identification of a molecular marker for response to lapatinib and letrozole in HER2 negative women would be of potential great value.

Previous biomarker work by Dr Richard Finn's group identified a correlation between quantitative hormone receptor measurements and response to lapatinib and paclitaxel in a HER2 negative cohort of women with advanced breast cancer (Finn RS, 2009). In addition other studies have suggested a relationship between peptide growth factor signaling and hormone receptor status (Arpino G W. H., 2005), specifically, that progesterone receptor (PR) loss in estrogen receptor (ER) positive disease is associated with higher expression of EGFR and/or HER2. In addition, a pre-surgical trial demonstrated cell-cycle inhibition in ER-positive and PR-weak or PR-negative patients with breast cancer who were exposed to a short course of the EGFR inhibitor gefitinib (Finn RS, 2006).

To further test the hypothesis that semi-quantitative ER and PR measurements are molecular markers for EGFR dependence, we performed a blinded, retrospective analysis of ER and PR in HER2 negative breast cancer in the EGF30008 cohort (Finn RS, 2009). In this analysis that compared the activity of letrozole versus letrozole and lapatinib in ER+ women, it was determined that those women with low ER expression (defined as the lowest quartile based on semi-quantitative IHC, H-score) had a significant improvement in PFS with the combination vs letrozole alone (13.6 mos vs 6.6 mos, HR= 0.65; 95% CI 0.47 to 0.9, $p<0.005$). This finding was of particular significance as the overall HER2 negative population did not show any significant benefit from the addition of lapatinib. Only when a specific criterion was applied to isolate patients with low ER expression, was a subpopulation of breast cancers with HER dependence identified. Also, to note, is that the low ER expressing patients had a very poor natural history with letrozole alone, with a PFS of 6.6 mos. This is much less than the overall population and higher ER expressing patients whose PFS was approximately 14 mos.

The proposed trial with afatinib was designed to test the hypothesis that low ER expression as determined by semi-quantitative immuno-histochemistry (IHC) is a biomarker for HER-dependence in women with HER2 negative breast cancer.

Afatinib is associated to letrozole which is one of the hormonal treatments of choice for treatment of advanced breast cancer in post-menopausal patients.

This is not the first trial combining letrozole and afatinib. There was a first phase II trial conducted by Boehringer Ingelheim and referred to as trial 1200.5 in the afatinib IB. The trial included 28 advanced breast cancer patients. Letrozole was used at its standard dose of 2.5 mg per day. Starting dose of afatinib was 50 mg (7 patients were treated at this dose) but due to toxicities (diarrhea and rash) afatinib dose was reduced to 40 mg (13 patients) and then 30 mg (8 patients). Patients on trial 1200.5 were heavily pre-treated, an amendment to the protocol allowed up to two prior chemo regimens in the advanced setting, 86 % of the patients had received prior chemotherapy and were letrozole resistant (patients were selected following progression under letrozole). In the proposed protocol, patients will receive letrozole + afatinib or letrozole alone as their first line in the advanced setting (all types of therapies confounded). They may have received prior chemotherapy but only in the neo-adjuvant or adjuvant setting. The two populations are therefore different in terms of prior treatment exposure.

The dose initially chosen for the clinical program of afatinib was 50 mg but this dose showed a significant rate of grade 3 diarrhea and rash events. Afatinib dose was then reduced to 40 mg for the continuation of the clinical program (see afatinib Investigator Brochure). In combination with letrozole, the dose of 40 mg was still associated with a high incidence of grade 3/4 diarrhea (30.8%) and grade 3 rash (23.1 %). At the dose of 30 mg, diarrhea and rash were of lower grade and incidence (grade 3 diarrhea was observed in 12.5 % of patients and no grade 3 rash was documented).

This, along with the relative good performance status of the patients and their light history of prior treatment compared to the one in the trial 1200.5, led to the choice of the dose of 30 mg for afatinib, to be associated with 2.5 mg of letrozole.

In trial 1200.5 Afatinib PK parameters were within the ranges observed in afatinib monotherapy studies (PK meta-analysis [U10-1153]), suggesting that continuous dosing in combination with 2.5 mg letrozole had no major influence on afatinib PK. Mean PK parameters for letrozole showed no trend to higher or lower values in conjunction with afatinib dosing. The observed letrozole PK parameters were in the ranges reported in the literature ([R10-4018] and [R10-4019]), suggesting that afatinib did not have a relevant effect on letrozole PK. Therefore, there was no indication of a DDI between letrozole and afatinib and vice versa (when compared with literature or historical data). Based on this data it is not planned to further evaluate PK interactions in this combination.

A detailed section on the management of adverse events, among which diarrhea and rash, has been incorporated in the protocol with some proactive precautions to avoid occurrence or aggravation of these specific adverse events at a very early point.

Protocol amendment 4.0 was released on 09 May 2016 and its main change was the enrollment closure due to insufficient efficacy data to pursue development of afatinib in breast cancer and low recruitment in the trial. As of the date of release of this new protocol amendment, there are 6 patients still on treatment in the trial and among those, only 2 patients are treated with the combination of letrozole and afatinib (Arm B). Due to the limited number of patients still on treatment, and especially in Arm B, TRIO and BI agreed to release this amendment to discontinue the trial, allowing patients receiving afatinib to continue with this treatment outside of the TRIO-020 trial.

2. OBJECTIVES

2.1 Planned primary and secondary objectives

2.1.1 Primary Objective

To assess the effect of letrozole plus afatinib and of letrozole alone on progression-free survival (PFS) in the first line treatment of ER+, HER2 negative postmenopausal ABC women with low ER expression.

The Primary endpoint was PFS. (Refer to section 8.4 for further details)

2.1.2 Secondary Objectives

- To assess secondary measures of efficacy for afatinib administered in combination with letrozole and for letrozole alone.

Endpoints:

Overall survival (OS)

Objective Response rate (OR)

Time to tumor progression (TTP)

- To assess the safety and tolerability of afatinib administered in combination with letrozole and of letrozole alone.

Endpoint: overall safety profile

The patient enrolment was closed prematurely on 05 MAR 2016 due to the small number of patients randomized compared to what was initially planned as per the statistical analysis. The data collected for all the patients will be described per arm but no statistical comparison will be made. Therefore the primary and secondary objectives are not applicable. .

2.2 Exploratory Objectives (Optional)

The area of research into the identification of tumor markers and biological processes / targets to aid in the identification of clinical benefit in certain subsets of populations or even in the identification of anticancer therapies to target the marker, is rapidly growing.

TRIO wishes to examine the molecular profiles of tumor tissue submitted by the patients to identify factors that may influence biological and clinical responses to afatinib and letrozole including but not limited to ER and PR H-score and the EGFR related downstream pathways.

As more development and information is revealed in the future, TRIO would like to use these tumor samples for measurement of the new markers. The tumor samples will be stored in the TRIO central laboratory until future use is required. TRIO may collaborate in the future with experts in the field, and the tumor material may be shared with other researchers.

This portion of the trial was optional. The Patient Informed Consent Form (PICF) contained a section dedicated to this sub-trial. Refusal to grant permission for further testing does not affect the quality of care the participant is to receive.

Tumor tissue provided for central determination of ER/PR and HER2 statuses will be used to perform this additional research for patients having given their consent. No additional sample will be required. If the patient refuses to participate in the optional sub-trial then tumor tissue will only be assessed for determination of ER/PR and HER2 statuses to assess patient's eligibility in the trial.

Tumor tissue samples will be destroyed after 20 years unless otherwise required per local regulations.

3. TRIAL DESIGN

This is an open-label, multicenter, international, randomized, Phase II clinical trial that aimed to assess the efficacy and safety of letrozole in combination with afatinib(oral EGFR inhibitor) versus letrozole monotherapy for the first-line treatment of postmenopausal women with ER+, HER2 negative advanced breast cancer with low ER expression.

Although hormone receptors (HR) are now routinely assessed by IHC, the estimate of the percentage of tumor cells stained or, more significantly, of staining intensity-based scoring systems have, necessarily, elements of patientivity within them and thus may be patient to errors in interpretation leading to notable variances across laboratories. In addition, the current reporting of hormone receptor status may be adequate for assessing patients for anti-estrogen therapy but not those for other targeted agents (i.e. EGFR targeted therapy).

In order to assess the level of ER expression we used a semi-quantitative scoring system (McClelland RA 1990) defined as :

H-score = (% of cells stained at intensity category 1x1) + (% of cells stained at intensity category 2x2) + (% of cells stained at intensity category 3x3).

This formula results in an H-score in the range of 0-300 where 300 equals 100% of tumor cells stained strongly (i.e., 3+).

Low ER expression was defined as tumor sample with H-score [1-159].

For all patients consented on the trial, a tumor sample was submitted to the designated central laboratory for central testing of ER/PR and HER2 and determination of the H-score. This was assessed prior to randomization.

Patients with HER2 negative, ER+ advanced breast cancer with low ER expression defined as H-score between 1 and 159 entered screening phase and performed the required screening assessments.

Eligible patients were randomly assigned in a 1:1 ratio and stratified according to sites of disease (bone only disease vs. other) and prior administration of hormonal therapy in neo/adjuvant setting (Yes vs. No) to either:

- Arm A: Continuous regimen of oral letrozole 2.5 mg until progression of disease or any other trial treatment discontinuation criteria as per section 5.3.3.

Or

- Arm B: Continuous regimen of oral letrozole 2.5 mg daily plus oral afatinib 30 mg daily until progression of disease or any other trial treatment discontinuation criteria as per section 5.3.3.

IN ADDITION the following applies whichever comes first:

- If the patients treated with the combination of afatinib and letrozole (arm B) discontinue the trial treatment (whatever the reason) before 30 November 2018, the patients from the other arm (arm A, letrozole alone) still on treatment will also be discontinued from the trial at the same time. They may continue receiving letrozole using commercial drug as standard of care according to their treating physician discretion.

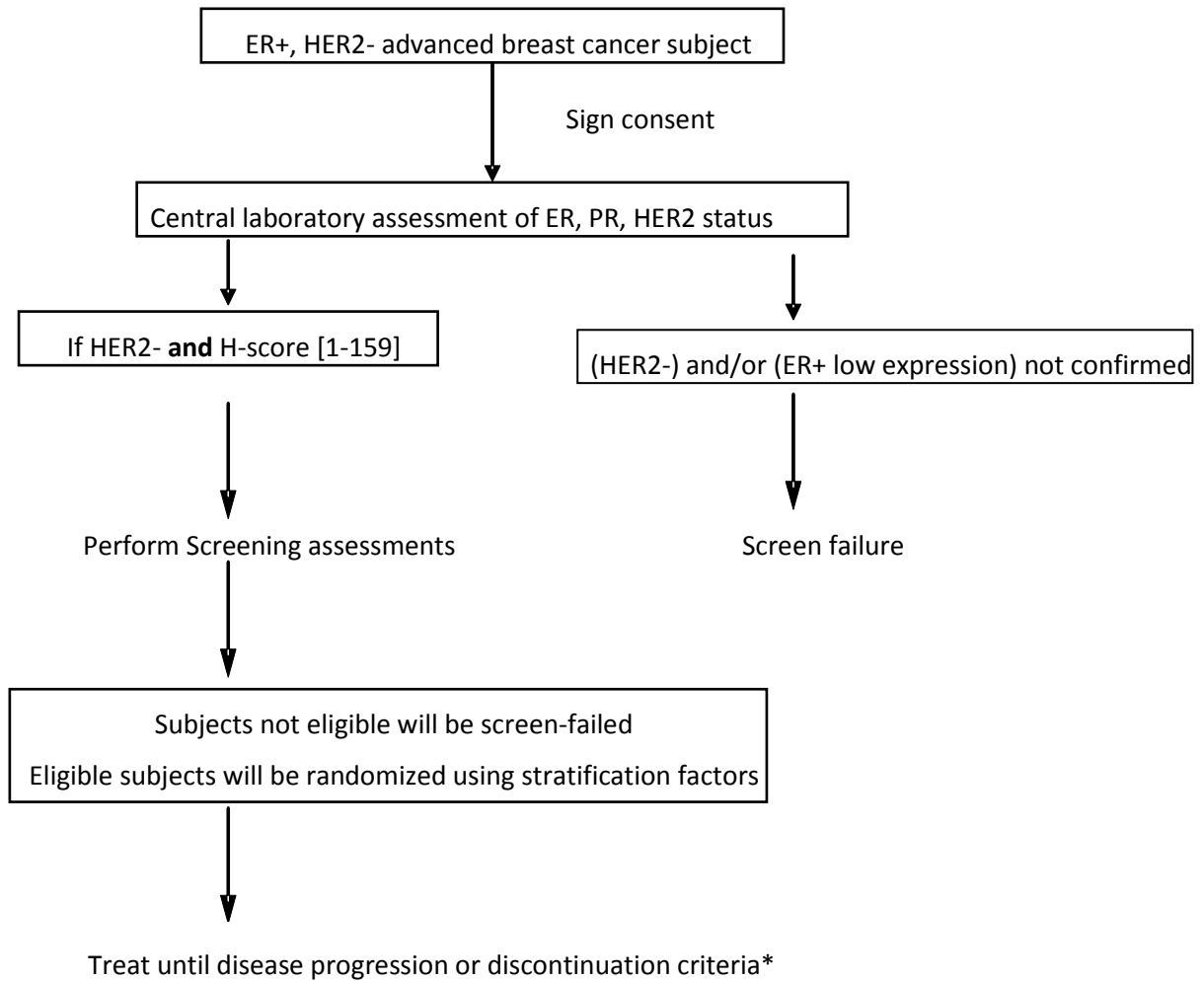
- If the patients treated with afatinib and letrozole (arm B) have not discontinued the trial treatment by 30 November 2018, all patients currently on treatment in the trial (including the ones only treated by letrozole alone (arm A)) will be discontinued from the trial at that time. They may continue receiving their treatment if in alignment with their treating physician judgment as follows:
 - Patients in arm A: may continue receiving letrozole using commercial drug as standard of care according to their treating physician discretion.
 - Patients in arm B: may continue receiving afatinib in the context of an alternative drug supply outside the clinical trial as appropriate according to local legislation. Additionally, they may continue receiving letrozole using commercial drug as standard of care according to their treating physician discretion.
- Note; In case no alternative drug supply outside the clinical trial as appropriate according to local legislation can be put in place and the 2 patients in Arm B are still on treatment on 30 November 2018, the protocol and PICF will need to be revised again.

Once the patient is discontinued from trial treatment and has undergone the End of Treatment visit (see section 6.3), the patient will be permanently discontinued from the trial.

This trial also included an optional exploratory research component. This optional portion of the trial is a molecular profiling assay aimed to assess the relationship of antitumor activity with the expression of a few cell cycle-related proteins and other markers that may be identified in the future. (See section 2.3)

Patients participated in this trial even if they had chosen not to participate in the sample banking component.

Figure 1 : Trial Scheme - Patient Selection and Treatment



* As described in section 3-Trial Design (IN ADDITION)

4. PATIENT SELECTION

The following eligibility criteria were designed to select patients for whom protocol treatment was considered appropriate. All relevant medical and non-medical conditions were taken into consideration when deciding whether this protocol is suitable for a particular patient.

4.1 Inclusion Criteria

Patients had to meet all of the following inclusion criteria to be eligible for enrollment into the trial:

1. Signed and dated informed consent document indicating that the patient (or legally acceptable representative) has been informed of all the pertinent aspects of the trial prior to enrollment.
2. Postmenopausal female, 18 years of age or older.
Postmenopausal status defined as:
 - Prior bilateral surgical oophorectomy or
 - Amenorrhea and age \geq 60 years or
 - Age < 60 years and amenorrhea for 12 or more months and FSH and estradiol in the postmenopausal ranges
3. Histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of locally recurrent disease not amenable to resection or radiation therapy with curative intent, or metastatic disease.
4. **HER2 negative breast cancer.** Local testing should demonstrate that the tumor is 0 or 1+ by immunohistochemistry (IHC) or is considered to be HER2 negative for gene amplification by fluorescence in-situ hybridization (FISH), chromogenic in-situ hybridization (CISH) or other in-situ hybridization (ISH) method. Central testing (required for all patients) must demonstrate that the tumor is HER2 negative by FISH or IHC.
5. **ER positive breast cancer.** Local testing should demonstrate that the tumor is ER positive. Central testing (required for all patients) must demonstrate that the tumor is ER+ with low expression (H-score[1-159]).
6. Paraffin-embedded tumor block(s) available for centralized assessment of ER, PR, and HER2. If no tumor block is available, 15 to 20 unstained slides of paraffin-embedded tissue from the tumor obtained at the initial diagnosis or prior biopsy or surgery (archived tumor tissue) will be accepted. Slides must be positively charged, frosted-end. Tumor biopsies may be from either the primary or metastatic site of disease.

When tumor tissue from the primary tumor and from metastatic sites is available, the sample from the most recent biopsy/surgery/procedure will be sent to Central laboratory.
7. Measurable disease according to RECIST 1.1 (E.A. Eisenhauer 2009) or bone-only non measurable disease according to RECIST 1.1. Previously irradiated lesions are deemed measurable only if progression is documented at the site after completion of radiation.
8. Eastern Cooperative Oncology Group (ECOG) Performance status 0 or 1 (APPENDIX 1).
9. Adequate organ function as defined by the following criteria:

- Hemoglobin ≥ 9 g/dL
 - Absolute neutrophils count (ANC) $\geq 1.2 \times 10^9/L$
 - Platelets $\geq 100 \times 10^9/L$
 - Serum aspartate transaminase (AST) and serum alanine transaminase (ALT) $< 2.5 \times$ upper limit of normal (ULN).
 - Total serum Bilirubin ≤ 1.5 mg/dL ($\leq 26 \mu$ mol/L) regardless of liver involvement secondary to tumor. Inclusion of patients with increased serum indirect bilirubin due to Gilbert's syndrome is permitted.
 - Serum creatinine $\leq 1.5 \times$ ULN. For patients with serum creatinine $> 1.5 \times$ ULN then calculated (Cockcroft-Gault formula) or measured Creatinine clearance ≥ 60 mL/min is required.
10. Baseline resting left ventricular ejection fraction (LVEF) $\geq 50\%$ measured by multigated acquisition scan (MUGA scan) or echocardiogram.
 11. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other trial procedures.

4.2 Exclusion Criteria

1. Brain metastases (even if treated and/or stable), spinal cord compression, carcinomatous meningitis, or leptomeningeal disease.
2. Prior treatment with any type of systemic therapy for locally-recurrent disease not amenable to resection or radiation therapy with curative intent, or for metastatic disease.
3. Prior treatment with letrozole in (neo)adjuvant setting with disease-free interval ≤ 12 months from completion of treatment until randomization.
4. Prior treatment with any anti HER-family targeted therapy in (neo)adjuvant setting.
5. Any concurrent or previous malignancy within 5 years prior to randomization except for adequately and radically treated basal or squamous skin cancer, or carcinoma in situ of the cervix, or other non-invasive/in-situ neoplasm. A patient with previous history of invasive malignancy (other than adequately and radically treated basal or squamous skin cancer) is eligible provided that she has been disease free for more than 5 years.
6. Non-measurable disease according to RECIST 1.1 (E.A. Eisenhauer 2009), with the exception of bone-only non-measurable disease.
7. Known pre-existing interstitial lung disease.
8. Significant or recent acute gastrointestinal disorders with diarrhea as a major symptom e.g. Crohn's disease, malabsorption or CTCAE v4.0 grade ≥ 2 diarrhea of any aetiology.
9. History or presence of clinically relevant cardiovascular abnormalities, as per investigator assessment such as uncontrolled hypertension, congestive heart failure NYHA Class \geq III (APPENDIX 2), unstable angina or poorly controlled arrhythmia. Myocardial infarction within 6 months prior to randomization.

10. Any other concomitant serious illness or organ system dysfunction which in the opinion of the investigator would either compromise patient safety or interfere with the evaluation of the safety of the test drug.
11. Any contraindication to oral agents.
12. Active hepatitis B infection (defined as presence of Hep B sAg and/or Hep B DNA), active hepatitis C infection (defined as presence of Hep C RNA) or known HIV carrier.
13. Known or suspected active drug or alcohol abuse.
14. Known hypersensitivity to afatinib or letrozole or the excipients of any of the trial drugs.
15. Concomitant treatment with strong inhibitor of P-gp (see section 5.5.2).
Note: Patients having received treatment with strong P-gp inhibitors must have discontinued treatment at least 7 days before start of trial drugs.
16. Any ongoing acute clinically significant toxic effect of prior anticancer therapy or any persisting complication of prior surgery.
17. Patients with known history of keratitis, ulcerative keratitis or severe dry eye.
18. Participation in the active phase of other clinical trials of investigational agents in which last trial treatment was administered within 2 weeks prior to randomization.

5. TREATMENT

5.1 Protocol Treatment

Eligible patients receive either oral letrozole 2.5 mg plus oral afatinib 30 mg daily or oral letrozole 2.5 mg daily until progression of disease or any other trial treatment discontinuation criteria as per section 5.3.3.

Treatment allocation was operated centrally after patients had given their written informed consent and had completed the necessary baseline assessments.

Refer to section 6.1.2 for registration and randomization process.

If a patient was randomized but did not receive any treatment, the reason was documented in the case report form (CRF). Patients remained on trial, baseline data was collected and follow-up continued. These patients will now be discontinued from the trial once their trial treatment is discontinued and they will be followed and treated as per local clinical practice.

Investigational Medicinal Product” (IMP), Non Investigational Medicinal Product” (NIMP):

According to the ICH Good Clinical Practice and EU Directive 2001/20/EC Article 2 (d), afatinib falls under the definition of Investigational Medicinal Product (IMP) while letrozole which is considered as Standard of Care (SoC) in this treatment population falls outside of this definition and is then to be considered as a “Non Investigational Medicinal Product” (NIMP).

Definition and management of IMP and NIMP are further described in a separate Trial Specific Guideline.

5.2 Protocol Treatment Management

5.2.1 Packaging and Labeling

5.2.1.1 Afatinib

Afatinib is an oral drug.

It is supplied by the manufacturer Boehringer Ingelheim (BI) to the sites. Initial shipment and re-supply are described in a separate document.

Two dose strengths of 20 and 30 mg afatinib are used in the trial to allow for any dose adjustment. These newly available dose strengths 20 and 30 mg film-coated immediate release tablets are prepared in a common blend, with higher drug load per tablet.

A color scheme was established in order to distinguish between the doses and tablet sizes. The 20 mg film-coated tablets are white to slightly yellowish, round, biconvex, bevel-edged shape with a diameter of approximately 8 mm. Film-coated 30 mg tablets are dark blue. 30 mg film-coated tablets are as well round, biconvex, bevel-edged shape with a diameter of approximately 9 mm. All doses are either one-sided embossed with the Boehringer Ingelheim Logo or double-sided embossed with the Boehringer Ingelheim Logo on one side and a combination of the letter “T20” with the dose strength on the other side (example: “T20” for the 20 mg tablet).

The medication is provided in HDPE bottles with a desiccant at 25°C/60%RH, 30°C/75%RH and 40°C/75%RH child-resistant, tamper-evident bottles.

Note: In the future, instead of an HDPE bottle a PP-bottle with more desiccant will be employed which allows a shelf-life of 36 months with the storage statement for climatic zone III/IV “Do not store above 25°C” and for CZI/II “This medicinal product does not require any special temperature storage conditions” and for all climatic zones “Store in the original bottle in order to protect from moisture and light”. Respective real time stability data are available.

Each bottle contains 30 tablets.

Labeling of afatinib supplies is done by BI, in accordance with local regulations.

For the purpose of this trial, the Single Reference Document to be used for afatinib is the Investigator’s Brochure.

5.2.1.2 **Letrozole**

Letrozole is an oral drug.

Letrozole is standard of care in this population. Commercial Letrozole is used.

Commercial Letrozole contains 2.5 mg letrozole as active ingredient.

Packaging depends on the commercial letrozole available locally.

For the purpose of this trial, the Single Reference Document to be used for letrozole is the UK Summary of Product Characteristics (SPC) for Femara®.

5.2.2 **Storage and Accountability**

5.2.2.1 **Afatinib**

Afatinib tablets are shipped and stored between 8 to 25°C or as specified by label for the given climate zone.

Temperature loggers shall be used.

Alert setting of the temperature loggers are

Climatic Zone I/II countries -20°C / +30°C (e.g. Europe, USA, Argentina, China)

Climatic Zone III/IV countries -20°C / +25°C (e.g. Brazil, India, most Asian and African countries)

Specific expiry date is provided on the label of each bottle.

Medication should be kept in their original container in a secured area at the trial site in accordance with applicable regulatory requirements.

Returned medication (empty containers and partially used containers) should be stored separately from medication that needs to be dispensed.

To ensure adequate records, dispensations, return and accountability of afatinib tablets are documented in a timely manner.

The following information are documented:

- Patient’s number
- Date dispensed

- Number of tabs dispensed/returned for each strength
- Batch number and expiry date

Bottles/boxes are labeled according to local regulations and include the following as a minimum:

- Trial number
- Product name (BIBW 2992)
- Contents of the bottle (30 tablets)
- Tablet strength
- Batch number
- Medication number
- Use-by date
- Storage information
- Instructions for use
- Manufacturer name and address
- A statement that the medication is for clinical trial use only
- A caution statement

A new bottle of medication is dispensed on day 1 of each course, regardless of the number of tablets remaining in the bottle from the previous course. The patient initially receives one bottle of 30mg tablets and in the event that dose reduction is necessary the patient returns to the clinic and new medication is dispensed.

According to the information reported in section 3-Trial Design (IN ADDITION) regarding the decision to discontinue the patients from the trial at the latest on 30 November 2018, the information reported in this section is applicable until 30 November 2018. After that date, the patients will not receive afatinib anymore in the scope of the trial but in the frame of an alternative drug supply outside the clinical trial as appropriate according to local legislation. At the end of the clinical trial all drug supplies unallocated or unused by the patients must be disposed of and accounted for according to local governing auspices and site SOPs. The documentation should be available.

5.2.2.2 **Letrozole**

Letrozole is stored according to the instructions detailed in the local package insert.

For each container of letrozole dispensed to a patient, the following information is documented in a specific form:

Trade name

Batch number

Date of dispensation

Patient ID

Quantity dispensed

It is recommended to collect the quantity returned to assess compliance

According to the information reported in section 3-Trial Design (IN ADDITION) regarding the decision to discontinue the patients from the trial at the latest on 30 November 2018, the information reported in this section is applicable until 30 November 2018. After that date, the patients will not receive letrozole anymore in the scope of the trial but as commercial drug.

5.2.3 Return / Destruction

5.2.3.1 Afatinib

Unused/expired afatinib should be destroyed locally once accountability performed and reconciled.

5.2.3.2 Letrozole

Unused Letrozole will be managed by the sites according to their local requirements.

5.3 Protocol Treatment Administration

5.3.1 Premedications and special precautions

No specific pre-medication is required for afatinib.

5.3.2 Standard treatment schedule

Afatinib:

At each monthly visit, patients should be given a 30-tablet bottle.

For administrative purposes treatment is divided into treatment cycles, which are each 4 weeks (28 days) in duration. However, treatment is given continuously unless treatment schedule adjustments are needed (as per section 5.4). Patients take a single oral dose of afatinib each day for the first and subsequent cycles. The medication should be taken at the same time each day (\pm 2 hours) at least one hour before food intake and at least three hours after the last food intake.

Afatinib tablets should be swallowed whole with water. If dosing of whole tablets is not possible, afatinib tablets can be dispersed in approximately 100 ml of noncarbonated drinking water. No other liquids should be used. The tablet should be dropped into the water without crushing it, and stirred occasionally for up to 15 min until the tablet is broken up into very small particles. The dispersion should be consumed immediately. The glass should be rinsed with approximately 100 ml of water which should also be consumed. The dispersion can also be administered through a gastric tube. . Administration of afatinib via gastric tube has to be recorded in the CRF.

No tablet should be ingested if it is broken, cracked, or otherwise not intact.

Missed/Vomited/Extra Doses:

If an entire daily dose is skipped, the patient should resume treatment the following day with her regular dose. No “make-up dose” or increased dosing should occur.

If a dose is vomited at any time, the patient should resume treatment the following day with her regular dose. No “make-up dose” or increased dosing should occur.

Patients should report all vomited, missed or delayed doses to the trial staff and will be provided with a medication diary which should be turned in at every visit.

If a patient inadvertently takes 1 extra dose during a day, she should not take the next day's dose.

Letrozole: Patients should be instructed to swallow letrozole tablet without regard to food. Patients should be encouraged to take their dose at approximately the same time each day.

For patients in Arm B (letrozole + afatinib), it is recommended to take letrozole and afatinib at the same time to ensure compliance.

5.3.2.1 Preparation

The trial medication is self administered. There is no specific preparation. Afatinib is an oral drug taken daily by the patient.

5.3.2.2 Treatment compliance

Treatment compliance will be assessed at the end of each visit. Patients will complete a diary to document their daily intakes. They will be instructed to return all unused drugs (partially used and empty containers) and their diary at each visit. Site staff will perform accountability of the returned drug and will assess compliance of the patient. Site staff must ensure that the patient clearly understands the directions for self-medication and follows adequately the schedule.

5.3.3 Protocol treatment discontinuation

By default, patients are treated until progressive disease as per RECIST 1.1.

Please refer to section 3-Trial Design (IN ADDITION) regarding the decision to discontinue the patients from the trial at the latest on 30 November 2018 and the conditions of this discontinuation.

The investigator will also discontinue the treatment if any of the following conditions is met:

- ✓ Intercurrent illness or change in patient's condition that warrants trial treatment discontinuation or unacceptable toxicity, such as interstitial lung disease, rash grade 4, hepatic injury, left ventricular systolic dysfunction grade ≥ 3 , ulcerative keratitis (see section 5.4)
- ✓ Any event which would warrant afatinib to be modified by > 1 dose reduction or afatinib to be held for > 14 days (see section 5.4.1)
- ✓ Need for additional local and/or systemic non-protocol anticancer therapy (see section 5.5.4)
- ✓ Patient's decision to withdraw
- ✓ Lost to follow up
- ✓ Death
- ✓ Pregnancy (see section 7.4.2)
- ✓ Investigator's decision
- ✓ Discontinuation of the trial by the sponsor

Refer to section 6.3 for the list of assessments to be performed at the end of treatment.

If letrozole needs to be discontinued for any reason then afatinib must also be discontinued and patient must be discontinued from the trial except if patient is deriving obvious clinical benefit from continuing treatment with afatinib alone. **Please refer to section 5.4.1 for the protocol definition of obvious clinical benefit.**

In this case, Medical Monitor/TRIO Medical Lead/Trial Chair should be contacted by the site prior to continuing with afatinib.

If afatinib needs to be discontinued for any reason, letrozole should be discontinued within the frame of the trial and the patient must be discontinued from the trial.

Last trial dose of letrozole as trial medication will be defined as last letrozole intake prior to End of Study Visit.

5.4 Adverse Event management and treatment schedule adjustments

5.4.1 General rules

Regular assessment and monitoring of adverse events is required throughout trial treatment period and up until 30 days after last intake of trial medication (last intake of letrozole in the single agent arm or last intake of afatinib + letrozole or letrozole -if afatinib previously discontinued- in the combination arm). Recommendations regarding monitoring and adequate management of specific events are provided below. CTCAE version 4.0 is used to assess the severity of adverse events.

Letrozole dose modification

No dose adjustment is permitted for letrozole.

Afatinib dose modification

Patients are monitored closely for toxicity and the dose of afatinib may be adjusted as indicated in tables below. Dose reduction to 20 mg is allowed depending on the type and severity of toxicity encountered. Patients requiring more than one dose reduction will be discontinued from afatinib.

Table 1 : Dose levels

Afatinib levels	Dose
Starting dose level	30 mg
Dose reduction	20 mg

Dose escalation is not allowed once afatinib dose has been reduced.

For toxicities requiring dose adjustment (see sections 5.4.2 to 5.4.7), afatinib will be held for up to 14 days to allow patient to recover to a grade ≤ 1 , **and will be resumed at 20 mg.**

Dose reduction should always follow a treatment pause in order to allow recovery to grade ≤ 1 toxicity. Nevertheless, the initial trial visits schedule should be kept unchanged (every 4 weeks regardless of any additional visits and treatment pauses).

If despite optimal care and afatinib pause, patient has not recovered to grade ≤ 1 within 14 days and is not deriving obvious clinical benefit from trial treatment, the patient should not receive any further treatment with afatinib. Letrozole should be discontinued within the frame of the trial and the patient must be discontinued from the trial.

In the event that the patient is deriving obvious clinical benefit in the opinion of the investigator but has not recovered to grade ≤ 1 within 14 days the further treatment of the patient will be decided by the Medical Monitor/TRIO Medical Lead/Trial Chair in agreement with the investigator.

Obvious clinical benefit is defined as:

SD or PR or CR as per RECIST 1.1 in the last tumor assessment performed; AND/OR

Improvement in cancer related symptoms from baseline as per investigator opinion, in absence of PD as per RECIST 1.1; AND/OR

Improvement in cancer related laboratory abnormalities in absence of PD as per RECIST 1.1

Additionally the following factors should be taken into consideration in order to decide about treatment continuation:

Type and grade of the AE that has not resolved to grade 1

Treatment tolerability since trial treatment start based on investigator judgment and reported AEs

ECOG PS (decrease ≤ 1 point from the last PS prior to start date of the AE that has not resolved to grade 1)

Absence of significant treatment related laboratory abnormalities.

In this case, Medical Monitor/TRIO Medical Lead/Trial Chair should be contacted by the site prior to reintroducing afatinib.

5.4.2 Management of diarrhea

Close monitoring and proactive management of diarrhea is essential for successful treatment of patients with afatinib. Early and appropriate intervention can prevent the development of more severe diarrhea. In most cases, loperamide controls diarrhea caused by afatinib. Loperamide should be available at the start of therapy and kept with the patient at all times; it is therefore advisable that patients be given a prescription at the time of initiating treatment with afatinib.

The recommendations for management are as follows:

Table 2 : Management of diarrhea

CTCAE v4.0 Grade	Recommended management	Dose adjustment
Diarrhea Grade 1	<p>Appropriate rehydration (e.g. 1.5 L/m²/day plus equivalent of actual fluid loss) is essential.</p> <p>Two (2) mg loperamide tablets should be taken immediately, followed by one 2 mg tablet with every loose bowel movement, up to a maximum daily dose of 10 tablets (20 mg).</p> <p>Patient should be advised to avoid lactose-containing products or any foods known to aggravate diarrhea.</p>	Trial treatment to be continued without dose delay/reduction

Diarrhea Grade 2	Same as for grade 1. Electrolyte replacement has to be ensured.	If diarrhea persists ≥ 2 days (48 hours) despite adequate anti-diarrheal treatment, hold afatinib up to 14 days until patient has recovered to grade ≤ 1 and resume at a 20 mg.
Diarrhea Grade ≥ 3	Same as for grade 1. Electrolyte replacement has to be ensured	Hold afatinib up to 14 days until patient has recovered to grade ≤ 1 and resume at 20 mg.

5.4.3 Management of nausea and vomiting

Nausea and vomiting may significantly affect patients' adherence to the treatment and their quality of life. In order to reduce the occurrence and the intensity of emesis, the patients should be treated with an aggressive antiemetic program such as the following:

Table 3: Management of nausea and vomiting

CTCAE v4.0 Grade	Recommended management	Dose adjustment
No event	No prophylactic antiemetic treatment	Trial treatment to be continued without dose delay/reduction
Nausea Grade 1 but no vomiting	No antiemetic treatment.	Trial treatment to be continued without dose delay/reduction
Nausea Grade 2 and/or Vomiting Grade 1-2	Appropriate hydration in case of vomiting (e.g. 1.5 L/m ² /day plus hydration deficit). Implement antiemetic treatment.	If vomiting grade 2 and/or nausea grade 2 persists for 3 or more consecutive days despite optimal supportive care, hold afatinib up to 14 days until patient has recovered from nausea and/or vomiting to grade ≤ 1 and resume at 20 mg.
Nausea Grade 3 and/or Vomiting grade ≥ 3	Appropriate hydration in case of vomiting (e.g. 1.5 L/m ² /day plus hydration deficit). Implement antiemetic treatment.	Hold afatinib up to 14 days until patient has recovered to grade ≤ 1 and resume at 20 mg.

5.4.4 Management of rash

A proactive and early approach to management of rash is crucial. Rash can be managed by a variety of treatment options to relieve symptoms and reduce the rash. The recommendations for management are as follows:

Table 4 : Management of rash

CTCAE v4.0 Grade	Recommended management	Dose adjustment
No event	General/Prevention: strict sun protection; use of a sunscreen of Sun Protection Factor 15 (SPF 15) or higher, preferably containing zinc oxide; use of a thick, alcohol-free emollient cream; avoid harsh detergents, avoid using a solarium.	Trial treatment to be continued without dose delay/reduction.
Rash Grade 1	Mild rash may not need treatment. However, if treatment is considered necessary, topical hydrocortisone (1% or 2.5%) cream and/or clindamycin 1% gel can be used.	Trial treatment to be continued without dose delay/reduction.
Rash Grade 2	Relief from major symptoms caused by grade 2 skin related adverse events should be achieved by a combination of local and systemic therapies including: 1) Systemic antibiotics (e.g. doxycycline or minocycline) 2) Topical treatment (hydrocortisone 2.5% cream, clindamycin 1% gel, pimecrolimus 1% cream) And / or 1) Antihistamines (e.g. diphenhydramine) 2) Oral prednisone (short term i.e., <14 days treatment) may be added at investigator's discretion Systemic and topical treatment should be initiated at the start of grade2 and continue until resolution or improvement to grade ≤1.	If grade 2 rash persists for 7 days or more despite treatment and is poorly tolerated by the patient, the investigator may choose to hold afatinib up to 14 days until patient has recovered to grade ≤ 1 and resume at 20 mg.
Rash Grade 3	May be treated in a manner similar to grade 2 rash.	Hold afatinib up to 14 days until patient has recovered to grade ≤ 1 and resume at 20 mg.

Rash Grade 4	Same treatment as grade 2-3 is recommended. Additionally, use of IV antibiotics and/or steroids is recommended if clinically indicated. Consultation with dermatologist.	Discontinue afatinib. Do not re-challenge with afatinib
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5.4.5 Management of Interstitial Lung Disease (ILD)

Careful assessment of all patients with an acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever) should be performed to exclude ILD.

Table 5 : Interstitial Lung Disease

CTCAE v4.0 Grade	Recommended management	Dose adjustment
Acute onset and/or unexplained worsening of pulmonary symptoms (dyspnea, cough, fever), any grade	Appropriate treatment instituted as necessary.	Afatinib should be held pending investigation of these symptoms.
Interstitial Lung Disease diagnosis (any grade)	Appropriate treatment instituted as necessary.	Discontinue afatinib. Do not re-challenge with afatinib.

5.4.6 Management of Protocol specified significant event: hepatic injury

The following event is defined as Protocol-specified significant event: **Hepatic injury** defined by the following alterations of liver parameters:

for patients with normal AST / ALT and bilirubin at baseline: an elevation of AST and/or ALT above >3 fold ULN combined with an elevation of bilirubin above >2 fold ULN measured in the same blood draw sample.

for patients with abnormal AST / ALT and bilirubin at baseline : an elevation of AST and/or ALT >5 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample.

Table 6 : Management of hepatic injury

Event	Recommended management	Dose adjustment
AST and/or ALT above > 3 fold ULN combined with an elevation of bilirubin above > 2 fold ULN (patient with normal LFT at baseline) or AST and/or ALT above > 5 fold ULN combined with an elevation of bilirubin above >2 fold ULN (patient with abnormal LFT at baseline)	Promptly report the event to TRIO within 24 hours of learning its occurrence (see section 7.3). Monitor every week until liver chemistries resolve or return to within baseline values. A specialist or hepatology consultation is recommended.	Discontinue afatinib. Do not re-challenge with afatinib.

5.4.7 Other Adverse events

Table 7: Treatment schedule adjustments

Type and CTCAE v4.0 Grade of event	Dose adjustment
Any drug related AE grade ≥ 3 (except Left Ventricular Systolic Dysfunction which requires special instruction below)	Hold afatinib up to 14 days until patient has recovered to grade ≤ 1 and resume at 20 mg.
Acute kidney injury (renal dysfunction) grade ≥ 2 (Worsening of renal function grade ≥ 2 as measured by serum creatinine)	
Keratitis symptoms (such as acute or worsening eye inflammation, lacrimation, light sensitivity, blurred vision, eye pain and/or red eye), any grade	<p>Refer promptly to an ophthalmology specialist.</p> <p>Hold afatinib during evaluation of suspected keratitis, up to 14 days until patient has recovered completely and resume at 20 mg.</p> <p>If keratitis is diagnosed, benefits and risks of continuing treatment should be carefully considered. Medical Monitor/TRIO Medical Lead/Trial Chair should be contacted.</p> <p>If diagnosis of ulcerative keratitis is confirmed, discontinue afatinib. Do not re-challenge with afatinib.</p>
Any other drug related AE prolonged (≥ 7 consecutive days) grade 2 poorly tolerated by the patient.	Investigator may choose to hold afatinib up to 14 days until patient has recovered to grade ≤ 1 and resume at 20 mg.
Any unrelated (serious or not serious) adverse event	<p>Investigator may choose to hold afatinib up to 7 days until patient has recovered to grade ≤ 1 and resume at the same dose.</p> <p>If the investigator chooses to pause the medication for more than 7 days and believes that the patient would derive clinical benefit from continuing medication, the decision to continue medication will be made by the trial medical monitor in agreement with the investigator.</p>
Left Ventricular Systolic Dysfunction grade ≥ 3	Discontinue afatinib. Do not re-challenge with afatinib.

5.5 Concomitant Medications and Procedures

5.5.1 Supportive care

Medication intended solely for supportive care (analgesics, antidiarrheals, antibiotics, antidepressants, etc.) may be used at the investigator's discretion. Erythropoietin and/or blood products may be used at the investigator's discretion for the supportive treatment of anemia.

5.5.2 Precautions – Treatment interaction with P-gp

There is no treatment interaction with letrozole.

Afatinib is a substrate of P-gp and its plasma concentrations can be affected by the use of P-gp inhibitors and it is also likely that P-gp inducers could also influence afatinib plasma concentrations. The use of potent P-gp inhibitors and potent P-gp inducers has to be avoided during treatment with afatinib.

For patients who require therapy with a P-gp inhibitor and who are receiving afatinib at a daily dose of 30 mg, afatinib dose may be reduced to 20 mg if not tolerated. If a P-gp inhibitor or inducer is planned to be administered to the patient, Medical Monitor/TRIO Medical Lead/Trial Chair should be contacted by the site prior to initiating therapy.

Table 8 below provides a non-exhaustive list of P-gp inhibitors or inducers to be avoided during trial treatment.

Table 8: Treatment interacting with P-gp

Strong P-gp inhibitors	P-gp inducers
Amiodarone	Carbamazepine
Clarithromycin	Phenobarbital
Cyclosporin	Phenytoin
Erythromycin	St John's wort
Ketoconazole	Rifampicin
Itraconazole	
Nelfinavir	
Quinidine	
Phenobarbital salt with Quinidine	
Ritonavir	
Tacrolimus	
Saquinavir	
Valspodar	
Verapamil	

This list is not meant to be considered all inclusive. See website for an available current list : <http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm>.

It is the investigator's responsibility to assess for potential drug interactions with afatinib and any P-gp inhibitor/inducer not listed above.

5.5.3 Surgery while on trial treatment

Based on the EGFR blocking mode of action, the risk that afatinib may interfere with skin wound healing process cannot be excluded. Therefore, interruption of afatinib should be considered before and after surgery to allow for adequate post-operative wound healing based on individual benefit/risk assessment. The maximum period of interruption for afatinib is 14 days. If interruption of greater than 14 days is required, treatment with afatinib should be discontinued.

5.5.4 Prohibited Treatments and/or Procedures

5.5.4.1 Local and/or systemic anticancer therapy

No additional local and/or systemic anticancer therapy will be permitted while patients are receiving trial therapy with the only exception of palliative radiotherapy (see section 5.5.3.3).

5.5.4.2 Bone-modifying agents

Bone-modifying agents (i.e. bisphosphonates, denosumab) may be continued for patients who are already receiving them at the time of randomization. However, the need to commence bone-modifying agents after randomization will be considered indicative of disease progression unless disease progression can be completely ruled out and bone-modifying agents treatment initiation is expressly agreed by the investigator in consultation with Medical Monitor/TRIO Medical Lead/Trial Chair.

Medical Monitor/TRIO Medical Lead/Trial Chair should be contacted by the site prior to initiating bone-modifying agents in this case.

5.5.4.3 Palliative radiotherapy

Palliative radiotherapy is permitted for the treatment of painful bony lesions providing the lesions were known to be present at the time of randomization and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of afatinib with radiotherapy, afatinib treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after. In case of afatinib discontinuation for more than 14 days then trial treatment should be discontinued.

6. SCHEDULE OF VISITS AND PROCEDURES

6.1 Patient Inclusion

6.1.1 Informed Consent

Prior to the screening evaluation, the patient or legally acceptable representative was informed of the nature of the trial treatments and was given pertinent information as to the intended purpose, possible benefits, and possible adverse experiences. The procedures and possible hazards to which the patient would be exposed were explained. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the trial.

An approved patient informed consent form (PICF) was then read and signed by the patient, and, when required, a witness, and the investigator or a person designated by the investigator, as per local regulations. The patient was provided with a copy of the signed PICF.

Further to this protocol amendment, the patient or legally acceptable representative will receive an approved addendum to the patient informed consent form that should be read and signed. Indeed, this PICF addendum will inform the patient or legally acceptable representative that all patients will be discontinued from the trial by 30 November 2018 at the latest.. The patient will be provided with a copy of the signed PICF addendum.

The patient can withdraw from the trial at anytime without prejudicing future medical treatment. In any case, the withdrawal should be documented on the initial informed consent form, and must be dated and signed by patient and by the investigator.

If a potential patient or legally acceptable representative is illiterate or visually impaired, the investigator must provide an impartial witness to read the PICF to the patient and must allow for questions. Thereafter, both the patient or legally acceptable representative and the witness must sign the PICF to attest that informed consent was freely given and understood. The PICF will include a statement by which the patient allows the Sponsor's duly authorized personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to their data, which will be processed according to the confidentiality regulations. In case important new information becomes available that may be relevant to the patient's consent and willingness to continue participation in the trial, the PICF will be revised and submitted to IRB/IEC for approval/favorable opinion. The new information will be discussed with the patient and if she agrees to continue participation in the trial, the revised PICF will be signed and dated and the patient will receive a copy.

This trial has an optional component described in the PICF, with a consent section dedicated to this optional trial. If a patient opted not to participate in the optional portion, this in no way affects the patient's ability to participate in the main research trial.

6.1.2 Registration/ Randomization

The treatment assigned was based on a dynamic minimization procedure using metastatic involvement (bone only YES or NO) and prior exposure to aromatase inhibitor (prior hormonal therapy YES or NO) as factors in the minimization algorithm. The ratio used was 1:1 and the randomization technique was using a stochastic treatment allocation algorithm based on the variance method.

The following steps for registering and randomizing a patient were chronologically performed:

The patient had to provide written informed consent prior to performing any trial specific procedure not considered standard practice by the institution.

The site registered the patient in the IWRS system (Date of ICF signed and patient year of birth needed). The system uniquely attributed a registration number to each patient in the trial. Each center was uniquely identified by a number assigned by TRIO to the investigative site. The site received a registration confirmation, containing patient registration number as well as HER2/Hormonal receptors screening form specific for the patient.

The site prepared a tumor sample fixated in formalin and embedded in paraffin (or 15 to 20 unstained slides) and shipped this sample along with the duly completed HER2/Hormonal receptors screening form to Dr Press' Central laboratory (see contact details on Information Resources page - Central laboratory's address and contact details are pre-printed on the form). The tumor material can be returned to the site after testing upon site's request.

Dr Press' laboratory entered in the IWRS system the HER2/Hormonal receptors results in a timely manner after receipt of the tumor material (usual turn-around-time was within 5 working days after receipt of the tumor material).

If (HER2-positive and/or H score not [1-159]) => The patient were moved to the Screen failure category.

If (HER2-negative and H-score [1-159]) => Screening of the patient continued at the site.

Upon completion of screening procedures and entry of screening data in TRIO eDC system, the investigator or his/her delegate checked if the patient met all eligibility criteria:

Patients who did not meet the eligibility criteria were moved to a screen failure category in the IWRS.

Patients who met all eligibility criteria were randomized in the IWRS using the following stratification factors:

Bone only disease : Yes versus No

Prior neo/adjuvant hormonal therapy : Yes versus No

Details regarding the Registration and Randomization processes were provided in the IWRS user manual and in the trial specific working instruction for Registration/Randomization.

Patients randomized in the trial had to start trial treatment within 7 days of randomization.

6.1.3 Blinding/Unblinding

The trial is open-label. There is no blinding of the treatment.

6.2 Trial Participation and Discontinuation

Once trial treatment is discontinued (both letrozole and afatinib) regardless of the reason, patients will be discontinued from the trial and will be followed and treated as per local clinical practice. If the patient withdraws from trial participation (consent withdrawn from trial, lost to follow-up, investigator's decision), no further trial procedures are performed, and no additional data will be collected. Medical care of the patient is not affected if the patient chooses to leave the trial at anytime.

Please refer to section 3-Trial Design (IN ADDITION) regarding the decision to discontinue the patients from the trial at the latest on 30 November 2018 and the conditions of this discontinuation.

6.3 Schedule of Procedures

All screening and baseline evaluations had to be completed prior to initiating trial treatments. Adherence to the schedule of assessments is required and visits should be planned accordingly. In the event a visit is missed because of an unforeseeable event, then the missed visit should be scheduled for the next day.

Prior to undergoing any trial specific procedures not considered standard practice by the institution, patients had to read and sign the consent form. All trial procedures are detailed in the Schedule of Activities table presented below.

According to the information reported in section 3-Trial Design (IN ADDITION) regarding the decision to discontinue the patients from the trial at the latest on 30 November 2018, the information reported in this section is applicable until 30 November 2018. After that date, the patients will be followed by their physician as per standard of care and the assessments will be performed as per local practice.

Table 9 : Schedule of activities

Protocol Activities	Pre-screening	Screening ¹ 28 days prior randomization	Treatment Period ²	End of treatment ³
Signed ICF ⁴	X			
Local determination of ER/HER2	X			
Tumor sample to central lab.	X			
Medical, surgical, disease history		X		
Signs and symptoms		X		
SAFETY			q4w	
Physical exam / Vital signs / PS		X	X	X
Review of adverse events		X	X	X
Hematology / Blood chemistry		X ^{5, 6}	X ⁶	X ⁶
LVEF		X within 42 days	X ⁷ q12w	X
TREATMENT			q4w	
Letrozole / Afatinib : Dispensation / Accountability			X	
EFFICACY			q12w	
Disease assessment		X	X	
Survival / Anticancer therapy				

¹¹ Pre-screening / Screening starts once the subject has signed the PICF.

² Visits are scheduled every 4 weeks +/- 3 days during treatment phase.

³ End of Treatment visit must be scheduled as close as possible to 30 days post last intake of any study drug or on 30 November 2018 whichever occurs first.

⁴ There is no window for obtaining the signed ICF. Study specific screening assessments not considered standard practice by the institution may start once the PICF has been obtained.

⁵ At screening only, Creatinine clearance will be assessed to check eligibility if serum creatinine $\geq 1.5 \times$ ULN.

⁶ During treatment phase, blood tests must be obtained up to 5 days prior to the visit and will assess the following parameters :

Hematology: Hemoglobin, Absolute Neutrophils Count (ANC), Platelets.

Blood chemistry: AST, ALT, Alkaline Phosphatase, Total Bilirubin and Creatinine.

⁷ LVEF will be assessed every 12 weeks during treatment phase and when clinically indicated.

6.3.1 Safety assessments

The following safety assessments were performed within 28 days of randomization of the patient and subsequently at each visit during treatment phase and at End of trial treatment visit. There was no need to repeat these safety assessments at Visit 1 since screening assessments were available, unless deemed clinically required by the investigator.

Physical exam: **included an examination of major body systems and weight.**

Vital signs: **blood pressure.**

Performance status (PS) **was assessed according to ECOG scale (APPENDIX 1).**

Blood tests:

Hematology: **Hemoglobin, Absolute Neutrophils Count (ANC) and Platelets.**

Blood chemistry: **AST, ALT, Alkaline Phosphatase, Total Bilirubin and Creatinine and Creatinine clearance (at baseline only).**

During treatment phase, blood tests may be obtained up to 5 days prior to the visit.

LVEF: will be obtained during screening and every 12 weeks during treatment phase, and as required when clinically indicated. LVEF will be performed by MUGA scan or echocardiogram, using the same method at each assessment.

6.3.2 Efficacy assessments

6.3.2.1 Schedule/details of tumor assessments

Screening/Baseline:

Baseline Disease assessment were performed during screening, within 28 days of randomization of the patient.

Disease assessment at screening was used to determine the nature of lesions (measurable versus non-measurable). Lesions must be clearly identified and documented as Target or Non-Target lesions as per RECIST 1.1.

Baseline assessment included at least:

- Baseline bone scan
- Other bone imaging had to be performed on bone lesions if the investigator intended to follow bone lesions with correlative imaging (e.g. CT with bone window, MRI or plain X-rays).
- CT or MRI scan of the chest, abdomen, and pelvis (CAP)
- Clinical assessment of superficial lesions (including measurement with calliper)
- Any additional imaging as deemed appropriate

Subsequent Disease assessments:

- Every 12 weeks (+/- 1 week) starting from date of randomization
- Whenever disease progression is suspected,
- To confirm a partial or complete response (at least 4 weeks after initial documentation of response). For patients with bone metastases identified at baseline bone scan is required at the time of confirmation of complete response.

Disease assessments will be performed until the end of treatment. The schedule of assessments should be fixed according to the calendar, regardless of treatment interruptions.

Disease assessments will comprise evaluation of all lesions identified at baseline, with the exception of bone lesions in some circumstances (see 6.3.2.2).

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up imaging.

Unless clinically required, it is not mandated to repeat imaging of an area where no lesion was documented at baseline.

Table 10 : Efficacy assessments

Baseline Within 28 days of randomization	Treatment phase until the End of Treatment
Bone scan CT or MRI of chest, abdomen and pelvis (CAP) Clinical assessment of superficial lesions Any additional imaging as deemed appropriate	Every 12 weeks +/- 1 week : repeat the CT/MRI and/or clinical assessment and/or any appropriate imaging used to document baseline lesions Confirmation of PR and CR: not less than 4 weeks after first documentation of response. Bone scan/bone imaging : <ul style="list-style-type: none"> • when progression is suspected in bone • Bone scan for confirmation of CR (if bone metastases were identified at baseline).

6.3.2.2 Special note for baseline determination of Bone lesions and follow-up assessments

In presence of other measurable lesions, the bone lesions are not mandatory to follow. Nevertheless, if followed by imaging, the technique was selected by the site at baseline and will be repeated until documentation of disease progression.

In absence of any other measurable lesions, the bone lesions will be followed every 12 weeks with the most appropriate imaging technique selected by the site at baseline (CT with bone window or MRI or plain X-ray or bone scan) and repeated until documentation of disease progression.

Bone scan/bone imaging is required when progression is suspected in bone.

Bone scan is required at the time of confirmation of CR (if bone metastases were identified at baseline).

6.3.2.3 Definitions of measurable/non measurable disease

At baseline, tumor lesions/lymph nodes were categorized as measurable or non-measurable according to RECIST 1.1 as follows:

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

10mm by CT scan for CT scan slice thickness no greater than 5 mm,

10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).

Special considerations regarding lymph nodes: lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm x 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

Non-measurable Tumor lesions: include all other lesions as follows:

Small lesions (longest diameter < 10 mm or $<$ twice the reconstruction interval)

Pathological lymph nodes with short axis ≥ 10 but <15 mm

Lesions considered truly non-measurable: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability: Bone lesions, cystic lesions, and lesions previously treated with local therapy:

Bone lesions:

Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- **Lytic bone lesions or mixed lytic-blastic lesions**, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- **Blastic bone lesions** are non-measurable.

Cystic lesions:

Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area patiented to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

6.3.2.4 Baseline Documentation of Target and Non-target Lesions

When more than one measurable lesion was present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs had to be identified as **target lesions** and are recorded and measured at baseline.

Target lesions were selected on the basis of their size (lesions with the longest diameter), were representative of all involved organs, but in addition had to be those that lend themselves to reproducible repeated measurements.

A sum of diameters (SoD) (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions is calculated and reported as the baseline sum of diameters. The baseline SoD is used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) were identified as **non-target lesions** and were also recorded at baseline. Measurements are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression”.

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the CRF (e.g. “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).

6.3.2.5 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations had to be performed as close as possible to the treatment start and never more than 4 weeks before randomization.

Method of assessment: the same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions are only considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging,

imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. For this trial Chest CT is the required method of assessment of lung lesions.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. Measurability threshold of lesions on CT scan is based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the trial, confirmation by CT or MRI is advised.

If there is concern about radiation exposure at CT, MRI may be used instead of CT.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response.

6.3.2.6 Response criteria

In case target lesions are present at baseline, at each assessment the SoD is defined as the sum of diameters of target lesions including short axis of lymph nodes selected as target lesions, and is used to assess the response.

Evaluation of target lesions:

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- **Partial Response (PR):** At least a 30% decrease in the SoD of target lesions, taking as reference the baseline SoD.
- **Progressive Disease (PD):** At least a 20% increase in the SoD of target lesions, taking as reference the smallest SoD on trial (this includes the baseline SoD if that is the smallest on trial). In addition to the relative increase of 20%, the SoD must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest SoD while on trial.

Note: Target lesions that become “too small to measure” (TSM) while on trial, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being

“too small to measure”. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned.

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 need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

- **Complete Response (CR):** Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (<10mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s).
- **Progressive Disease (PD):** Unequivocal progression of existing non-target lesions. The appearance of one or more new lesions is also considered progression.

Overall response at each time point:

Table 11 below provides a summary of evaluation of the overall response at each time point for patients with target +/- non-target lesions. Table 12 provides a summary of the evaluation of the overall response at each time point for patients with non-target lesions only.

Table 11 : Evaluation of the overall response (OR) in patients with target +/- non-target lesions

Target lesion	Non-target lesion	New lesion	Overall response
CR	CR	No	CR
CR	Non CR / Non PD	No	PR
CR	Not evaluated	No	PR
PR	Non PD or not all evaluated	No	PR
SD	Non PD or not all evaluated	No	SD
Not all evaluated	Non PD	No	NE (Not Evaluable)
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD

Table 12 : Evaluation of the overall response (OR) in patients with non-target lesions only

Non-target lesion	New lesion	Overall response
CR	No	CR
Non CR / Non PD	No	Non CR / Non PD
Not evaluated	No	NE
Unequivocal PD*	Yes or No	PD
Any	Yes	PD

*Note: The concept of progression of non-target disease requires additional explanation as follows: when the patient also has both measurable and non measurable disease, 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 presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. 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 SD or PR of target disease will therefore be extremely rare.

7. SAFETY MONITORING

7.1 Definitions

7.1.1 Period of Observation

At each visit and any contact during the trial, the investigator or designee will inquire about the occurrence of adverse events and will document them in the patient file.

The investigator or designee will report the adverse events in the CRF and to TRIO Safety department when required as per the table below

Table 13 : Reporting of AEs/SAEs

Trial period	Adverse events	Serious Adverse Events
From ICF to first dose	No	Related to trial participation
Trial treatment period*	All (regardless of relationship)	All (regardless of relationship)

*All adverse events (serious or non-serious) must be followed up to 30 days after the last intake of trial medication (see Section 5.4), or 30 November 2018 whichever occurs first.

7.1.2 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relationship with this treatment.

Worsening of pre-existing conditions:

A pre-existing condition present at baseline, which remains unchanged during the trial, does not need to be recorded as adverse event.

Any worsening of any pre-existing baseline condition should be reported as an adverse event in the CRF. Examples of worsening of a preexisting condition that should be recorded as an AE are given below:

Worsening of condition meets the criteria for an SAE

Action is taken with the investigational drug (e.g. dose is reduced or treatment is discontinued)

Treatment is required (concomitant medication is added or changed)

The investigator believes a patient has shown a clear deterioration from baseline symptoms

Expected fluctuations or expected deterioration of the breast cancer (symptoms of disease progression) should not be recorded as an AE.

Changes in vital signs, ECG, physical examination, and laboratory test results.

Changes in vital signs, ECG, physical examination and laboratory test results will be recorded as an AE in the CRF if they are judged clinically relevant by the investigator.

7.1.3 Protocol-specified significant event to be reported in an expedited manner

In addition to the cases defined above as SAE, the investigator must report the following events to the sponsor in an expedited manner, with the same timelines as SAEs:

Hepatic injury defined by the following alterations of liver parameters (measured in the same blood draw sample):

for patients with normal AST / ALT and bilirubin at baseline: an elevation of AST and/or ALT above >3 fold ULN combined with an elevation of bilirubin above >2 fold ULN measured in the same blood draw sample.

for patients with abnormal AST / ALT and bilirubin at baseline : an elevation of AST and/or ALT >5 fold ULN combined with an elevation of bilirubin >2 fold ULN measured in the same blood draw sample.

Protocol-specified significant events are to be reported in an expedited manner to the sponsor similar to Serious Adverse Events, even if they do not meet any of the seriousness criteria.

Patients showing these lab abnormalities need to be followed up appropriately.

7.1.4 Serious Adverse Event

7.1.4.1 General definition

A serious adverse event (SAE) is defined as any AE which:

- results in death
- is immediately life-threatening
- results in persistent or significant disability / incapacity
- requires or prolongs patient hospitalization
- is a congenital anomaly / birth defect
- is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

7.1.4.2 Disease-related events

An event which is part of the natural course of the disease under trial (i.e. disease progression) does not need to be reported as an SAE. Progression of the patient's breast cancer will be recorded in the appropriate pages of the CRF. Death due to progressive disease is to be recorded on Death Report Form of the CRF and not as an SAE.

However, if the progression of the underlying disease is greater than that which would normally be expected for the patient, or if the Investigator considers that there was a causal relationship between treatment with investigational product or protocol design/procedures and the disease progression, then this must be reported as an SAE.

Any **new primary cancer** must be reported as an SAE.

7.1.4.3 Planned or administrative hospitalization

Patients may be hospitalized for administrative or social reasons during the trial (e.g. days on which infusion takes place, long distance from home to site...). These and other hospitalizations planned at the beginning of or before the trial do not need to be reported as an SAE in case they have been reported at screening visit in the source data and have been performed as planned.

7.1.4.4 Unexpected Adverse Event

Afatinib Investigator's Brochure provides an overview of the adverse events reported across Afatinib clinical trial in monotherapy and in combination.

Any serious adverse event assessed as related to Afatinib but not reported in the listed adverse events' section of the Afatinib IB will be documented as a suspected unexpected serious adverse reaction (SUSAR) and will be carried out in accordance with applicable local regulations.

7.2 Performing Adverse Event Assessment

7.2.1 Collection of Adverse Event Information

The following information will be collected on the CRF:

Description of event, start date, worst grade experienced (severity), seriousness, stop date, action taken on trial treatments and relationship to trial treatments.

Intensity of adverse event:

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 in the CRF.

7.2.2 Assessment of Causality

The investigator will determine the relationship of the investigational drug to all AEs as defined in Boehringer Ingelheim's (BI's) Investigator Brochure for the Product.

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship must be recorded for each adverse event.

Relationship to trial drugs will be reported as either "Yes" or "No".

Yes: There is a reasonable causal relationship between the investigational product administered and the AE.

No: There is no reasonable causal relationship between the investigational product administered and the AE.

7.3 Reporting of Serious Adverse Events

7.3.1 Reporting of SAEs from the sites to TRIO

SAEs, pregnancies, and Protocol-specified significant events will be reported promptly to TRIO Safety Department as described in Table 14 once the investigator determines that the event meets the protocol definition for that event.

TRIO Safety Department: safety@trioncology.org

Fax number: **North America** : + 1 780-702-2273 / **Rest of the World**: +33. 1.58.10.09.05

Table 14: Reporting of SAEs

Type of Event	Initial Reports		Follow-up Information	
	Time Frame	Documents	Time Frame	Documents
All SAEs	24 hours	SAE form	24 hours	Updated SAE form
Protocol-specified significant event	24 hours	SAE form	24 hours	Updated SAE form
Pregnancy	24 hours	Pregnancy Form	24 hours	Updated Pregnancy Form

7.3.2 SAE information provided by TRIO to BI

TRIO will report to BI all SAEs (and protocol-specified significant events independently from their seriousness) by fax or other secure method. All SAE reports will be forwarded to BI with the following timelines:

- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one (1) fatal or immediately life-threatening event,
- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

The SAE reports will include a summary of the case, including relevant information provided by the investigator to TRIO and, in particular, the following information: the expectedness of the reported events based on BI Investigator’s Brochure for the Trial Drug, the investigator’s/TRIO’s causal assessment as to whether the event(s) is/are related to the use of the Trial Drug, and the seriousness of each AE.

7.4 Management of specific cases

7.4.1 Drug misuse

Cases of drug abuse or dependency (per investigator’s assessment) should be reported as SAEs.

Drug misuse and overdose of trial product(s) should be submitted as Serious Adverse Events if the misuse/overdose resulted in an event which the Investigator considers fulfills one or more of the criteria for SAE reporting.

7.4.2 Pregnancy

Women of childbearing potential are not eligible for this trial.

Nevertheless, should a pregnancy occur, the investigator must discontinue treatment immediately, capture any drug exposure during pregnancy, report the pregnancy through Pregnancy form (see Table 13) and follow the pregnancy until outcome is known.

A SAE report must be forwarded to the sponsor if the outcome of the pregnancy results in an abortion/miscarriage or the occurrence of any other SAE(s).

TRIO will be responsible to follow-up on all information regarding a reported Drug Exposure during Pregnancy. TRIO will ensure that any SAEs during and after pregnancy will be reported to BI in accordance with the following timelines:

- within five (5) calendar days upon receipt of initial and follow-up SAEs containing at least one (1) fatal or immediately life-threatening event,
- within ten (10) calendar days upon receipt of any other initial and follow-up SAEs.

7.5 Reporting to Ethics Committees, Regulatory Authorities and other Investigators

Prompt notification of SAEs by the investigator to the sponsor (TRIO) is essential so that legal obligations and ethical responsibilities towards the safety of patients are met.

TRIO will comply with country specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and investigators.

Investigator safety reports are prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and are forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing a SAE(s) or other specific safety information (e.g., summary or listing of SAEs) from TRIO will file it with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8. STATISTICAL CONSIDERATIONS

Descriptive analyses will be conducted according to the Statistical Analysis Plan.

8.1 Populations for analyses

The Intent-to-treat (ITT) population will consist of all patients who were randomized/registered to trial treatment, regardless of whether they actually received trial medication..

The Safety population will be used to present data relevant to clinical safety and tolerability. It consists of all patients who were randomized and received at least one dose of trial medication. This population will be based on the actual treatment received, if this differs from that to which the patient was randomized and will be used for the analysis of safety data.

8.2 Demographics and baseline characteristics

Demographics and baseline characteristics data will be listed and summarized by treatment group using the ITT population.

8.3 Protocol Treatment

Duration of treatment exposure, cumulative dose and dose intensity will be summarized by treatment group using the Safety population. The patients with dose modifications will be presented by treatment group, along with reasons for the dose change.

8.4 Safety Endpoints

Adverse Events - The latest version of the Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all adverse events to a preferred term and system organ class. Adverse events will be graded using the Common Terminology Criteria for Adverse Events (NCI CTCAE v4.0). Patient's incidence of adverse events will be tabulated by system organ class, preferred term and toxicity grade by treatment arm. Adverse events leading to death or drug discontinuation, drug related and serious adverse events will also be summarized by treatment arm.

Detailed listings for all adverse events will also be provided.

Laboratory parameters - Laboratory parameters, graded according to the NCI CTCAE v4.0, will be summarized at baseline, along visits and at the end of trial treatment by treatment arm. Tables of shifts in toxicity will also be provided.

Other Safety Data – Vital signs (weight and blood pressure), ECOG and LVEF will be summarized at baseline, along visits and at the end of trial treatment by treatment arm. Tables of shifts in toxicity will also be provided when applicable.

8.5 Interim and Final Analyses

The following analyses are planned:

A first analysis of safety was performed on the first 20 patients who complete 28 days of treatment. The steering committee reviewed this formal analysis.

The final analysis will be performed when all patients discontinue the trial.

8.6 Criteria for trial termination

The trial will stop once the last patient reaches end of trial treatment visit (30 days post last drug intake or 30 November 2018 whichever occurs first).

9. ADMINISTRATIVE, ETHICAL AND REGULATORY STANDARDS

9.1 Steering Committee

The Study Steering Committee (SSC) of the trial was set-up and operated as per TRIO SOPs. The SSC had the sole responsibility for the scientific conduct and integrity of the trial. Responsibilities included development and approval of the protocol document, monitoring of accrual, compliance and safety during the conduct of the trial. The SSC will be solely responsible for the analysis, interpretation and public disclosure of the results of the trial in accordance with the statistical plan.

Note: No additional SSC has taken place since the release of the previous amendment (09 May 2016) and no further SSC will take place after the release of this amendment.

9.2 Ethical Conduct of the Trial

This clinical trial was designed and shall be implemented and reported in accordance with the protocol, the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directives 2001/20/EC and 2005/28/EC and the US Code of Federal Regulations Title 21), and with the ethical principles laid down in the Declaration of Helsinki.

9.3 Institutional Review Board/Independent Ethics Committee (IRB/IEC)

The final approved protocol and its amendment and the informed consent statement /addendum will be reviewed by a properly constituted Ethics Committee/IRB. The Ethics Committee's/Board's decision concerning the conduct of the trial will be made in writing to the investigator and a copy of this decision will be provided to TRIO.

Particular attention is drawn to the FDA's regulation regarding the IRBs. By signing the "Statement of Investigator" form (Form 1572), the investigator provides TRIO with the necessary assurance that an IRB is responsible for the initial and continuing review and approval of the proposed clinical trial in accordance with these regulations when applicable.

The investigator will agree to make required progress reports to the Ethics committee/IRB, as well as report any serious adverse events, life-threatening problems or deaths. The Ethics Committee/IRB will be informed of serious adverse events in other clinical studies conducted with the trial drug by the investigator or the Sponsor according to the local regulations. The Ethics Committee/IRB must be informed by the investigator of the termination of the trial.

9.4 Compliance with the protocol and protocol amendments

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact TRIO or its agents, if any, monitoring the trial to request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is agreed upon by TRIO and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

Any modifications to the protocol which may impact on the conduct of the trial, potential benefit of the patient or may affect patient safety, including changes of trial objectives, trial design, patient population, sample sizes, trial procedures, or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be agreed upon by TRIO, and approved by the Ethics Committee/IRB and Health Authorities where required, prior to implementation. Only amendments that are required to eliminate an immediate hazard to patients for patient safety can be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this trial, even if this action represents a deviation from the protocol. In such cases, TRIO should be notified of this action and the IRB/IEC at the trial site should be informed.

9.5 Monitoring, auditing and inspecting

TRIO or its representatives must be allowed to visit all trial site locations periodically to assess the data, quality, and trial integrity. On site, they will notably review trial records and **directly** compare them with source documents, review regulatory documents, discuss the conduct of the trial with the investigator, verify trial drug accountability, and verify that the facilities remain acceptable.

9.6 Recording, processing and retention of data

An investigator will be required to prepare and maintain adequate case histories designed to record all observations and other data pertinent to the trial patients. All data reported on the CRF must be derived from source documents and as such be consistent with the source documents, or the discrepancies must be explained.

Data is entered and collected via an Electronic Data Capture System (EDC) using eCRFs (electronic Case Report Form). EDC is a validated system, designed for entry of data in a way that is attributable, secure, accurate, and in compliance with U.S. Food and Drug Administration (FDA) regulations for electronic records (21 CFR Part 11). Sites received training and got access to a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained site staff. The eCRFs should be reviewed and electronically signed and dated by the investigator or a designee. Only an identified and trained user may view the data, and their actions become part of the audit trail.

Sites are responsible for data entry into the EDC system. TRIO is responsible for data management of this trial, including quality checks of the data.

The eCRF must be completed shortly after the patient's visit. All requested information must be entered on the eCRF. If an item is not available or is not applicable, it must be documented as such. The completed eCRF must be promptly reviewed, signed, and dated by the investigator or authorized designee. In the event of discrepant data, TRIO will request data clarification from the sites. The sites will resolve the discrepancy electronically in the EDC system. eCRFs and correction documentation will be maintained in the EDC system's audit trail.

At the end of the trial, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the trial records. Acknowledgement of receipt of the compact disc is required.

The investigator will retain copies of trial documentation for a period of at least 15 years from trial completion. Additional considerations must be made about complying with applicable local laws, guidelines, etc.

9.7 Data Protection

The patient's personal data and Investigator's personal data which may be included in the sponsor database shall be treated in compliance with all applicable laws and regulations. When archiving or processing personal data pertaining to the Investigator and/or to the patients, the sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party. The anonymity of participating patients will be respected with strict adherence to professional standards of confidentiality and applicable privacy rules.

9.8 Confidentiality and Data Protection

All information concerning the trial supplied by TRIO in connection with this trial and/or by any other party collaborating with TRIO, and not previously published, is considered confidential and proprietary information. This information includes the Investigator's Brochure, clinical protocol, workbooks (if applicable), case report forms, assay methods, TRIO technical methodology, and technical and scientific data. This confidential information shall remain the sole property of TRIO and, shall not be disclosed to others without prior written consent from TRIO and shall not be used except in the performance of this trial.

9.9 Insurance of liabilities

If required, the investigator may forward to the Ethics Committee/IRB a copy of the insurance document required by TRIO, in order to cover his/her liabilities, and those of any other participating parties.

9.10 Use of information and publication

All information concerning the trial drug or in connection with this trial, supplied by TRIO and/or by any other party collaborating with TRIO within this trial and not previously published, is considered confidential and proprietary information. This information includes the Investigator's Brochure, clinical protocol, workbooks (if applicable), case report forms, assay methods, TRIO technical methodology, and basic scientific data. This confidential information shall remain the sole property of TRIO the respective collaborating party and, shall not be disclosed to others without prior written consent from TRIO and shall not be used except in the performance of this trial.

To allow for the use of the information derived from this clinical trial and to insure compliance to current regulations, the investigator is obliged to provide TRIO with complete test results and all data developed in this trial. No publication, abstract or presentation of the trial will be made without the approval of the Steering Committee. The Steering Committee will review the manuscript to prevent forfeiture of patent rights to data not in the public domain. Prior to publication, the authorship list will be agreed upon by the Steering Committee. For the purpose of the efficacy and safety analyses, the names on the author list will be given according to the participation in the concept of the trial design as well as accrual input (number of eligible patients accrued) by the investigators at each center. The maximum number of authors will be determined by the publication policy established by the targeted journal. Abstracts and publications will be

submitted to the authors and to the Study Steering Committee at least 30 days prior to the expected date of submission to the intended publisher.

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APPENDIX 1 : EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS SCALE

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

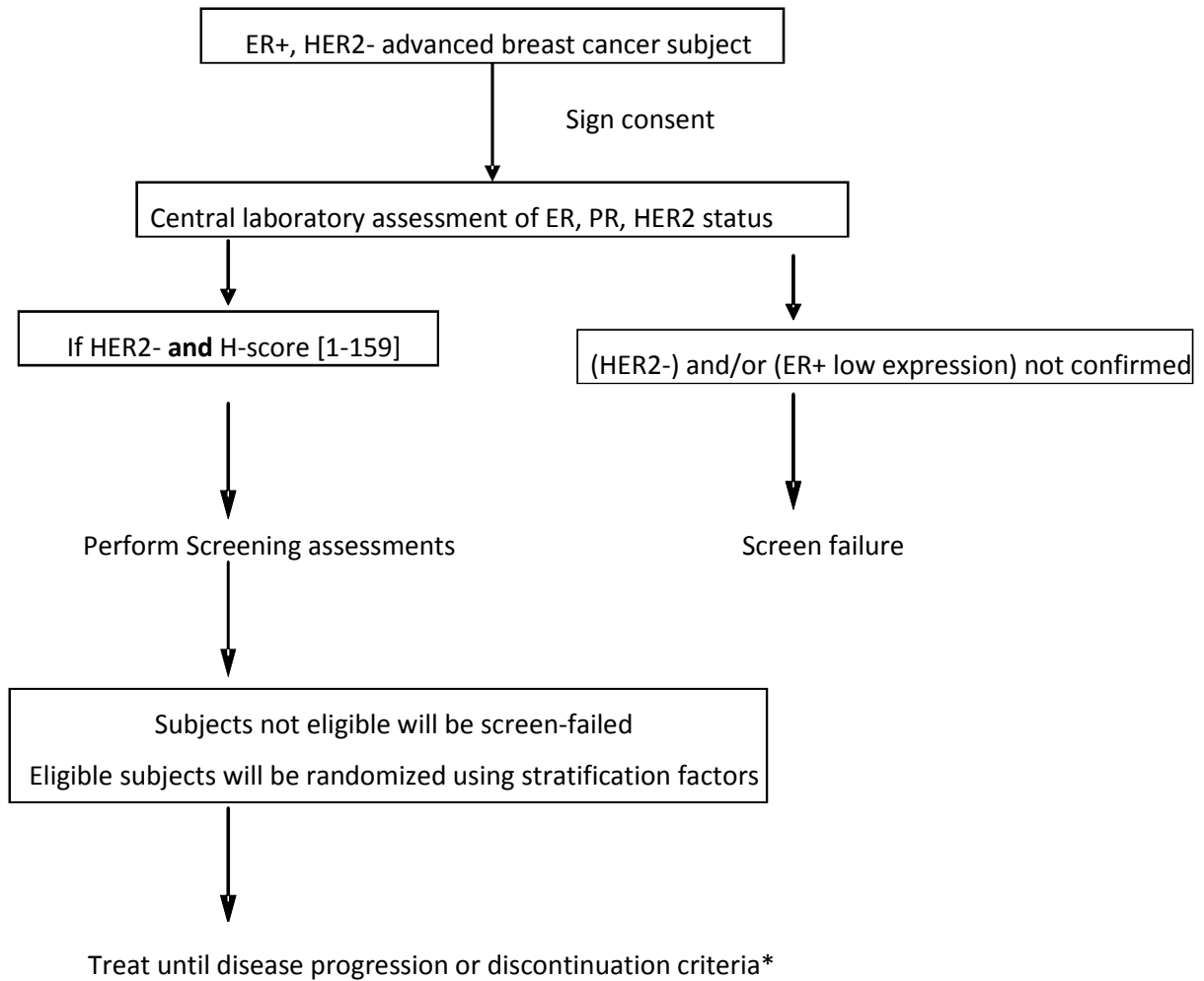
APPENDIX 2 : NYHA CLASSIFICATION

Clinical Evaluation of Functional Capacity of Patients with Heart Disease in Relation to Ordinary Physical Activity

NYHA	Functional Class	Description	Objective Assessment
I	Mild	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation or dyspnoea.	No objective evidence of cardiovascular disease.
II	Mild	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation or dyspnoea	Objective evidence of minimal cardiovascular disease
III	Moderate	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation or dyspnoea.	Objective evidence of moderately severe cardiovascular disease.
IV	Severe	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

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Figure 1 : Trial Scheme - Patient Selection and Treatment



* As described in section 3-Trial Design (IN ADDITION)