Nordic Trip/NBG-19-01; SWEBCG 19-01

A TRANSLATIONAL RANDOMIZED PHASE III STUDY EXPLORING THE EFFECT OF THE ADDITION OF CAPECITABINE TO CARBOPLATINUM BASED CHEMOTHERAPY IN EARLY "TRIPLE NEGATIVE" BREAST CANCER

Protocol Identification Number: NordicTrip / NBG-19-01

EudraCT Number: 2018-002080-25

Sponsor: Department of Hematology, Oncology and Radiation Physics, Skåne Univerisity Hospital

National organisations:

Swedish Breast Cancer Group (SweBCG) and Swedish Association of Breast Oncologists (SABO)

Danish Breast cancer Group (DBCG)

Finnish Breast Cancer Group (FBCG)

Icelandic Breast Cancer Group (IBCG)

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SIGNATURE PAGE

Title: **NORDIC TRIP/NBG-1; A TRANSLATIONAL RANDOMIZED PHASE III STUDY EXPLORING THE EFFECT OF THE ADDITION OF CAPECITABINE TO CARBOPLATINUM BASED CHEMOTHERAPY IN EARLY "TRIPLE NEGATIVE" BREAST CANCER**

Protocol ID no: NordicTrip / NBG-1

EudraCT no: 2018-002080-25

I hereby declare that I will conduct the study in compliance with the Protocol, ICH-GCP and all applicable regulatory requirements:

To be signed by Principal Investigator and Study Statistician.

Name	Title	Role	Signature	Date

PROTOCOL SYNOPSIS

A translational randomized phase III study exploring the effect of the addition of capecitabine to carboplatin based chemotherapy in early "triple negative" breast cancer

Sponsor	Skåne University Hospital
Phase and study type	Phase III, translational
Investigational Medical Product (IMP) (including active comparator):	Capecitabine, carboplatin, cyclophosphamide, epirubicin, paclitaxel, pembrolizumab.
Participating countries:	Sweden, Denmark, Finland, Iceland
Participating centers	21 sites in Sweden, 10 sites in Denmark, 2 site in Finland, 1 site in Iceland
Study Period:	Estimated date of first patient enrolled: 1 December 2019 Anticipated recruitment period: 5 years Estimated date of last patient last visit: 30 June 2035
Treatment Duration:	20-23 weeks
Follow-up:	10 years
Objectives	Primary objectives: • To compare the effect on pathologic complete response (pCR) rate of adding capecitabine to carboplatin based preoperative chemotherapy in early ER-negative and HER2-negative breast cancer. Pembrolizumab is allowed in both arms after approval for TNBC 2022. Secondary objectives: • To compare invasive disease free survival (IDFS), breast cancer specific survival (BCSS), distant recurrence free survival (DRFS), and overall survival (OS). • To evaluate the tolerability defined by toxicity and dose intensity.

- To evaluate the pCR rate separately in cohorts of patients treated with or without the addition of pembrolizumab during preoperative chemotherapy.

- To evaluate the effect of the addition of immunotherapy to platinum-based chemotherapy in a cohorts treated before vs. after the addition of pembrolizumab to both study arms.

Translational objectives:

- To determine the pCR rates in different treatment arms stratified for Homologous Repair Deficiency (HRD) positive vs. HRD-negative/HRD-intermediate.
- To characterize different subsets of TNBC in terms of morphology, epigenetic alterations as well as somatic and inherited genetic alterations.
- To determine the pCR rate and long-term outcome in subsets of TNBC with defined molecular genetic alterations including BRCA1, BRCA2 and PALB2 germline mutations and others, BRCA1, BRCA2 and PALB2 somatic mutations and others and BRCA1 or RAD51 promoter methylation.
- To determine the pCR rate and long-term outcome in different histological subtypes of TNBC
- To determine the pCR rate and long-term outcome in subsets defined based on markers of immune response, e.g., tumor infiltrating lymphocytes and PDL1-expression.
- Analysis of circulating tumor DNA and circulating immune-markers as a marker of treatment response and long-term prognosis.

- Exploration of potential biomarkers predicting benefit of the addition of pembrolizumab to preoperative chemotherapy.

Endpoints:

Primary endpoint: pCR rate

Primary Translational Endpoint: pCR rate in the different study arms stratified for HRD status

Secondary endpoints: IDFS, OS, BCSS, DRFS, toxicity and outcome correlated with potential predictive biomarkers of response and toxicity.

Study Design:

Two armed, open label, multicenter.

Study treatment arms

A: **ddEC x 4 + pembrolizumab→ PK x 4 + pembrolizumab,** i.e.: (epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2) every 2 weeks (q2w) x 4 followed by (paclitaxel 80 mg/m^2 day 1, 8, 15 + carboplatin AUC 5 day 1) every 3 weeks (q3w) x 4. Pembrolizumab is given as a 400 mg iv dosis every 6 weeks for the duration of preoperative chemotherapy.*

B: **CEX x 4→ PK x 4**, i.e. (epirubicin 75 mg/m^2 + cyclophosphamide 600 mg/m^2 + capecitabine 1800 mg/m^2 day 1-14) q3w x 4 followed by

(paclitaxel 80 mg/m^2 day 1, 8, 15 + carboplatin AUC 5 day 1) q3w x 4. Pembrolizumab is given as a 400 mg iv dosis every 6 weeks for the duration of preoperative chemotherapy.*

*The addition of pembrolizumab is strongly recommended to all participating patients. However, patients with a documented contraindication, or unwilling to receive immunotherapy may be included in the study without the administration of pembrolizumab.

Inclusion Criteria:

Patients must meet all of the following criteria to be eligible:

1. Signed written informed consent approved by the Ethical Review Board (IRB).
2. Age ≥ 18 to < 76 years.
3. Histologically confirmed unilateral adenocarcinoma of the breast where neoadjuvant chemotherapy followed by definitive surgery is planned.
4. Node positive disease (N1-3) or if clinically N0 Tumor size ≥20 mm.

   When deciding T-stage the following hierarchy applies,
   a. MRI
   b. Ultrasound
   c. Mammography
   d. Clinical examination
5. ER negative tumor defined by at least one the following:
   a. ER < 1% cells positive by immunohistochemistry (IHC) or ER ≤ 10% cells positive by IHC and basal-like subtype using gene expression analysis
   b. ER ≤ 10% cells positive by IHC and PgR ≤ 10% cells positive by IHC
6. HER2-normal tumor defined according to applicable national guidelines
7. Consent for germline mutation screening for BRCA1, BRCA2 and other inherited breast cancer associated genes.
8. WHO performance status 0 or 1.
9. Negative pregnancy test in women of childbearing potential (premenopausal or <12 months of amenorrhea post-menopause and who have not undergone surgical sterilization).
10. Willingness of female patients of childbearing potential, male patients, and their sexual partners to use an effective means of contraception during the treatment period and at least 6 months thereafter.
11. Willingness by the patient to undergo treatment and study related procedures according to the protocol.

Exclusion Criteria

Patients meeting any of the following criteria are not eligible:

1. Clinical or radiological signs of metastatic disease.

2. History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix or non-melanoma skin cancer.

3. Previous chemotherapy for cancer or other malignant disease.

4. Charlson comorbidity index, excluding score for malignancy: (CCI) > 2, Comment: In patients 70-75 a CCI = 3 is allowed, see appendix B.

5. Inadequate organ function, suggested by the following laboratory results:
   a Absolute neutrophil count < 1,5 x 10^9/L
   b Platelet count < 100 x 10^9/L
   c Hemoglobin < 90 g/L
   d Total bilirubin greater than the upper limit of normal (ULN) unless the patient has documented Gilbert´s syndrome
   e ASAT (SGOT) and/or ALAT (SGPT) > 2,5 x ULN
   f ASAT (SGOT) and/or ALAT (SGPT) > 1,5 x ULN with concurrent serum alkaline phosphatase (ALP) > 2,5 x ULN
   g Serum creatinine clearance < 50 ml/min

6. Concurrent peripheral neuropathy of grade 3 or greater (NCI-CTCAE, Version 5.0).

7. Patient who is actively breast feeding.

8. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

9. Patients with known deficiency of the DPD-enzyme who completely lack DPD.

Primary aim:

Pathological complete response rate after preoperative chemotherapy is the primary endpoint of the study, which will be evaluated by comparing the effects of neoadjuvant administration of a carboplatin-based treatment (A) and treatment adding capecitabine (B) on pCR.

After the approval of pembrolizumab in the preoperative treatment of early TNBC in 2022 the study will consist of two cohorts, one (cohort 1) without the addition of pembrolizumab, and one (cohort 2) with the addition of pembrolizumab to both study arms. The primary evaluation will be performed on the entire study population including both cohorts. The estimated number of patients in cohort 1 is 160.
Before the approval of pembrolizumab, the detectable alternative of the study was defined as an absolute difference in pCR rate of 10 percentage units (from 52% to 62%). This absolute difference corresponds to an odds ratio (OR) of 1.51. By assuming a pCR rate of 52% in arm A of cohort 1 (Poggio F., Bruzzone M. et al. 2018) and a pCR rate of 65% in arm A of cohort 2 (Schmidt, Cortez et al 2022), a sample size of 908 patients, 454 in each arm, is required to have 80% power to detect the same relative effect (OR=1.51) using a two-sided Chi-squared test with the significance level set at 5%. The expected pCR rate for arm A is 62.7% which is a weighted average of 80 patients (18%) with rate 52% (cohort 1) and 374 patients (82%) with rate 65% (cohort 2). To account for an expected low fraction of non-evaluated patients, the sample size is set at 920. Patients that are included in the study and receive study treatment, but do not undergo surgery will be evaluated as having a non-pCR.

Primary translational aim:

To investigate if the effects of the treatments depend on HRD-status. More specifically, the aim is to test for differential effect of the two treatments on pCR for HRD-negative (HRD low and intermediate by oncoscan) and HRD-positive (HRD high by oncoscan) patients.

Assuming that

a. 59% of the patients are HRD-positive (implying 41% HRD-negative)
b. that the pCR rates in arm A and B are 52% and 62%, respectively, and
c. that the effects of the two treatments are equal (same odds of pCR; OR=1.00) for HRD-positive patients

the OR for B vs A in the HRD-negative group can be calculated for different pCR rates for HRD-positive patients in treatment group A.

Below two examples:

- 63% pCR in HRD+ (for both arms) implies 36.2% pCR in HRD- for arm A and 60.6% pCR in HRD- for arm B corresponding to an OR of 2.71 for B vs A in HRD-. This differential effect of treatment on pCR rates in HRD+ and HRD- can be detected with 92% power with a sample size of 800 patients using a two-sided test for interaction with significance level set to 0.05.
- 67% pCR in HRD+ (for both arms) implies 30.4% pCR in HRD- for arm A and 54.8% pCR in HRD- for arm B corresponding to an OR of 2.77 for B vs A in HRD-. Also this differential effect can be detected with 92% power with a sample size of 800 patients using a two-sided test for interaction with significance level set to 0.05.

Randomization will be performed 1 : 1 between the two treatment arms A and B, with stratification for the country of inclusion, N-status, T-status and pembrolizumab yes/no.

Efficacy Assessments: Pathological response rate in the breast and axilla, with a disappearance of all signs of invasive cancer. Cases with residual in situ deposits in the breast are included in the definition of pCR. Relapse, new cancer, survival in all patients. Quality of life will be investigated in a subset of included patients.

Safety Assessments: Breast imaging at baseline and after 4-5 weeks of treatment, in order to exclude on-treatment disease progression.

Reporting of adverse events, biochemistry, hematology, vital signs and performance status.

An evaluation and analysis of the feasibility of the prescribed doses and pCR rate irrespective of treatment allocation will be performed after the treatment of 60 patients.

A second evaluation of the feasibility of the prescribed doses and pCR rate irrespective of treatment allocation will be performed after the treatment of 60 patients following the amendment (Protocol version 4.0) that recommends the addition of pembrolizumab to the study treatment.

Data Management Data will be collected in a database run by the Danish Breast Cancer Group (DBCG).

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Explanation
AE	Adverse Event
ALAT (SGPT)	Alanine Aminotransferase (Serum Glutamic Pyruvic Transaminase)
ASAT (SGOT)	Aspartate Aminotransferase (Serum Glutamic Oxaloacetic Transaminase)
AUC	Area Under the Curve
BCSS	Breast Cancer specific Survival
BRCA	Breast Cancer Gene
CCI	Charlson Comorbidity Index
ClinR	Clinical Response
CR	Complete Remission
CRF	Case Report Form (electronic/paper)
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DBCG	The Danish Breast Cancer Group
ddEC	Dose Dense EC (Epirubicine and Cyclophosphamide)
DRFS	Distant Recurrence Free Survival
EBCTCG	Early Breast Cancer Trialists Collaborative Group
EC	Epirubicine and Cyclophophamide
ECG	Electrocardiogram
ER	Estrogen Receptor
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
HER2	Human Epidermal Growth Factor Receptor
HRD	Homologus repair deficiency
ICH	International Conference on Harmonization
IDFS	Invasive Disease Free Survival
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
ISH	In Situ Hybridization
MRI	Magnetic Resonance Imaging
OS	Overall Survival
pCR	Pathological Complete Response
PD	Progressive Disease
PgR	Progesterone Receptor
q3w	Every 3 weeks
q2w	Every 2 weeks
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SD	Stable Disease
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	Upper Limit of Normal

1 INTRODUCTION

1.1 Background – Early breast cancer

1.1.1 Adjuvant and preoperative chemotherapy in early breast cancer

In early breast cancer disease, the administration of adjuvant chemotherapy significantly reduces the risk of recurrence and breast cancer-specific death (Peto, Davies et al. 2012). Adjuvant polychemotherapy typically leads to a one-third reduction of breast cancer-specific mortality at ten years. With the exception of HER2-positive disease, the chemotherapy regimens administered do not include targeted treatment agents, but instead depends on the general chemosensitivity of micrometastatic cancer cells. Shortly after the year 2000, when the gene-expression based "intrinsic" subtypes of breast cancer were first presented by Sorlie and colleagues, the need to sub-classify breast cancer into distinct entities in order to better understand the biological and clinical differences between breast cancers has become increasingly evident (Perou et al. 2000; Sorlie er al. 2001). The two subtypes with the least beneficial prognosis are the "HER2-enriched" and "basal-like" groups. The latter subset has a considerable overlap with so-called triple negative breast cancers (TNBC), i.e., cancers that express neither the estrogen or progesterone receptors nor overexpressing HER2. The adjuvant treatment and outcomes for patients with HER2 and ER-positive breast cancers has undergone a substantial improvement during recent decades since the advent of anti-HER2 antibody-based treatment, the more generous use of chemotherapy in ER-positive disease, and a more rational use of endocrine treatment. In TNBC a similarly positive development is still eagerly awaited. In a recent meta-analysis, the addition of carboplatin to conventional chemotherapy has been shown to lead to an increased rate of pathological complete response after preoperative treatment. However, the long-term effect regarding event-free and overall survival with the addition of carboplatin is still unclear (Poggio, Bruzzone et al. 2018).

1.1.2 Triple negative breast cancer (TNBC)

TNBC is characterized by the absence of expression of estrogen and progesterone receptors and the lack of signs of amplification of the oncogene HER2. TNBCs constitute about 8% of new breast cancers in Sweden, i.e., more than 600 cases yearly in Sweden, and an estimated incidence and mortality of more than 1500 and up to 500 cases per year, respectively, in the Nordic countries (Sweden, Denmark, Norway, Finland and Iceland). Apart from the absence of markers of endocrine sensitivity and HER2-positivity, TNBC remains a poorly defined and heterogeneous subset of breast cancers with the most adverse prognosis of all breast cancers. In the absence of treatable targets, chemotherapy and potentially bisphosphonates remain the sole medical intervention with a proven effect on long-term survival in TNBC. Although there have been some indications of benefit of the anti-VEGF antibody bevacizumab, the long-term effect of this costly drug has been a disappointment. Recent results indicate that immunotherapy may have a role in TNBC (Schmid, Adams et al. 2018) and investigations on the effect are under way.

A recent metaanalysis strongly suggests a benefit in terms of an increased pathologic complete response rate in unselected TNBC adding carboplatin to preoperative chemotherapy (Poggio, Bruzzone et al. 2018). Furthermore, subgroup analyses from four large randomized clinical trials suggest a selective benefit of the addition of capecitabine to standard adjuvant chemotherapy in this subtype.

There is strong evidence to suggest that the biology and the effect of chemotherapy differs between subsets of TNBCs both in general and regarding response to specific agents (Rakha, Elsheikh et al. 2009). Histopathological subtypes among TNBCs include high-grade invasive carcinoma of no special type, medullary and atypical medullary cancers, and metaplastic cancer; and among low-grade cancers, adenoid cystic, low-grade adenosquamous, and low-grade spindle carcinomas (Dawson, Provenzano et al. 2009). Among the intrinsic subtypes, most TNBCs fall into the basal-like cluster (Sorlie, Perou et al. 2001). Furthermore, gene expression-based subtyping within the triple negative cohort shows that it may be subdivided into four different subtypes (Brian, Lehmann, et al. 2016; Prat, Adamo 2013).

Subsets of TNBC have a defective DNA-repair. Most notably, BRCA1-associated breast cancer typically displays a triple negative histopathological phenotype and basal-like gene expression pattern and does indeed display defective DNA-repair as illustrated by heightened responsiveness to PARP-inhibition in these cancers, both in vitro (Farmer, McCabe et al. 2005) and clinically (Tutt, Robson et al. 2010; Robson, Im, et al. 2018; Litton, Hope et al. 2018). Also, breast cancers with a somatic mutation in BRCA1 or an epigenetic inactivation of BRCA1 typically displays a triple negative phenotype (Winter, Nilsson et al 2016; Hedenfalk, Duggan et al.2001). Data from the population-based Swedish SCAN-B study indicate that in TNBC, 59% display an HRD-high (positive) phenotype, with 41% being either HRD-low (36%), or HRD-intermediate (5%), i.e., HRD-negative. In this study, that included 254 cases of primary TNBC, HRD-positivity was associated with a better outcome after adjuvant chemotherapy for invasive disease-free survival, suggesting a more pronounced chemosensitivity in HRD-positive cancers in contrast to HRD-negative cases. In 67% of the HRD-positive cases, an identifiable molecular genetic alteration, presumably associated with the HRD-positive phenotype could be identified, e.g., BRCA1 or BRCA2 germline or somatic mutations, or BRCA1 promoter methylation (Johan Staaf, submitted). In addition, the occurrence of tumour infiltrating lymphocytes appears to be an important prognostic marker in ER-negative HER2-negative breast cancer (Mao, Qu et al 2016).

1.2 Background – chemotherapy in triple negative breast cancer (TNBC)

1.2.1 Standard adjuvant chemotherapy in triple negative breast cancer

Modern adjuvant chemotherapy in early HER2-negative breast cancer typically consists of a sequential anthracycline and taxane based therapy. Treatment is similar in ER-positive, and ER-negative disease. According to the Early Breast Cancer Trialists Collaborative Group (EBCTCG) metaanalysis the absolute added benefit of giving a taxane as part of the adjuvant treatment is in the order of 2% on survival at 8 years (EBCTCG 2012). In Europe many patients are treated with the regimen explored in the FNCLCC PACS01 trial that was evaluating the effect of the switch to three three-weekly cycles of docetaxel following three cycles of FEC100 (5-fluorouracil, epirubicine and cyclophosphamide), compared with a standard regimen consisting of six cycles of FEC100 (Roché, Fumoleau 2006). Different weekly, and three-weekly taxane regimens, following four cycles of adriamycin and cyclophosphamide (AC), have been compared in a large four-armed study indicating equivalent outcomes using three-weekly docetaxel and weekly paclitaxel, suggesting that either the three-weekly docetaxel regimen or the weekly paclitaxel regimen are the preferred options (Sparano, Wang 2008). The added benefit of the IV injection of 5-fluorouracil together with an anthracycline has been questioned and is today omitted from standard treatment based on data from an Italian randomized trial (Del Mastro, De Placido 2015). A recently presented metaanalysis from the EBCTCG strongly suggests that dose-dense chemotherapy given every two weeks decreases the disease recurrence rate, the 10-year breast cancer mortality and increases the overall survival compared with three-weekly treatment (EBCTCG 2017). In TNBC, a recent metaanalysis including more than 2000 patients from nine individual phase 2 and 3 studies showed that the addition of platinum to preoperative treatment in early TNBC adds a benefit in terms of an increased pathological complete response (pCR) rate. The long-term effect in terms of disease-free survival (DFS) and overall survival (OS) is still unclear but based of the promising results the authors of the metaanalysis consider the addition of platinum an option in unselected TNBC (Poggio, Bruzzone et al 2018).

In recent years, there has been an increasing interest to explore the advantage of studying treatment response in the preoperative (neoadjuvant) setting. Preoperative treatment of breast cancer generally leads to equal results in terms of DFS and OS compared with postoperative chemotherapy (Mieog, van der Hage et al. 2007; EBCTCG 2018). In a proportion of cases the preoperative chemotherapy treatment strategy leads to a clinically significant down-staging and a possibility of breast conservation that is not otherwise feasible. Equally importantly, the preoperative administration and response evaluation of preoperative medical treatment provides information regarding the prognosis of individual patients. In addition, it creates a unique opportunity to study the biological effects of treatment on site, and thus a possibility to assess the effect of chemotherapy in terms of response in individual patients and molecular genetic events in different and specific subgroups of breast cancer. Lastly, it is the fastest way of initiating

medical treatment effective throughout the body, which is suggested of being of special importance in ER negative disease (Colleoni, Bonetti 2010; Gagliato de Melo, Gonzalez-Angulo 2014).

Although pCR has a strong prognostic value for the individual, the translation of pCR differences on a study level to differences in terms of event-free and OS, remains controversial (Cortazar P, Zhang L et al. 2014; Nekljudova V, Loibl S et al 2018). None the less, the prognostic value of a pCR differs between breast cancer subtypes, being greater among ER-negative breast cancers compared to ER-positive cases. In TNBC, the prognostic value of pCR/non-pCR is strong and has a potential of being a surrogate endpoint for long-term outcome (Cortazar, Zhang et al. 2012; von Minckwitz, Untch et al. 2013). In addition to the prognostic value of the pCR/non-pCR itself, the properties of the residual cancer burden are associated with different outcomes, e.g., the rate of Ki67 positive cells in the residual tumour was prognostic for recurrence-free and overall survival in two studies (Symmans, Peintinger et al. 2007; Jones, Salter et al. 2009). Most importantly, preoperative trials give us the potential to study response to treatment with the tumour in its original human environment and allows for the identification of biomarkers in the primary tumour predicting response or resistance to chemotherapy.

1.2.2 Carboplatin in early TNBC

The German GeparSixto trial investigated the effect of the addition of carboplatin in 595 HER2-positive and triple negative patients, randomized in two different strata. The primary endpoint was the difference in pCR rate with the addition to carboplatin to a polychemotherapy regimen consisting of paclitaxel and liposomal doxorubicin and bevacizumab for TNBC and trastuzumab + lapatinib for HER2-positive cases, and failed to show a statistically significant difference. However, a higher pCR rate was indeed observed in the triple negative subset associated with the addition of carboplatin, with rates of 38% without vs. 59% with the addition. The treatment regimen did show a significant toxicity only allowing 52% of the patients in the carboplatin-containing arm complete their preoperative chemotherapy (von Minckwitz, Schneeweiss et al. 2014).

The CALGB A 40603 included 443 TNBCs with clinical stage 2-3 (excluding inflammatory breast cancers) into a two-by-two randomized preoperative study adding carboplatin, bevacizumab, or both, to a chemo backbone consisting of paclitaxel q1w x 12 followed by AC q2w x 4. Carboplatin was given AUC6 x 4 together with paclitaxel. The addition of carboplatin was associated with a higher pCR rate in breast + axilla (41% vs. 54%) corresponding to an OR of 1,71; p=0.0029 (Sikov, Berry et al. 2015).

The I-SPY 2 randomized 72 + 62 HER2-negative breast cancer patients in a sophisticated adaptive design to standard treatment (paclitaxel q1w x 12 followed by AC q3w x 4) versus standard + carboplatin AUC6 q3w and the PARP-inhibitor veliparib 50 mg x 2 during the paclitaxel treatment. Among TNBCs the addition of carboplatin + veliparib resulted in a 26% to 51% increment in the pCR rate, indicating superiority with the addition of these drugs to standard treatment (Rugo, Olopade et al. 2016).

Recently, the BrighTNess trial was published. The study was designed following the I-SPY 2 results and investigated the effect of the addition of carboplatin alone or in combination with the oral PARP-inhibitor veliparib to standard chemotherapy. In this important trial that included 952 patients randomized in a 1:1:2 manner to conventional taxane and anthracycline based treatment vs. treatment with the addition of carboplatin + placebo vs. carboplatin + veliparib. The primary endpoint was pCR rate. pCR was significantly higher with the addition of carboplatin to standard chemotherapy, (58% vs. 31 %) but was not further increased with the addition of the combination of carboplatin and veliparib (53%) (Loibl S, O'Shaughnessy J, et al 2018). A recent update of the study suggests that the increased pCR observed with the addition of platinum to preoperative chemotherapy in early TNBC is translated into a meaningful increase of the eventfree survival corresponding to a HR of 0,57 (95%CI = 0,36-0,91) for the addition of carboplatin to paclitaxel in the preoperative setting, giving further support for the addition of platinum to preoperative chemotherapy in early TNBC. There was no suggestion in the study that the outcome in relation to platinum was any different in patients with a gBRCA mutation vs. gBRCA wild type (Geyer, Sikov et al. 2022).

The aforementioned metaanalysis by Poggio and co-workers included these four studies and an additional five trials investigating the effect on the pCR rate with the addition of carboplatin or cisplatin (one study

only). The metaanalysis reported that the pCR rate was significantly higher with regimens including platinum (52.1%) compared with platinum free regimens (37.0%) (OR 1.96, 95% CI 1.46–2.62, P<0.001). Platinum based treatment increased the rate of grade 3-4 hematological toxicity, but the rate of neuropathy grade 3-4 was equal (Poggio, Bruzzone et al 2018).

1.2.3 Chemotherapy in BRCA-deficient and HRD-positive breast cancer

Attention has been drawn to the use of platinum salts in the treatment of BRCA deficient cancer as a way of exploiting the biological feature that is associated with homologous repair deficiency (Curigliano and Goldhirsch 2011). In one preoperative study, the pCR rate after four cycles of cisplatin 75 mg/m^2 was 22% among 28 patients with stage 2-3 triple negative breast cancer. Signs of BRCA1-deficiency (low mRNA level, BRCA1 promoter methylation and BRCA1 germline mutation status) were predictive of a clinical response to treatment (Silver, Richardson et al. 2010). The pathological response rate in the breast and axilla was 62% in a set of 74 women treated after eight cycles of preoperative cisplatin, epirubicine, and paclitaxel (Frasci, D'Aiuto et al. 2010), and 61% among 104 patients with a deleterious BRCA1 germline mutation treated with four cycles of cisplatin 75 mg/m^2 (Byrski, Huzarsky et al 2014). In a Dutch study of high-dose chemotherapy, survival was significantly better after platinum- and thiotepa-based chemotherapy in cases with a comparative genomic hybridization classifier indicating BRCA-deficiency in the tumour (Vollebegh, Lips et al 2014). More recent studies have shown that not only BRCA germline mutations but also homologous repair deficiency in general is a predictor of response to conventional as well as platinum-based chemotherapy in triple negative and BRCA-associated breast cancer. In two small studies, Telli and co-workers have observed that HRD-positivity strongly predicts a pathologic complete response after conventional (Telli, Hellyer et al 2018) and platinum-based chemotherapy (Telli, Timm et al. 2016). In our own research, we could observe that the effect of adjuvant chemotherapy was more pronounced in the HRD-positive subset compared with the HRD-negative breast cancers, giving support to the view that HRD is a marker of chemosensitivity in TNBC (Staaf, Glodzik 2019). Thus, it seems clear that markers of BRCA-deficiency and other indicators of homologous repair deficiency may be associated with an increased likelihood of response to platinum-based and conventional chemotherapy in subsets of TNBC.

1.2.4 Capecitabine in early breast cancer

Capecitabine is an oral prodrug to 5-fluorouracil, and an agent with a generally advantageous side-effect profile, and therefore frequently used in the palliative setting in breast cancer. Adding capecitabine to standard chemotherapy as an adjuvant treatment in early breast cancer has been exclusively evaluated in terms of long-term outcome in tree large, randomized trials of adjuvant treatment, and in one study of postoperative capecitabine after non-pCR to preoperative treatment. The FinXX study showed a non-significant but borderline benefit with adding capecitabine to docetaxel and EC (Epirubicine and Cyclophosphamide) at all cycles (p = 0.087, HR 0.79) (Joensuu, Kellokumpu-Lehtinen et al. 2009). In the TNBC sub-group consisting of 202 cases, however, the benefit appeared to be greater (p = 0.018, HR 0.48) (Lindman, Kellokumpu-Lehtinen et al. 2010). In the larger US Oncology study with similar design except less capecitabine was given (50% of cycles), the results were similar with a HR for DFS of 0.84 (p=0.12) and HR for OS of 0.68 (p = 0.01). Again, the results indicated a better relative effect in the TNBC sub-group (HR 0.81 for DFS and 0.62) and significant benefit in highly proliferative tumours (Ki67 > 10%, HR 0.70) (O'Shaughnessy, Paul et al. 2010; O'Shaughnessy, Koeppen et al. 2015). A study similar to the FinXX study is now being repeated in the TNBC sub-population in China (CBCSG10; ClinicalTrials.gov identifier NCT01642771). The study has included 585 cases of TNBC, treated adjuvant with three cycles of docetaxel followed by three cycles of EC +/- capecitabine for the whole treatment course. At an interim analysis at 30 months of follow-up, recurrence free survival was numerically, however not significantly, advantageous in the capecitabine group corresponding to a HR of 0.57 (95% CI: 0.33-1.0).

In the Japanese-Korean CREATE-X/JBCRG04 trial, 910 HER2-negative breast cancer patients not achieving a pathological complete remission after conventional preoperative chemotherapy, were randomized to the addition of postoperative 6-8 cycles of capecitabine treatment versus no additional chemotherapy. A third of included patients were cases of TNBC. At the first planned interim analysis, DFS and OS was superior among patients receiving the additional capecitabine treatment (HR for OS = 0.59 95% CI 0.39-0.90;

p=0.01). In the TNBC subset, the benefit in terms of OS of adding capecitabine corresponded to a HR of 0.52 95% CI 0.30-0.90 with an 8.5% absolute difference in survival at 5 years (Masuda, Lee et al 2017).

The Spanish CIOMBA/2004-01_GEICAM/2003-11 study investigated the effect of adding capecitabine to standard neo/adjuvant chemotherapy in TNBC. The total number of included patients in the study was 876 patients. DFS at five years of follow-up was 79,6 % with the addition of 8 cycles of capecitabine vs. 76,8 % without, corresponding to a HR of 0,82; p=0,14. However, in the subset of patients with a non basal-like phenotype, defined by the absence of cytokeratine 5/6 expression, there was a clinically relevant increased DFS and OS with the addition of capecitabine. The effect corresponded to a HR of 0,53 (p=0,02) with an absolute difference of 9,7 % (82,6 % vs. 72,9 %) between the study arms for DFS, and a HR of 0,42 (p= 0,007) with an absolute difference of 9,9 % (89,5 % vs. 79,6 %) for OS at five years of follow-up (Miguel, Barrios et al. 2018).

A subgroup analysis of the FinXX trial provides further suggestive evidence that the effect of capecitabine in TNBC is associated with the non-BRCA1-like, i.e., non-basal-like correlating with HRD-negative, phenotype (de Boo, Jóźwiak et al 2022).

In brief, several pieces of evidence support a beneficial effect of capecitabine in the neo/adjuvant treatment setting in TNBC, but it is unclear whether this effect is attributable to unselected TNBC, or if it is restricted to a certain subset of cases. The Spanish CIOBMA-study and data from the FinXX suggest that the effect is preferential for the third of cases with a non-basal like TNBC phenotype. It should be noted that treatment schedules adding additional capecitabine after standard chemotherapy such as in the CREATE-X trial and the CIOBMA-study, leads to a protracted period of treatment for the patients, and that including it to the primary treatment would potentially be an advantage for the treated patients, provided equal effect, and that the subset with benefit could be identified.

1.2.5 Immunotherapy in early breast cancer

During the recent decade immunotherapy has been introduced in the treatment of recurrent as well as early cancer. In a subset of instances, the addition of immunotherapy has resulted in major improvements in a number of previously prognostically adverse malignant diagnoses. In breast cancer, the triple negative subset has attracted the most attention and in Europe currently two agents (atezolizumab and pembrolizumab) are approved for use in combination with chemotherapy in PDL1 positive inoperable and recurrent disease and pembrolizumab in the combined preoperative and adjuvant treatment setting in TNBC, curiously independent of PDL1 status.

In the pivotal randomized placebo-controlled Keynote 522 trial, 1174 patients with previously untreated TNBC clinical stage 2-3 were randomized in at 2:1 fashion to chemotherapy (four cycles of three-weekly paclitaxel and carboplatin followed by four cycles of three-weekly doxorubicin or epirubicin and cyclophosphamide) with or without 8 cycles of three-weekly pembrolizumab or placebo, followed by an additional up to nine three-weekly cycles of pembrolizumab/placebo. The addition of pembrolizumab resulted in a higher pCR rate (51.2% vs. 64.8%), and a significantly improved event-free survival at 36 months of follow-up to 84.5% with pembrolizumab (95% CI 81.7-86.9%) vs. 76.8 % (95% CI 72.2-80.7%) with placebo. Adverse events occurred predominantly during the preoperative phase and were consistent with previously established safety profiles of pembrolizumab and chemotherapy. Treatment associated toxicities grade 3 and higher were observed in 77.1 % of the patients treated with pembrolizumab and 73.3 % in the patients treated with chemotherapy alone. Immunrelated adverse events (any grade) occurred in 33.5 % of the pembrolizumab treated patients (12.9 % grade 3 and higher) and in in 11.3 % among control patients (1.0 % grade 3 and higher). 27.7 % vs. 14.1 % of the patients discontinued due to treatment-associated side effects. Treatment associated deaths occurred in 0.5 % (N = 4) and 0.3 % (N = 1) of the patients respectively, two patients in the pembrolizumab arm died due to immunrelated side-effects.

Based on these data, EMA recently approved pembrolizumab for the use in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery, for the treatment of adults with locally advanced, or early-stage TNBC at high risk of recurrence (clinical stage 2-3).

1.2.6 Pembrolizumab and capecitabine

The chemotherapy regimen A in NordicTrip equates the regimen given in the pivotal Keynote 522 study. In order to allow for the addition of pembrolizumab also to arm B, the combination of pembrolizumab with a capecitabine based regimen must be feasible and tolerable. Here follows a brief overview of reported treatments including pembrolizumab and capecitabine.

The combination of pembrolizumab (200 mg q3w) and capecitabine (1000 mg /m^2 for two weeks followed by a one-week interval) in breast cancer was investigated in a phase 2 trial including 30 patients with dissiminated TNBC or luminal breast cancer. The toxicities recorded was not different from what would have been expected from capecitabine monotherapy (Shah, Flaum et al. 2020). Another small study of metastatic TNBC included 14 patients treated with pembrolizumab in combination with paclitaxel and an equal number of patients in combination with capecitabine. All evaluable patients (N = 22) tolerated the treatment. The combination with capecitabine showed an encouraging response rate according to Recist 1.1 of 43 %. No significant differences in immunomodulation were observed according to chemotherapy type, and both types of chemotherapy resulted in a time dependent lymphodepletion (Page, Chun et al. 2019, ASCO abstract; Chun, Pucilowska 2022). More data on the toxicity related with the combination of capecitabine and pembrolizumab are available from studies on gastrointestinal cancers. Pembrolizumab in combination with oxaliplatin and capecitabine was evaluated in a small study (N = 11) in biliary tract cancer (Monge, Pehrsson et al. 2022), with cisplatin and fluorouracil or capecitabine in two studies (Keynote 059 and 062) of gastric cancer (N = 25 and N = 257) (Shitara, van Cutsem et al. 2020; Bang, Kang et al. 2019), and finally in locally advanced rectal cancer where capecitabine was given in sequence after FOLFOX together with pembrolizumab and radiotherapy (N = 90) (Rahma, Yothers et al 2021). In summary, the combination of pembrolizumab and chemotherapy regimens including capecitabine are reported feasible and tolerable.

1.3 Rationale for the Study and Purpose

The overall purpose of the NordicTrip study is to optimize chemotherapy in the curative treatment of early TNBC.

Standard adjuvant chemotherapy for unselected TNBC is currently based on the sequential use of anthracyclines with cyclophosphamide and taxanes. A recent metaanalysis has confirmed a beneficial effect in terms of pCR rate with the addition of carboplatin to conventional chemotherapy. A preliminary evaluation of the long-term outcome in the metaanalysis suggests a potential effect beyond response to platinum-based chemotherapy compared with conventional chemotherapy, with hazard ratios for DFS of 0.72 (95 % CI 0.49–1.06, P=0.094) and HR 0.86 for OS (95% CI 0.46–1.63, P=0.651). As a consequence, the authors state that platinum may be considered an option in unselected cases of TNBC (Poggio F., Bruzzone M, et al 2018). Based on these results we decided to include carboplatin in the baseline comparator arm in this trial, and to explore the potential additional effect of capecitabine in unselected and subsets of TNBC.

Based on subgroup analyses from three large trials, capecitabine appears to have an effect in unselected early TNBC. The CREATE-X, where capecitabine was given to patients following non-pCR to preoperative chemotherapy, has attracted the most attention. Here, RFS and OS was reported to be increased with the addition of capecitabine to standard chemotherapy with HRs of 0.58 and 0.52, respectively. The apparent benefit comes with the drawback of a protracted treatment period of almost a whole year on active chemotherapy, and indeed, the duration of capecitabine treatment in the study was reduced from 8 to 6 three-weekly cycles during the study. The effect of capecitabine treatment in the CREATE-X study is observed in a subset of patients with a relatively chemoresistant phenotype, i.e., cases that did not respond with a pCR on conventional chemotherapy (Masuda N., Lee SJ., et al. 2017). A fourth trial (the Spanish CIOBMA-study) suggests a benefit preferentially among non-basal-like TNBCs.

In TNBC, HRD has been observed to predict response to both conventional and platinum-based preoperative chemotherapy (Telli ML, Hellyer J., et al 2018; Telli ML, Timms KM, et al. 2016). However, the recent BrighTNess trial failed to show an additional benefit by the addition of a PARP-inhibitor to platinum

based preoperative chemotherapy (Loibl S, O'Shaughnessy J, et al 2018). We hypothesise that this might be an effect of a lack of further improved outcome in chemosensitive TNBC. Given the pronounced heterogeneity among TNBCs, it is reasonable to assume that the effect of capecitabine among TNBC may not be the same across different subsets of TNBC, and that it may primarily exert its effect in a relatively chemoresistant subset of TNBC.

The aim of the current study is to explore the effect of the addition of capecitabine in terms of pCR rate and long-term outcome to carboplatin-based preoperative chemotherapy in early TNBC, and to identify markers of response to treatment. We hypothesise that HRD, a marker of chemosensitivity in TNBC is a potential marker of response to the addition of capecitabine to platinum-based therapy in TNBC, with the most pronounced effect being seen in the HRD-negative subset. In addition, other pre-defined and exploratory biomarkers for response to treatment will be identified in the tumours and the blood and evaluated within the study.

In the study a marker of HRD-positivity (Oncoscan; Affymetrix) will be investigated as a potential predictor of response to preoperative treatment in the different treatment arms, and more specifically to the response of capecitabine.

The approval of pembrolizumab in early TNBC has prompted an update of the protocol recommending the addition of pembrolizumab to the two study arms. The treatment is recommended for all study participants. However, patients that are not eligible or do not wish to receive immunotherapy as part of treatment may be included in the study according to the original protocol, excluding pembolicumab.

2 STUDY OBJECTIVES AND RELATED ENDPOINTS

2.1 Primary and Secondary Endpoints

	Objectives	**Endpoints**
Primary	To compare the effect on pCR rate (ypTis, ypN0) of adding capecitabine to carboplatin-based preoperative chemotherapy in early ER-negative and HER2-negative breast cancer. Pembrolizumab is allowed in both arms after approval for TNBC 2022.	– pCR with the addition of capecitabine compared with carboplatin-based chemotherapy alone.
Primary translational	Evaluate HRD-status as a potential biomarker for response to the addition of capecitabine to carboplatin-based preoperative chemotherapy.	– Investigation of the potential interaction between the pCR-rate and treatment allocation based on stratification between HRD-positive and HRD-negative patients.
Secondary	To evaluate invasive disease free survival (IDFS), breast cancer specific survival (BCSS), distant recurrent free survival (DRFS) and overall survival	– IDFS, BCSS, DRFS and OS with the addition of capecitabine compared with carboplatin-based chemotherapy alone.

	(OS) with and without the addition of capecitabine. To evaluate the pCR rate separately in cohorts of patients treated with or without the addition of pembrolizumab during preoperative chemotherapy. To evaluate the effect of the addition of immunotherapy to platinum-based chemotherapy in a cohorts treated before vs. after the addition of pembrolizumab to both study arms.	
	Toxicity and dose intensity in the treatment arms.	– CTCAE (version 5.0) grade 3 to 5. – SAE. – Dose intensity for each drug
Additional translational end-points	Comparing the pCR rate in the two treatment arms in different TNBC subtypes.	– pCR rate, IDFS, BCSS and OS in different subsets of molecularly characterized TNBC in the different treatment arms, this includes: – 1) Comparisons of patients with BRCA-deficiency vs. not – 2) Comparisons of patients with a germline vs. somatic vs. epigenetic loss of BRCA-function. – 3) Comparisons of patients with different subtypes of TNBC based on gene expression profiling – 4) Comparisons based on levels of markers of immune response (e.g., TILs and PDL1-expression. – 5) Explorative analysis of biomarkers predicting the effect of immunotherapy

3 OVERALL STUDY DESIGN

The study is a prospective, multicenter, open-label, phase III trial of preoperative chemotherapy with 1:1 randomization to one of two treatment arms.

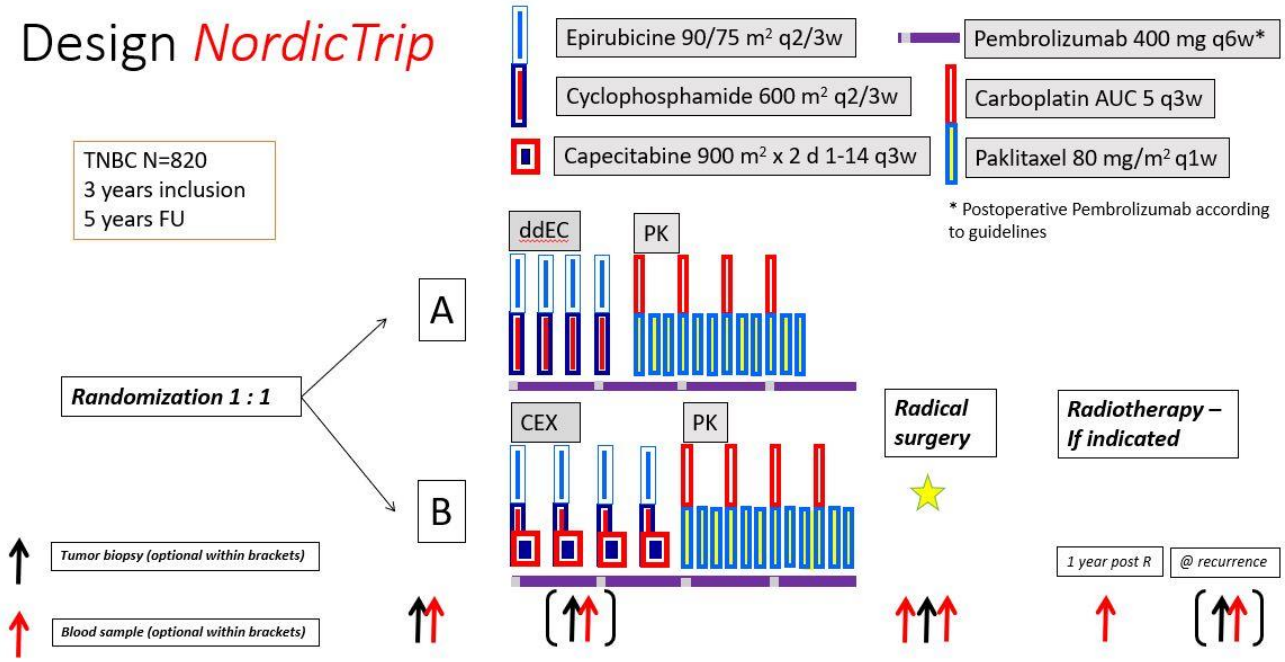
Study Period Estimated date of first patient enrolled: 1 December 2019

Anticipated recruitment period: 5 years

Estimated date of last patient last visit 30 June 2035

Treatment Duration: 20 - 23 weeks

Follow-up: 10 years (annual visits for 5 years and then yearly telephone contacts/visits up to 10 years



4 STUDY POPULATION

4.1 Selection of Study Population

Patients at participating hospitals that is planned for preoperative chemotherapy due to TNBC will be screened for inclusion in this study:

4.2 Number of Patients

820 patients will be included in this trial, see power calculation.

4.3 Inclusion Criteria

Patients must meet all of the following criteria to be eligible:

1) Signed written informed consent approved by the Ethical Review Board (IRB).

2) Age ≥ 18 to < 76 years.

3) Histologically confirmed unilateral adenocarcinoma of the breast where neoadjuvant chemotherapy followed by definitive surgery is planned.

4) Node positive disease (N1-3) or if clinically N0 Tumor size ≥20 mm.

When deciding T-stage the following hierarchy applies,

a. MRI
b. Ultrasound
c. Mammography
d. Clinical examination

5) ER negative tumor defined by at least one the following:

a. ER < 1% cells positive by immunohistochemistry (IH.C) or ER ≤ 10% cells positive by IHC and basal-like subtype using gene expression analysis

b. ER ≤ 10% cells positive by IHC and PgR ≤ 10% cells positive by IHC.

6) HER2-normal tumor defined according to applicable national guidelines.

7) Consent for germline mutation screening for BRCA1, BRCA2 and other inherited breast cancer associated genes.

8) WHO performance status 0 or 1.

9) Negative pregnancy test in women of childbearing potential (premenopausal or <12 months of amenorrhea post-menopause and who have not undergone surgical sterilization).

10) Willingness of female patients of childbearing potential, male patients, and their sexual partners to use an effective means of contraception during the treatment period and at least 6 months thereafter.

11) Willingness by the patient to undergo treatment and study related procedures according to the protocol.

4.4 Exclusion Criteria

Patients meeting any of the following criteria are not eligible:

1. Clinical or radiological signs of metastatic disease.

2. History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix or non-melanoma skin cancer.

3. Previous chemotherapy for cancer or other malignant disease.

4. Charlson comorbidity index, excluding score for malignancy: (CCI) > 2, Comment: In patients 70-75 a CCI = 3 is allowed, see appendix B.

5. Inadequate organ function, suggested by the following laboratory results:

a Absolute neutrophil count < 1,5 x 10^9/L
b Platelet count < 100 x 10^9/L
c Haemoglobin < 90 g/L
d Total bilirubin greater than the upper limit of normal (ULN) unless the patient has documented Gilbert´s syndrome
e ASAT (SGOT) and/or ALAT (SGPT) > 2,5 x ULN
f ASAT (SGOT) and/or ALAT (SGPT) > 1,5 x ULN with concurrent serum alkaline phosphatase (ALP) > 2,5 x ULN
g Serum creatinine clearance < 50 ml/min

6. Concurrent peripheral neuropathy of grade 3 or greater (NCI-CTCAE, Version 5.0)

7. Patient who is actively breast feeding.

8. Assessed by the Investigator to be unable or unwilling to comply with the requirements of the protocol.

9. Patients with known deficiency of the DPD-enzyme who completely lack DPD.

5 TREATMENT

Initial chemotherapy, see under 5.2, Dosage and drug administration.

After completion of chemotherapy, definitive surgery is performed followed by adjuvant radiotherapy according to local guidelines. Adjuvant postoperative bisphosphonates will be given according to local guidelines, but should not be initiated during the preoperative phase.

Patients that convert from a TNBC phenotype at baseline to an ER-positive or HER2-positive phenotype should receive additional adjuvant treatment as appropriate. Adjuvant capecitabine according to the CreateX-trial is not part of the study. In case additional adjuvant treatment is given, it should be thoroughly recorded in the CRF.

5.1 Drug Identity, Supply and Storage

All participating departments have experience of administration of epirubicin, cyclophosphamide, capecitabine, carboplatin and paclitaxel. Commercial formulations will be used and administered for all drugs. Known toxicities/side-effects are listed in Summary of Product Characteristics (SPC), see appendix C for the drugs used in the study. All investigational medicinal products (IMP) will be handled, labelled, delivered, and administered according to clinical routines and local regulations at the respective site/in the respective country. Different manufacturers of generic products will be involved, all medical products will undergo quality assurance according to national and local routines that involves the hospital pharmacy and the local chemotherapy treatment units.

5.2 Dosage and Drug Administration

Patients will be randomized between two treatment arms, A and B (see 10.2 Randomization).

A : **ddEC → PK,** i.e.: (epirubicin 90 mg/m^2 + cyclophosphamide 600 mg/m^2 q2w) x 4 + pembrolizumab followed by (paclitaxel 80 mg/m^2 day 1, 8, 15 + carboplatin AUC 5 day 1) x 4 + pembrolizumab, Pembrolizumab is given as a 400 mg iv dosis every 6 weeks for the duration of preoperative chemotherapy.*

B : **CEX → PK**, (epirubicin 75 mg/m^2 + cyclophosphamide 600 mg/m^2 + capecitabine 1800 mg/m^2 day 1-14) q3w x 4 + pembrolizumab followed by (paclitaxel 80 mg/m^2 day 1, 8, 15 + carboplatin AUC 5 day 1) x 4 + pembrolizumab, pembrolizumab is given as a 400 mg iv dosis every 6 weeks for the duration of preoperative chemotherapy.*

*The addition of pembrolizumab is strongly recommended to all participating patients. However, patients with a documented contraindication, or unwilling to receive immunotherapy may be included in the study without the administration of pembrolizumab.

Primary prophylaxis with G-CSF should be used in the ddEC regimen and might be used at the discretion of the treating physician as part of the PK regimen.

5.2.1 Dosing of Arm A

Cycle 1-4: ddEC

- **Pembrolizumab** will be administered on day 1 of cycle 1 and thereafter on day 1 of cycle 4. A flat dose of 400 mg will be given as a 30-minute intravenous infusion.

- **Pembrolizumab** will be administered as the first infusion at all cycles were pembrolizumab is given.

- **ddEC** will be administered on day 1 of every 2-week cycle. Four cycles in total will be given. Regimen consists of epirubicin (E) 90 mg/m^2 as a 30 to 60-minute intravenous infusion followed by

cyclophosphamide (C): 600 mg/m^2 as a 30-minute intravenous infusion. Epirubicin dose could be rounded to the closest 5 mg and cyclophosphamide dose to the closest 50 mg.

- **ddEC** doses should not be adjusted based on changes in body weight after the first given cycle.

- **Hematopoietic growth factors (G-CSF)** G-CSF should be used daily day 4 to day 11 (treatment day is day 1) or, when using pegylated G-CSF, only given day 2. G-CSF is given SC and should be dosed based on patient's weight according to local guidelines. G-CSF could be terminated before day 11 in case of neutrophils > 10.000 cells/mm^3

- Patients aged 65-75 should start treatment on dose level -1, see table 1. If the regimen is well tolerated it can be escalated to level 0 from cycle 2 onwards at the treating physician's discretion

- For dose reduction recommendations see table 2 in section 5.4.

Cycle 5-8: PK
In Arm A the first PK dosis will be administered three weeks after the last ddEC-dosis.

- **Pembrolizumab** will be administered on day 1 of the 2nd PK-cycle and thereafter on day 1 of the 4th PK-cycle. A flat dose of 400 mg will be given as a 30-minute intravenous infusion.

- **Pembrolizumab** will be administered as the first infusion at all cycles were pembrolizumab is given.

- **Paclitaxel (P)** will be given at 80 mg/m^2 as a 60-minute intravenous infusion, on day 1, 8 and 15 at each 3 weekly cycle. Four cycles in total will be given. Doses could be rounded by 5 %. If treatment on day 8 or 15 is not given due to hematological toxicity, that treatment step is omitted. Paclitaxel doses should not be adjusted based on changes in body weight after cycle 1.

- **Carboplatin (K)** will be administered on day 1 of every 3-week cycle immediately after the infusion of paclitaxel. Regimen consists of carboplatin dosed based on Calvert formula at AUC (area under the curve) 5 as a 30-minute intravenous infusion. The carboplatin dose should not exceed 750 mg. Doses could be rounded to closest 10 mg. Calvert formula is based on patients GFR (glomular filtration rate). GFR should be defined according to local guidelines. A total number of four doses should be given.

- **Calvert Formula**: Carboplatin dose in mg = Target AUC x (absolute GFR + 25)

- **Hematopoietic growth factors (G-CSF)** may be used to prevent and/or reduce the length and severity of neutropenia and thereby reducing the risk for febrile neutropenia and treatment delay. If used, G-CSF is to be given daily on day 3-5, 10-12 and 17-19 (treatment day is day 1) and should be dosed based on patient's weight according to local guidelines.

- Patients aged 65-75 should start carboplatin treatment on dose level -1, see table 1. If the regimen is well tolerated it can be escalated to level 0 from cycle 6 (second PK cycle) onwards at the treating physician's discretion.

- For dose reduction recommendations see table 4 and 5 in section 5.4.

5.2.2 Dosing of Arm B

Cycle 1-4: CEX

- **Pembrolizumab** will be administered on day 1 of cycle 1 and thereafter on day 1 of cycle 3. A flat dose of 400 mg will be given as a 30-minute intravenous infusion.

- **Pembrolizumab** will be administered as the first infusion at all cycles were pembrolizumab is given.

- **EC** will be administered on day 1 of every 3-week cycle. Four cycles in total will be given. Regimen consists of epirubicin 75 mg/m^2 as a 30 to 60-minute intravenous infusion followed by cyclophosphamide: 600 mg/m^2 as a 30-minute intravenous infusion. Epirubicin dose could be rounded to the closest 5 mg and cyclophosphamide dose to the closest 50 mg.

- **Capecitabine** (X) will be self-administered by the patient at home as twice-daily 900 mg/m2 oral doses (total daily dose of 1800 mg/m2 calculated for a maximum body surface of 2,19 m2) in the morning and evening in 3-week cycles consisting of 2 weeks of capecitabine treatment followed by 1 week without capecitabine treatment. Doses could be rounded to closest 150 mg. The first dose of each cycle will be administered as the evening dose on day 1 and the last dose of each cycle is scheduled the morning of day 15, followed by a 7-day rest period. This provides for a total of 28 single doses per cycle over 15 calendar days. The morning and evening dose should be given approximately 12 hours apart and taken within 30 minutes after the ingestion of food with approximately 200 mL of water, ideally after the breakfast and evening meal.

- Doses should not be adjusted based on changes in body weight after the first CEX cycle.

- Patients aged 65-75 should start treatment on dose level -1, see table 1. If the regimen is well tolerated it can be escalated to level 0 from cycle 2 onwards at the treating physician's discretion

- For dose reduction recommendations section 5.4.2 and table 3.

- Test for DPD deficiency should be carried out according to clinical routine at each participating center. For patients with partial deficiency, the treating physician may consider starting capecitabine treatment at a lower dose level.

Cycle 5-8: PK

- See 5.2.1 above, with the following exceptions,
    - In Arm B the first PK dosis will be administered three weeks after the last CEX-treatments first treatment day.
    - **Pembrolizumab** will be administered as a 400 mg flat dose on day 1 of the 1st PK-cycle and on day 1 of the 3rd PK-cycle.

5.3 Premedication and Monitoring

5.3.1 Pembrolizumab premedication and precautions (Arm A and B)

- A low-protein binding 0.2 to 5 µm in-line or add-on filter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles.

- Measures to handle anaphylactic reactions should be in place.

- Patients who experience an infusion related reaction can be given premedication with Paracetamol and Desloratadin.

5.3.2 Premedication ddEC Cycle 1-4 (Arm A)

An adequate antiemetic regimen should be given to prevent nausea and vomiting. G-CSF is mandatory on day 4-11, in case pegylated G-CSF is given it should be administered 24 h after chemotherapy.

5.3.3 Premedication CEX Cycle 1-4 (Arm B)

An adequate antiemetic regimen should be given to prevent nausea and vomiting. G-CSF should be avoided concomitantly with capecitabin treatment.

5.3.4 Paclitaxel premedication and precautions Cycle 5-8 (Arm A and B)

- Infusion bags, filters and sets should be PVC-free.

- **Cycle 5 (1st PK cycle):** (Day 1, 8 and 15) paclitaxel is given as 60-minute infusion. The patient is monitored for hypersensitivity reactions with repeated blood pressure, pulse and general observation. In case of an infusion related reaction grade 1-2, stop infusion and treat according to local guidelines. Restart but de-escalate the infusion rate by 50 %. If no reaction occurs, the infusion rate may be increased again by 25 % after 15 minutes. If no reaction occurs during the first 30 minutes, the remaining amount of infusion is given at the regular rate.

- **Premedication** with corticosteroids, antihistamines and a H1 antagonist should be given according to local guidelines (e.g., oral doses of betamethasone 8 mg, clemastine 2 mg and ranitidine 150 mg 1-2 hours before paclitaxel).

Patients who experience a severe hypersensitivity reaction to paclitaxel should not be re-challenged with the drug, however nab-paclitaxel 100 mg/m^2 could replace paclitaxel at the discretion of the investigator.

5.3.5 Premedication carboplatin Cycle 5-8 (Arm A and B)

An adequate antiemetic regimen should be given to prevent nausea and vomiting. Patients who experience a severe hypersensitivity reaction to carboplatin should not be re-challenged with the drug.

5.3.6 Monitoring of blood count

ANC, leucocytes, and platelets should be measured ≤3 days before each treatment cycle.

5.4 Dose modifications

Patients will be monitored for toxicity during treatment. Dose adjustments will be performed according to dose levels in table 1 and the below guidelines for the drugs in the respective treatment arms. Patients aged 65-75 should start on dos level -1, see table 1.

Table 1 Dose reduction levels

	Level 0 (start)	**Level -1**	**Level -2**	**Level -3**
Epirubicin in Arm A – ddEC	90 mg/m^2	75 mg/m^2 (83%)	60 mg/m^2 (67%)	-
Epirubicin in Arm B – CEX	75 mg/m^2	60 mg/m^2 (80%)	50 mg/m^2 (67%)	-
Cyclophosphamide	600 mg/m^2	500 mg/m^2 (83%)	400 mg/m^2 (67%)	-
Capecitabine (per dose)	900 mg/m^2	700 mg/m^2 (78%)	500 mg/m^2 (56%)	300 mg/m^2 (33%)
Carboplatin	AUC 5	AUC 4	AUC 3	-
Paclitaxel	80 mg/m^2	65 mg/m^2 (81%)	50 mg/m^2 (63%)	-
Pembrolizumab	400 mg flat dose	Pembrolizumab is not dose reduced, but may be delayed in case of side effects according to clinical practice		

5.4.1 Arm A and B (pembrolizumab) dose reductions

Pembrolizumab is not dose reduced but may be delayed or discontinued in case of side effects according to clinical practice. Refer to pembrolizumabs Summary of product characteristics for recommendations regarding treatment interruptions, treatment for adverse events and rechallenge of pembrolizumab.

General remarks regarding Pembrolizumab treatment:

Pembrolizumab therapy might result in immune-related adverse events and caution is important. Immune-related adverse events most commonly involve the gastrointestinal tract, liver, skin, kidneys, lungs, neurological and endocrine systems. The nurse or treating physician should be in contact with patients to check for adverse events one week after the first pembrolizumab treatment, and thereafter contacts should be scheduled according to individual assessments. Immune-related adverse events typically occur quite early – mostly, within weeks to three months after treatment starts; however, first onset of side effects has also been recorded months after treatment has finished.

5.4.2 Arm A, Cycle 1-4 (ddEC) dose reduction

Epirubicin and cyclophosphamide should be reduced together in case of severe hematological toxicity. In order to treat with ddEC on day 1, ANC should be at least 1.0 x 10^9/L and platelets should be at least 100 x 10^9/L. If these values are not fulfilled, treatment is postponed until the values are achieved. Dose adjustments at the initiation of treatment are recommended as follows. Dose levels are defined above in the table in chapter 5.4 and represent reductions of about 20%. Non-hematological treatment related grade 3-4 toxicity should result in dose reductions of 1-2 levels (20-40%) at the discretion of the treating physician.

Table 2 Dose reductions for dose dense epirubicin and cyclophosphamide (ddEC) based on hematological toxicity

Neutrophils (x10^9/L) at treatment day	**ddEC dose level**	**Platelets (x10^9/L) at treatment day**	**ddEC dose level**
ANC ≥ 1.0	Stay on previous level	**Platelets ≥ 100**	Stay on previous level
ANC 0.5 – 0.9	Delay until ANC ≥ 1.0 and restart on previous level. On the second occasion reduce by one dose level	Platelets 50 – 99	Delay until Platelets ≥ 100 and restart on previous level. On second occasion: reduce by one dose level.
ANC < 0.5	Delay ddEC 1 week and reduce by one dose level. Restart when ANC ≥1.0.	Platelets < 50	Delay until platelets ≥ 100 and reduce by one dose level.

Hematopoietic growth factors (G-CSF*)* G-CSF should be used day 4-11 (treatment day is day 1). In case pegylated G-CFS is given it should be administrated 24 h after chemotherapy. G-CSF is given SC and should be dosed based on patient's weight according to local guidelines.

5.4.3 Arm B Cycle 1-4 (CEX) dose reduction

General remarks regarding capecitabine treatment:

Capecitabine therapy might result in severe hand-foot syndrome or diarrhea in about 20-25 % of treated patients and caution is important. Other non-hematological toxicity could occur as well. Reduced renal function and old age are risk factors. The nurse or treating physician are strongly recommended to check patients for adverse events at a weekly basis in cycle 1, and thereafter in cases of toxicity related dose modifications. Compliance will be checked and recorded per treatment cycle when data on treatment related toxicity is collected after each cycle.

- If grade 2-4 toxicity occurs during the 14 days of ongoing capecitabine treatment, interrupt capecitabine treatment until next cycle.

- If greater than grade 1 non-hematological treatment related toxicity persists at the time for next cycle (day 22), treatment should be delayed until the toxicity has resolved to grade $\leq$ 1 before starting next cycle and reduce by one dose-level according to table 1.

Epirubicin and cyclophosphamide should be reduced together in case of severe hematological toxicity. Capecitabine should be reduced alone based on capecitabine related toxicities (diarrhea, hand-foot). Dose levels are defined at table 1 and represent reductions of about 20%. Non-hematological treatment related grade 3-4 toxicity should result in dose reductions of 1-2 levels (20-40%) at the discretion of the treating physician.

Table 3 Dose reductions for cyclophosphamide, epirubicin and capecitabine (CEX) based on hematological toxicity. In case of hematological toxicity only, the capecitabine dosis should not be altered.

Neutrophils ($x10^9$/L) at treatment day	**CEX dose level**	**Platelets ($x10^9$/L) at treatment day**	**CEX dose level**
ANC $\geq$ 1.0	Stay on previous level	Platelets $\geq$ 100	Stay on previous level
ANC 0.5-0.9	Delay until ANC $\geq$ 1.0 and restart on previous level. On the second occasion: reduce by one dose level.	Platelets 50 – 99	Delay until Platelets $\geq$ 100 and restart on previous level. On second occasion: reduce by one dose level.
ANC < 0.5	Delay until ANC $\geq$ 1.0 and reduce by one dose level.	Platelets < 50	Delay until platelets $\geq$ 100 and reduce by one dose level.

5.4.4 Arm A and B, Cycle 5-8 dose reduction

Based on partly different toxicity profiles, delivered doses of carboplatin and paclitaxel may be adjusted individually, according to clinical practice. Non-hematological/non-neurological treatment related grade 3-4 toxicity should result in dose reductions of 1-2 levels (20-40%) at the discretion of the treating physician. Moderate to severe thrombocytopenia should lead to a dose reduction of carboplatin while neurotoxicity should lead to a dose reduction of paclitaxel according to Arm A table 5. G-CSF may be used from the start of cycle 5 to prevent neutropenia, if not used up-front the addition of G-CSF is recommended in case of neutropenia. If toxicity cannot be attributed to one of the drugs, both drugs could be reduced one or two steps according to the treating physician's discretion. If carboplatin is discontinued before cycle 4, the last cycle/-es should be given with only paclitaxel. If paclitaxel is discontinued before cycle 4 the last cycle/-es should be given with only carboplatin, in these cases re-escalation of carboplatin should be considered up to a maximal dosis corresponding to AUC = 5. However, if both drugs are discontinued, omitted cycles could be replaced by EC (i.e., if cycle 4 is omitted due to toxicity, one additional course of EC could be given to a total of 5 cycles of EC).

In the case of severe hypersensitivity reactions to paclitaxel or carboplatin, the drug should be stopped and discontinued for remaining cycles. Paclitaxel could be replaced by nab-paclitaxel 100 mg/m^2 if hypersensitivity is related to paclitaxel. Long lasting bone-marrow depression is the dominating toxicity of carboplatin, and the table below is to be used at each treatment course for dose reductions, delays, or the addition of G-CSF.

Carboplatin hematological toxicity: In order to treat with carboplatin on day 1 ANC should be at least 1.0 x 10^9/L and platelets should be at least 100 x 10^9/L. If these values are not fulfilled, treatment is postponed until the values are achieved. Dose adjustments at the initiation of treatment are recommended as follows:

Table 4 Arm A and B: Dose reductions of carboplatin day 1 based on hematological toxicity			
Neutrophils ($x10^9$/L) at treatment day	**Carboplatin dose**	**Platelets ($x10^9$/L) at treatment day**	**Carboplatin dose**
ANC $\geq$ 1.0	Stay on the same dose level	Platelets $\geq$ 100	Stay on the same dose level
ANC < 1.0	Postpone treatment until ANC $\geq$ 1.0 and stay on the same dose level, add G-CSF, on the second occasion reduce by one dose level	Platelets <100	Postpone treatment until platelets $\geq$ 100 and reduce by one dose level

Hematopoietic growth factors (G-CSF) may be used to prevent and/or reduce the length and severity of neutropenia and thereby reducing the risk for febrile neutropenia and treatment delay. If used G-CSF is to be given daily on day 3-5, 10-12 and 17-19 (treatment day is day 1) and should be dosed based on patients' weight according to local guidelines.

Table 5 Arm A and B: Dose reductions for paclitaxel based on neurotoxicity (CTCAE grades)	
Cycle 1 Paclitaxel	Cycle 2-4 Paclitaxel
If no sign of neuropathy give: **80 mg/m2**	If no neurotoxicity give **80 mg/m2**
If prevalent grade 1 neurotoxicity give: **65 mg/m2**	If grade 1 neurotoxicity give **65 mg/m2**
If prevalent grade 2 neurotoxicity give: **50 mg/m2**	If grade 2 neurotoxicity give **50 mg/m2**
If prevalent grade 3-4 neurotoxicity: patient cannot be included in the study	If grade 3-4 neurotoxicity **discontinue paclitaxel**

Paclitaxel hematological toxicity: In order to treat with paclitaxel on day 8 and 15 ANC should be at least 1.0 x 10^9/L Platelets should be at least 75 x 10^9/L. If these values are not fulfilled, that weekly paclitaxel treatment is omitted. No other action is taken. At the second occasion, either the addition of GCSF or a dose reduction by one step is considered at the next treatment day.

5.5 Concomitant Medication

At study initiation, patients should continue with their concomitant medications, as directed by their physician. Any cancer therapeutic or surgical procedure related to the breast cancer diagnosis performed during the study period up to 30 days after the last treatment should be recorded in the CRF including the date, indication, description of the procedure(s) and any clinical findings.

5.5.1 Supportive Care

Supportive care for disease-related symptoms will be offered as needed to all patients in this study.

5.5.2 Hematopoietic Growth Factors

Hematopoietic growth factors (G-CSF) may be used to treat symptomatic neutropenia as well as prophylactically according to this protocol chapter 5.4 or based on local guidelines or responsible physicians´ choice. The use of G-CSF should be registered in the eCRF as well as in the patient's medical records. The use of hematopoietic growth factors should be avoided concomitantly with capecitabine treatment.

5.5.3 Other Supportive Measures

Patients should not routinely receive prophylactic antibiotics during the study.

5.5.4 Oral Coumarin-Derived Anticoagulants

Patients receiving concomitant capecitabine and oral coumarin-derived anticoagulants should have their anticoagulant response (INR or prothrombin time) monitored frequently in order to adjust the anticoagulant dose accordingly. Altered coagulation parameters and/or bleeding, including death, have been reported in patients taking capecitabine concomitantly with coumarin-derived anticoagulants such as warfarin and phenprocoumon. A PK interaction has been observed. The use of low molecular weight heparin instead of coumarin during chemotherapy is at the discretion of the investigator but is strongly recommended.

5.5.5 Phenytoin

Increased phenytoin plasma concentrations have been reported during concomitant use of capecitabine and phenytoin. Formal drug-drug interaction studies with phenytoin have not been conducted. Patients taking phenytoin concomitantly with capecitabine should be regularly monitored for increased phenytoin plasma concentrations and associated clinical symptoms.

5.5.6 Allopurinol

Interactions with allopurinol have been observed for fluorouracil, with possible decreased efficacy of fluorouracil. Concomitant use of allopurinol with capecitabine should be avoided.

5.5.7 Antivirals and Antiprotozoals

Capecitabine should not be administered together with the antiviral drug sorivudine or its chemically related analogues, such as brivudine. A clinically significant drug-drug interaction between sorivudine and fluorouracil, resulting from the inhibition of DPD by sorivudine, has been described in the literature. This interaction, which leads to increased fluoropyrimidine toxicity, is potentially fatal.

Metronidazole increased the toxicity of fluorouracil in patients with colorectal cancer, apparently by reducing the clearance of the antineoplastic. As it has been described in the literature, caution should be exercised.

5.5.8 Gastrointestinal Drugs

Pretreatment with cimetidine for 4 weeks led to increased plasma concentrations of fluorouracil following intravenous and oral administration in six patients. The effect was probably due to a combination of hepatic enzyme inhibition and reduced hepatic blood flow. No such effect was seen following single doses of cimetidine in five patients or pretreatment for just one week in six. Care is required in patients taking both drugs simultaneously.

5.5.9 Other Anticancer Therapies

The use of other cytotoxic agents, investigational drugs, breast cancer or immunotherapy drugs (other than that specified by the protocol), are not allowed during the study treatment period.

The use of GnRH-analogues for the purpose of preservation of ovarian function in premenopausal patients is allowed during the treatment phase of the study.

Patients requiring radiotherapy during study to other body sites than the breast and the regional lymphatic nodes will be considered to have had relapsed and should discontinue study before the start of radiotherapy. Such patients will be evaluated based of intention to treat and will be considered to not having fulfilled criteria for pCR.

Patients converting from a triple negative phenotype in the pretherapeutic biopsy to an ER-positive or HER2-positive phenotype at radical surgery should receive endocrine and/or HER2-dicected treatment as appropriate. If such treatment is considered it should be thoroughly reported in the CRF.

5.6 Subject Compliance

The timing and doses of IMPs used in this trial are to be recorded in the CRFs. For capecitabine, the dosis and treatment interval should be recorded. Relative given dose will be calculated for each IMP.

6 STUDY PROCEDURES

6.1 Subject Numbering

Each subject is identified in the study by a unique subject number that is assigned when the subject is randomized in the study. Once assigned the subject number cannot be reused for any other subject.

6.2 Study Phases

6.2.1 Screening phase

The Screening Phase is the time between the date a patient provides written informed consent, and the date of randomization. Data collection and procedures during this time period include patient demographics, eligibility requirements, concomitant medications, medical history, physical examination/vital signs including assessment of WHO performance status, adverse events, serious adverse events, laboratory measurements, pregnancy testing (if applicable), biospecimens (blood and tissue samples), evaluations of tumor burden and report from sentinel node biopsy procedure if performed before treatment. CT (Computed Tomography) of thorax and abdomen is mandatory in high risk patients with clinical lymph node positive disease or T3-4 disease. All procedures should be performed within 28 days prior to randomization See table 6. Pregnancy test (when applicable) must be performed within 14 days prior to randomization.

6.2.2 Treatment phase

Study treatment should begin within 14 days after randomization. During the treatment phase, data collection and procedures include the following: assessment of physical examination/vital signs, WHO performance status, laboratory measurements including mutation analyses for hereditary breast cancer genes, registration of adverse events, serious adverse events, use of G-CSF and new menstrual cycles, treatment adherence (interruptions, dose modifications and termination), any postoperative chemotherapy, and determination of recurrence status.

Collection of biomaterial from the primary tumor site before and after study treatment, and blood samples for study specific analyses in the baseline, as well as pre- and postoperatively is mandatory. Further material collection of biomaterial (see table 6), blood samples and tissue from recurrence (loco-regional, distant metastasis or a contralateral breast cancer) is optional.

6.2.3 Follow-up phase

During Follow-Up, patient visits should be performed yearly until 5 years after randomization. Visit dates are calculated from the date of randomization. During year 6-10, yearly telephone contacts should be performed and documented by the study nurse or investigator.

6.3 TABLE 6 SCHEDULE OF ASSESSMENTS AND PROCEDURES:

Assessment procedures:	**Screening phase**		**Treatment phase**			**Before surgery**	**At surgery**	**End-of-treatment visit**	**Post-Therapy Follow-up**	**Post-Therapy Follow-up**
	Completed no more than (time) prior to randomization		Cycle 1 day 1	Before treatment cycle: 2, 4, 5, 6, 7 & 8	Before treatment cycle: 3			1-4 weeks after surgery	1-5 years after randomiza-tion (Annual +/- 4 weeks)	6-10 years after randomizat ion (Annual +/- 4 weeks)
Informed consent (a)	X	28 days								
Inclusion/exclusion criteria	X	14 days								
Demographics, medical history (b)	X	14 days								
Cancer/treatment history (c)	X	28 days								
Physical examination incl vital signs (d)	X	14 days			X	X		X	X	
Clinical assessment of locoregional tumor extent	X	14 days		If clinically indicated before c5	X	X				
Blood samples for local laboratories (7-13 ml) (e)	X	14 days		X	X					
Pregnancy test (f)	X	14 days		X	X			X		
Serum estradiol and FSH (g)	X	14 days						X	X (@ year 1 and year 2)	
Determination of renal clearance (h)				Before cycle 5						
Blood sample 7 ml for mutation screening of germline alterations associated with an increased breast cancer risk or homologous repair deficiency, Clinical analysis (i)			X							
Blood sample (7 ml) for research purpose (j)			X		X					
Blood sample (9 ml) for the study of circulating tumour markers (k)			X		X	X		X	X (Only year 1 and in case of recurrence)	
ECG	X	28 days								
CT thorax/abdomen (l)	X	28 days								

Assessment procedures:	**Screening phase**		**Treatment phase**			**Before surgery**	**At surgery**	**End-of-treatment visit**	**Post-Therapy Follow-up**	**Post-Therapy Follow-up**
	Completed no more than (time) prior to randomization		Cycle 1 day 1	Before treatment cycle: 2, 4, 5, 6, 7 & 8	Before treatment cycle: 3			1-4 weeks after surgery	1-5 years after randomiza-tion (Annual +/- 4 weeks)	6-10 years after randomiza-tion (Annual +/- 4 weeks)
Collection of FFPE tissue from primary tumour (m)	X	28 days			X (optional)		X		In case of recurrence (optional)	
Collection of tumour tissue in RNA later at selected sites (optional) (n)	X	28 days			X		X			
Breast imaging Mammography/US, or MRI (MRI optional) (o)	X	28 days		If clinically indicated before c5	X	X				
Axillary staging, i.e., Fine needle aspiration (cN+) and/or SN biopsy in cN0 disease (p)	X						X			
Study drug compliance				X	X	X				
Registration of AE, new menstrual cycle, use of G-CSF (study nurse or treatment nurse) (q)			X	X	X	X				
Survival follow-up / additional cancer therapies (r)									X	X
Screening mammography (according to local policies)									X	X
Quality of life assessment (s) (Selected patients only)	X	14 days		**Before cycle 5**		**X**			X (@ year 1 and year 2)	
Telephone contact										X

a. Written informed consent must be obtained before any study-specific screening procedures are performed

b. Includes year and month of birth and menopausal status

c. Includes data on current breast cancer (i.e., date of diagnosis, histological type, histological grade, ER/PgR-receptor status, HER-2 status, Ki-67).

d. Includes a clinical examination, WHO performance status (see Appendix E), height (baseline only), weight, pulse rate and blood pressure and clinical TNM-status. Preoperative visit may be performed at the department of surgery.

e. Hematology (haemoglobin, white blood cell (WBC) count, absolute neutrophils and platelet count) and serum chemistry (ASAT/ALAT, alkaline phosphatase, sodium, potassium, total calcium or ionized Calcium,

total bilirubin, serum creatinine and albumin.) will be sampled within 14 days prior to randomization and within 3 days prior to the start of subsequent chemotherapy cycles. Before weekly paclitaxel only hematology is required. In addition to the analyses mentioned above the following should be taken during screening, before each pembrolizumab treatment and once a month for six months after completed Pembrolizumab treatment (LD, CRP, Glucose, Amylase, TSH, T4). For an overview of the local laboratory assessments, see table 7.

f. Pregnancy test (P-hCG or U-hCG) is required within 14 days prior to randomization for all women of childbearing potential (menstruating women or women with menstruation within 12 months of study entry), during the entire treatment phase, and 1-4 weeks after radical surgery. In the case surgery is not performed, a pregnancy test should be performed at the corresponding time point about 5-6 weeks after the last chemotherapy cycle.

g. For women with postmenopausal values at baseline no further samples should be taken.

h. GFR should be defined according to local guidelines.

i. Whole blood (7 ml) for screening for germline alterations associated with an increased breast cancer risk will be collected after randomization but before start of first chemotherapy treatment

j. Blood sample (7 ml) used for the analysis of circulating immune markers, and as a reference to differentiate between germline and somatic genetic alterations in tumor tissue will be collected after randomization but before start of first chemotherapy treatment.

k. Blood samples (9 ml at each occasion) for the assessment of circulating tumour DNA and other circulating tumor and immune markers will be collected from all patients before start of first chemotherapy treatment, at Cycle 3 Day 1, at the end of Treatment Phase (before and after surgery), at 1 year after randomization and at the time of recurrence.

l. Screening for metastatic disease is mandatory in clinical N+ disease or T3 disease. In the case of N+ disease at pretherapeutic sentinel node biopsy only, such screening may be omitted. All staging studies including physical exam and CT must show no evidence of metastatic disease, including suspicious lymphadenopathy or skin nodules on physical exam. The firsthand choice is a CT scan with iv contrast. Other staging studies are at the treating physician's discretion or in a situation where a CT is contraindicated. In these cases, e.g., magnetic resonance imaging (MRI) of the thorax, an ultrasound examination of the liver and a bone scan may replace a CT scan. Any other staging test being performed as clinically indicated (e.g., CT scans, MRI, ultrasound of abdomen, PET scans) must be negative for metastatic disease.

m. At screening four ultrasound guided core needle biopsies collected in formalin are sent to the tissue coordinating center. Two cores are the absolute minimum, four cores are preferred and strongly encouraged. Two cores each will be used for pathologic evaluation and biomolecule extraction respectively. At surgery: In case of pCR a sample from the tumor bed is taken. In case of non-pCR a sample of the residual tumor. If consented by the patient, tumor tissue is collected from metastatic tissue in case of a recurrence,

n. Optional core needle biopsies (N=1-2) collected in RNA later at baseline and after 2 treatment cycles at selected sites.

o. All patients should undergo breast imaging after two treatment cycles using the same methods as during screening. In the case of a poor or questionable response after two treatment cycles, extra imaging and clinical evaluation could be done after four treatment cycles, i.e., before the change of treatment phases.

p. The assessment of N-stage is performed according to local routines, but fine needle aspiration of clinically suspicious axillary lymph nodes (cN1) is mandatory. If cytologically negative cN1, or in cN0, a sentinel node biopsy before start of treatment or at radical surgery is recommended.

q. Adverse events are collected during study treatment by the responsible physician, treatment nurse or study nurse before each treatment and reported in the CRF.

r. New cancers or additional cancer therapies documented for all patients until recurrence or for a minimum of 5 years following randomization. All patients should at least have annual visits until 5 years post-randomization and phone contact for additional 5 years.

s. In a subset of the Swedish patients, quality of life assessments will be performed using validated instruments during screening but before information from randomization is conveyed to the patient, after the completition of ddEC/CEX - before start of carboplatin-paclitaxel, before surgery and at the visits one- and two-years post randomization.

6.4 Procedures and Investigations

For specific timepoints, see section 6.3, Table 6. Study Flow Chart.

Informed consent

Informed consent must have been given voluntarily by each subject before any study specific procedures are initiated.

Clinical status and vital signs

At screening, a physical examination including WHO performance status, a palpation of breast/chest wall, axillae, supra- and infraclavicular region, cardio-pulmonary examination, blood pressure, pulse rate, height and weight is required. Symptom-directed physical examinations, cardio-pulmonary examination, blood pressure, weight and pulse rate will be performed at subsequent visits. Data on the medical history including disease history and corresponding treatment details is registered.

Concomitant medication

During follow-up, information on all breast cancer related therapies must be recorded.

Tumour evaluation

- CT or MRI scan of thorax/abdomen as screening for metastatic disease in cases with clinically node positive disease (N+ by sentinel node biopsy only excluded) or clinically T3-4 tumors.
- Breast imaging (mammography and ultrasound and/or MRI) before and after two treatment cycles and according to local routines during follow-up. In case of uncertain response, a second on treatment evaluation can be added after four treatment cycles.
- Clinical assessment of the locoregional tumor extent will be recorded during screening, after two treatment cycles and preoperatively after the end of preoperative chemotherapy. For details see 7.1.
- Pathological assessment of the breast (and axilla) at time of surgery. For details see 7.1.

Laboratory analysis

- It is recommended that the following assessments be at the same laboratory for each patient. The frequency of assessments is provided in the schedule of assessments (Table 6) and in the overview of timing of local laboratory analysis in table 7. All initial laboratory assessments during the screening period must be performed within 14 days prior to randomization.
- Hematology: haemoglobin, white blood cell (WBC) count, absolute neutrophils and platelet count.
- Blood chemistry with liver function tests: ASAT/ALAT, alkaline phosphatase, sodium, potassium, total or ionized calcium, total bilirubin, serum creatinine and albumin.
- LD, CRP, Glucos, Amylas, TSH, T4.
- Plasma/Serum/urine pregnancy test for women of child-bearing potential (within 14 days before randomization).
- Serum Estradiol and FSH.
- Additional hematology/chemistry panels will be performed as clinically indicated.
- Determination of glomular filtration rate (GFR) must be done prior to start of carboplatin treatment (see section 5.2.1).

Table 7 Overview of timing of local laboratory analysis

	Hematology; Haemoglobin, white blood cell (WBC) count, absolute neutrophils and platelet count	**Chemistry**; ASAT/ALAT, alkaline phosphatase, sodium, potassium, total or ionized calcium, total bilirubin, serum creatinine and albumin	**Other;** LD, CRP, Glucose, Amylase, TSH, T4	**Pregnancy test**	**FSH, Estradiol**	**GFR**
During screening and before each chemotherapy cycles day 1	X	X		X (and at EoT)		
Before paclitaxel day 8 and 15	X					
When pembrolizumab is given	X	X	X			
Once a month for six months following the last pembrolizumab treatment	X	X	X			
During screening, end of treatment and 1- and 2-years post randomization					X	
Before cycle 5 (first PK cycle)						X

Study specific parameters – biospecimens, for details see protocol for translational research.

- Collection of blood (7 ml) for the analysis of inherited breast cancer genes, including BRCA1 and BRCA2, this analysis will be performed as a clinical analysis where all clinically relevant result will be reported back to the study site for documentation in the CRF and will be shared with the patient. The reported gene panel will be defined based on what is considered clinical practice at the participating study sites and will generally follow national guidelines.
- Collection of blood (7 ml) for study specific analysis of germline alterations in order to be able to differentiate somatic from germline alterations when analyzing the tumor tissue, these analyzes will not be reported back to the patient.
- Collection of blood samples for ctDNA and other circulating tumor markers before first chemotherapy treatment (9 ml), after two treatment cycles, after completed chemotherapy, after radical surgery and year one post randomization. In addition, an optional blood sample may be collected and at tumor recurrence.
- Collection of FFPE tissue from primary tumour at baseline including two to four ultra-sound guided core needle biopsies of the primary tumor for study specific biomarker analysis. Four cores are preferred and at least two are needed. Preferably two (but at least one) cores will be used for pathologic analyses, and preferably two (but at least one) for biomolecule extraction.
- Collection of FFPE tissue after two treatment cycles preferably two cores, but a minimum of one core (optional).
- Collection of FFPE tissue at surgery, either from residual disease or from the tumor bed in the case of a complete remission (required).
- Collection of FFPE tissue in the event of a recurrence, preferably two cores, but a minimum of one core (optional).
- Collection of tumour tissue in RNA later at baseline, after two treatment cycles and at surgery (optional, one core/tissue specimen at each occasion) at selected sites.

Quality of life assessments
In a subset of the Swedish patients, quality of life assessments will be performed using validated instruments during screening but before information about randomization is conveyed to the patient, after the completition of ddEC/CEX - before start of carboplatin-paclitaxel, after surgery and at the visits one- and two-years post randomization.

6.4.1 By visit

Screening phase

- Collection of Informed Consent.
- Inclusion/exclusion criteria assessment.
- Demographics, Medical history including data on current breast cancer, and assessment of prevalent symptoms using NCI common Terminology Criteria for Adverse Events, CTCAE Version 5.0.
- Physical examination.
- Baseline mammography and ultrasound (and/or MRI) of the affected breast.
- Fine needle aspiration of clinically suspicious axillary lymph nodes.
- Marking of the tumor area e.g., using charcoal or a coil will be performed according to local routines and is strongly encouraged.
- CT or other metastatic screening for patients with cN+ or cT3-4.
- Baseline assessment of routine blood analyses.
- Pregnancy test for women of childbearing potential.
- Serum Estradiol and FSH.
- Electrocardiogram (ECG)
- Collection of FFPE tissue from primary tumor, and collection of tumor tissue in RNA-later (optional).
- In a subset of the Swedish patients, quality of life assessment.
- In case of clinically N0 disease, a sentinel node biopsy procedure is performed according to local praxis, i.e., preferentially after the administration of preoperative chemotherapy. However, if a sentinel node biopsy is performed during the screening phase the results should be reported in the eCRF.

Treatment phase

- After randomization but before start of first chemotherapy treatment: Clinical screening for germline mutations in inherited breast cancer genes including BRCA1 and BRCA2 and other germline alterations that are in clinical use.
- At d1 of each cycle: Toxicity assessment using NCI CTCAE Version 5.0 (may be registered by the study nurse) and registration av new menstrual cycles and use of G-CSF.
- Physical examination, including locoregional status of the breast and lymph nodes before c3 and after the completion of chemotherapy. In the case of a poor response to treatment after two cycles, if clinically indicated an extra tumor evaluation should be initiated after the completion of the first treatment phase (four treatment cycles).
- In case of objective progression (see below) at the evaluation before c3, an early switch to carboplatin-paclitaxel may be considered.
- Research blood samples before start of first chemotherapy treatment and before c3.
- Routine blood analyses according to table 7.
- In a subset of the Swedish patients, quality of life assessment after the completition of ddEC/CEX - before start of carboplatin-paclitaxel
- Determination of renal clearence before the carboplatin treatment phase.
- Breast imaging (mammography and ultrasound and/or MRI) before c3 and before surgery. In the case of a poor response to treatment after two cycles, if clinically indicated an extra tumor evaluation should be initiated after the completion of the first treatment phase.
- Before c3 (optional) collection of FFPE tumor tissue and at selected sites tumor tissue in RNA-later.

- Study drug compliance.

Before surgery
To be performed after completion of chemotherapy (could be done at the department of surgery).

- Physical examination, and overall assessment of clinical treatment response: Clinical response (ClinR), Stable disease (SD), and Progressive disease (PD) (This assessment is meant to correspond to RECIST 1.1 criteria although RECIST is not defined primarily for mammography and ultrasound of breast tumors. ClinR will be used for a situation corresponding to complete response and partial response according to RECIST 1.1, see appendix F.).
- Breast imaging.
- Research blood sample before surgery (circulating tumor markers).
- Study drug compliance.
- Toxicity assessment using NCI, CTCAE Version 5.0 and registration of new menstrual cycle and use of G-CSF after the last chemotherapy cycle.
- In a subset of the Swedish patients, quality of life assessment.

At surgery

- Tissue collection for the study of residual disease.
- Axillary staging according to local guidelines including sentinel node biopsy if not performed during screening.

End of Treatment visit

- Collection of a research blood sample.
- Physical examination.
- Pregnancy test.
- Serum Estradiol and FSH.
- Blood sample for the study of circulating tumor markers.

Post therapy follow-up

- Annual follow-up visits for 5 years followed by annual phone contacts for an additional 5 years, the telephone contacts could be replaced by physical visits.
- Physical exam year 1-5 after randomization.
- Screening mammography for 10 years according to local guidelines.
- Routine blood analyses according to table 7.
- Serum Estradiol and FSH, at the visits one and two years after randomization.
- Blood sample for the study of circulating tumor markers, year 1 after randomization.
- Other investigations as appropriate if the patient presents with symptoms suggesting a recurrence.
- In the event of a recurrence collection of blood sample for the study of circulating tumor markers and of FFPE tumor tissue is optional and strongly encouraged.
- In a subset of the Swedish patients, quality of life assessment, at the visits one and two years after randomization.

6.5 Procedures for Discontinuation

6.5.1 Patient Discontinuation

Patients who withdraw or are withdrawn from the study, will stop further treatment but will be followed up regarding potential outcome of radical breast surgery, recurrence, and death according to what the patient consents to.

If possible, a final assessment will be made (end of study visit). The reason for discontinuation will be recorded. If the patient makes a partial withdrawal of consent this should be thoroughly recorded in the medical record by the treating physician. The investigator is obliged to follow up any significant adverse events until the outcome either is recovered or resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal or unknown.

Patients who withdraw or are withdrawn from the study before start of treatment, will be replaced.

6.5.2 Criteria for Patient Discontinuation

Patients may be discontinued from study treatment and/or assessments at any time. Specific reasons for discontinuing a patient for this study should, when feasible and the patient's safety is not jeopardized, be discussed with the sponsor. Reasons for patient discontinuation can be:

- Voluntary discontinuation by the patient who is at any time free to discontinue his/her participation in the study, without prejudice to further treatment.
- Safety reason as judged by the Principal Investigator
- Major protocol deviation
- Incorrect enrollment i.e., the patient does not meet the required inclusion/exclusion criteria for the study
- Patient lost to follow-up
- Pregnancy (only applicable during the treatment phase of the study)
- Disease progression, even though continued post-therapy follow-up is strongly encouraged
- Patient's serious non-compliance to study treatment and/or procedures

Patients that discontinue study participation will be evaluated according to intention-to- treat (patients not undergoing definitive surgery will be evaluated as having a non-pCR for the primary endpoint).

6.5.3 Trial Discontinuation

The whole trial may be discontinued at the discretion of the sponsor in the event of any of the following:

- Occurrence of AEs unknown to date in respect of their nature, severity, and duration
- Medical or ethical reasons affecting the continued performance of the trial
- Difficulties in the recruitment of patients

The sponsor will inform all investigators, the relevant Competent Authorities and if applicable Ethics Committees of the termination of the trial along with the reasons for such action. If the study is terminated early on grounds of safety, the Competent Authorities and Ethics Committees will be informed within 15 days.

7 ASSESSMENTS

7.1 Assessment of Efficacy

The following parameters of response will be recorded:

- Clinical evaluation and imaging of the locoregional tumor extent during screening, before c3 and before radical surgery. In case of an uncertain response before c3, additional clinical and imaging-

based evaluation may be performed as clinically indicated before c5 and should in those cases be recorded in the CRF. This evaluation is primarily for security purpose in order to exclude the possibility of progressive disease. The result before cycle three and before surgery will be evaluated in three categories based on imaging and clinical examination: Clinical response (ClinR), Stable disease (SD), and Progressive disease (PD) (This assessment is meant to correspond to RECIST 1.1 criteria (Eisenhauer et al.) although RECIST is not defined primarily for mammography and ultrasound of breast tumors. ClinR will be used for a situation corresponding to complete response and partial response according to RECIST 1.1), see appendix F.

- Pathological evaluation at time of radical surgery. Here a pathological complete response is defined as the complete disappearance of signs of invasive breast cancer cells in the breast and locoregional lymph nodes. Residual insitu deposits are allowed. It should be noted that a patient that has undergone a negative sentinel node biopsy at baseline, or a sentinel node biopsy with only signs of microscopic disease (Nmic) does not have to undergo further axillary surgery provided there is a clinR in the breast. In the case such a patient does not show signs of invasive disease in the breast at surgery, he or she is considered to have a pathological complete response.
- Optionally response will also be reported according to Miller-Payne or Residual Cancer burden criteria.
- Assessment of tumour recurrence when clinically indicated: CT/MRI scans of thorax and abdomen and bone scintigrams. In addition, CT/MRI scans must be obtained for anatomic regions not covered by the thorax and abdomen scans, in subjects where there is clinical suspicion for deep soft tissue metastases. If possible, use the same methods as at baseline in patients subjected to distant metastases screening. Histologic verification of metastatic disease during follow-up is strongly encouraged.

7.2 Safety and Tolerability Assessments

Safety will be monitored by the assessments described below as well as the collection of AEs at every treatment visit. For details on AE collection and reporting, refer to Section 8.

For the assessment schedule refer to Flow chart, see table 6.

Clinical status and vital signs

Physical examination including WHO performance status, a palpation of breast/chest wall, axillae, supra- and infraclavicular region, cardio-pulmonary examination, blood pressure, pulse rate, height (screening only) and weight is required.

Laboratory evaluation

Local laboratory will be used for the following analysis:

- Hematology: haemoglobin, white blood cell (WBC) count, absolute neutrophils and platelet count.
- Blood chemistry with liver function tests: ASAT/ALAT, alkaline phosphatase, sodium, potassium, total or ionized calcium, total bilirubin, serum creatinine and albumin.
- Serum Estradiol and FSH.
- LD, CRP, Glucos, Amylas, TSH, T4.
- Additional hematology/chemistry panels will be performed as clinically indicated.

For the timing of these analysis see table 6 and 7.

7.3 Quality of life (QoL)

A subset of included patients in Sweden (N=250) will be evaluated for QoL during screening, after the completition of ddEC/CEX - before start of carboplatin-paclitaxel, before surgery and at the visits one- and two-years post randomization. For more detailed information about this substudy see appendix J.

8 SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or serious adverse event (SAE) or pregnancy in a patient or a patient's partner

The methods for collection of safety data are described below.

After the inclusion of 60 patients of the study, a thorough data analysis will be performed in order to evaluate the safety, tolerability and feasibility of the study regimens. If necessary an amendment to the protocol will be submitted, including adjustments in the treatment schedules and dosing recommendations.

A second evaluation of the feasibility of the prescribed doses and pCR rate irrespective of treatment allocation will be performed after the treatment of 60 patients following the amendment (Protocol version 4.0) that recommends the addition of pembrolizumab of the study treatment.

8.1 Definitions

8.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

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

For this particular study, only AEs grade 3-5 (CTCAE, version 5.0) will be registered and reported from the signing of the informed consent and until 30 days after the last dose of study drug. However, for sensory and motor neuropathy toxicity grade 1-5 should be reported in order to adjust paclitaxel treatment doses.

Disease progression, breast cancer recurrences and/or death due to breast cancer are excluded from reporting AEs/SAEs. If an abnormal laboratory value/vital sign are associated with clinical signs and symptoms, the sign/symptom should be reported as an AE and the associated laboratory result/vital sign should be considered additional information that must be collected on the relevant CRF.

8.1.2 Serious Adverse Event (SAE)

Any untoward medical occurrence that:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect

- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

Medical and scientific judgment is to be exercised in deciding on the seriousness of a case. Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the listed outcomes in the definitions above. In such situations, or in doubtful cases, the case should be considered as serious. Hospitalization for administrative reason (for observation or social reasons) is allowed at the investigator's discretion and will not qualify as serious unless there is an associated AE warranting hospitalization.

For this particular study, planned hospitalization in association with breast cancer surgery, treatment and other study procedures, including sentinel node biopsy will not be reported as SAEs.

8.1.3 Suspected Unexpected Serious Adverse Reactions (SUSAR)

SUSAR is the term used to refer to an AE that occurs in a clinical trial subject, which is assessed by the sponsor and/or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study drug. To meet the criterium unexpected the AE nature or severity could not be listed in the applicable product information.

8.2 Disease Progression/Recurrence

Events which are definitely due to disease progression will not be reported as an AE/SAE. However, if the investigator considers that there was a causal relationship between treatment with IP or protocol design/procedures and the disease progression/recurrence, then this must be reported as an SAE.

Death due to progressive disease is to be recorded on a specific from in the CRF but not as an SAE.

Any new primary cancer (non-related to the cancer under study) should be considered for reporting as an SAE.

8.3 Time Period for Reporting AE and SAE

For each patient the standard time period for collecting and recording AE and SAEs will begin at the start of the screening phase (signature of informed consent), throughout the treatment phase and will continue for at least 30 days following the last dose of study treatment for each patient. After 30 days the investigator is not obliged to actively seek any new AEs/SAEs, but if the investigator becomes aware of a possibly related AE/SAE this should be reported. At the 1-year follow-up visit ongoing AEs/SAEs should be evaluated and any new related AEs/SAEs reported.

During the course of the study all AEs and SAEs will be proactively followed up for each patient; events should be followed up to resolution, unless the event is considered by the investigator to be unlikely to resolve due to the underlying disease. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation/study completion. Note that during the screening phase, only SAEs due to procedures stated by the protocol and not performed routinely will be reported, E.g., an allergic reaction to intravenous contrast infusion associated with a CAT scan that would have been performed as part of clinical routine.

8.4 Recording of Adverse Events

If the patient has experienced AE(s), the following information will be recorded in the CRF:

- The nature of the event(s) will be described in precise standard medical terminology (i.e., not necessarily the exact words used by the patient).

- The duration of the event will be described in terms of event onset date and end date.

- The intensity of the AE: Grade according to CTCAE version 5.0.
- The causal relationship of the event to the study medication will be assessed as one of the following:

  Not Related:

  There is not a temporal relationship to investigational product administration (too early, or late, or investigational product not taken), or there is a reasonable causal relationship between non-investigational product, concurrent disease, or circumstance and the AE.

  Possibly Related:

  There is reasonable causal relationship between the investigational product and the AE. Dechallenge information is lacking or unclear.

  Related:

  There is a definite causal relationship between the investigational product and the AE. The event responds to dechallenge.

- Action taken
- The outcome of the AE – whether the event is resolved or still ongoing.

8.5 Reporting Procedure

8.5.1 AEs and SAEs

All adverse events and serious adverse events that should be reported as defined in section 7.2 will be recorded in the patient's CRF. SAEs must be reported by the investigator to the sponsor/coordinating center, Clinical Research Unit, KFE Dept. of Hematology, Oncology and Radiation Physics, Skåne University Hospital, SE-205 02 Malmö, Sweden, email: SAE.onkologi@skane.se, within 24 hours after the site has gained knowledge of the SAE. In case of an SAE the Serious Adverse Event Report Form must be completed, signed and sent by e-mail to the coordinating center. The initial report shall promptly be followed by detailed, written reports if necessary. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The sponsor keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality, and expectedness.

8.5.2 SUSARs

SUSARs will be reported to the Competent Authority and Ethics Committee according to national regulation. The following timelines should be followed:

The sponsor will ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal are reported to the Competent Authority within seven days, for other SUSARs the corresponding time limit is 15 days after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions will be reported to the Competent Authority concerned and to the Ethics Committee concerned as soon as possible but within a maximum of fifteen (15) days of first knowledge by the sponsor.

SUSARS will be reported to the sponsor using the CIOMS-form by the site and to the respective competent authority in the country of the site, according to applicable regulations in each country.

8.5.3 Annual Safety Report

Once a year throughout the clinical trial, the sponsor will provide the Competent Authority with an annual safety report. The format will comply with national requirements.

8.6 Procedures in Case of Emergency

The investigator is responsible for assuring that there are procedures and expertise available to cope with emergencies during the study.

8.7 Data Monitoring Committee (DMC)

The conduct of the study and will be supervised by an independent data monitoring committee that will ensure patient safety and that the study is carried out according to International Conference on Harmonization – Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki (October 2013), in the best interest of the patients. The committee will perform a toxicity analysis after the inclusion and treatment of the first 60 patients. A second evaluation of the feasibility of the prescribed doses and pCR rate irrespective of treatment allocation will be performed after the treatment of 60 patients following the amendment (Protocol version 4.0) that recommends the addition of pembrolizumab to the study treatment.

8.8 Contraconception, pregnancy testing and pregnancy

Participating patients with childbearing potential, and male patients should actively avoid pregnancy using a highly effective means of birth control during the treatment period and at least 30 days thereafter. Study treatment could only be initiated after a negative pregnancy test no more than 14 days prior to randomization. Pregnancy tests will be performed before each treatment cycle and 1-4 weeks after radical surgery. Highly effective means of contraception include the use of an intrauterine device, surgical sterilization (bilateral tubal ligation in females or bilateral vasectomy in males), or heterosexual abstinence. In theory, also combined hormonal and progestogen-only contraception associated with inhibition of ovulation are classified as a highly effective means of birth control, but these are not recommended in association with breast cancer.

The use of progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action, male or female condom with or without spermicide and cap, diaphragm or sponge with spermicide are birth control measures that are *not considered as highly effective*. This includes the combined use of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods).

In case of a pregnancy in a female patient or a pregnancy in a partner of a male patient the event must be reported by the investigator to the sponsor/coordinating center within 24 hours after the site has gained knowledge of the pregnancy. Complete and sign the pregnancy event report form and send it via email to SAE.onkologi@skane.se

9 DATA MANAGEMENT AND MONITORING

9.1 Case Report Form (CRF)

The designated investigator staff will enter the data required by the protocol into the electronical case report forms (eCRF). The Principal Investigator is responsible for assuring that data entered in the eCRF is complete, accurate, and that entry is performed in a timely manner. The signature of the investigator will attest the accuracy of the data in the eCRF. If any assessments are omitted, the reason for such omissions will be noted on the eCRFs. Corrections will also be recorded.

9.2 Source Data

The medical records for each patient should contain information, which is important for the patient's safety and continued care, and to fulfill the requirement that critical study data should be verifiable.

To achieve this, the medical records of each patient should clearly describe at least:

- That the patient is participating in the study, e.g., by including the enrollment number and the study code or other study identification.
- Date when Informed Consent was obtained from the patient and statement that patient received a copy of the signed and dated Informed Consent and version.
- Results of all assessments confirming a patient's eligibility for the study.
- Diseases (past and current; both the disease studied and others, as relevant).
- Surgical history, as relevant.
- Results of assessments performed during the study.
- WHO performance status assessments conducted as part of the study.
- Treatments given, changes in treatments during the study and the time points for the changes.
- Visits to the clinic / telephone contacts during the study, including those for study purposes only.
- Serious Adverse Events (if any) including causality assessments.
- Adverse Events will be reported in a work sheet (source data) at each treatment cycle if needed, and relevant parts will be described in the medical record.
- Date of, and reason for, discontinuation from study treatment.
- Date of, and reason for, withdrawal from study.
- Date of death and cause of death, if available.
- Additional information according to local regulations and practice.

9.3 Study Monitoring

The investigator will be visited by the Clinical Study Monitor, who will check the following: Informed consent process, reporting of adverse events and all other safety data, adherence to protocol, maintenance of required regulatory documents and source data verification (SDV).

The Data Manager will regularly review the relevant eCRFs for completeness and a risk-based monitoring plan will be performed meaning that centers with better completeness and accuracy will have fewer visits by the study monitor.

The study monitor looks for accuracy and will ask the site staff to adjust any discrepancies as required.

When the data manager has checked and verified the eCRFs, the database will be locked for further handling and statistical evaluation.

Sponsor's representatives (e.g., monitors, auditors) and/or competent authorities will be allowed access to source data for source data verification in which case a review of those parts of the hospital records relevant to the study may be required.

9.4 Confidentiality

The investigator shall arrange for the secure retention of the patient identification and the code list. Patient files shall be kept for the maximum period of time permitted by each hospital. The study documentation (CRFs, Site File etc.) shall be retained and stored during the study and for 15 years after study closure. All information concerning the study will be stored in a safe place inaccessible to unauthorized personnel.

9.5 Database management

The data reported in this trial will be collected in the data base held by the DBCG. The eCRF will provide range check for relevant data and the data base will regularly be reviewed by the Data Manager. Queries will be sent to centers in case of unclear or missing data. Statistical calculations as part of the risk-based monitoring plan will be performed to optimize accuracy. At time for the feasibility analysis, interim analyses and completion of the study statistical analyses will be performed after cleaning and locking of the data.

10 STATISTICAL METHODS AND DATA ANALYSIS

10.1 Determination of Sample Size

For statistical analysis plan see Appendix G.

Primary aim: Pathological complete response rate after preoperative chemotherapy is the primary end-point of the study, which will be evaluated by comparing the effects of neoadjuvant administration of a carboplatin-based treatment (A) and treatment adding capecitabine (B) on pCR.

After the approval of pembrolizumab in the preoperative treatment of early TNBC in 2022 the study will consist of two cohorts, one (cohort 1) without the addition of pembrolizumab, and one (cohort 2) with the addition of pembrolizumab to both study arms. The primary evaluation will be performed on the entire study population including both cohorts. The estimated number of patients in cohort 1 is 160. Before the approval of pembrolizumab, the detectable alternative of the study was defined as an absolute difference in pCR rate of 10 percentage units (from 52% to 62%). This absolute difference corresponds to an odds ratio (OR) of 1.51. By assuming a pCR rate of 52% in arm A of cohort 1 (Poggio F., Bruzzone M. et al. 2018) and a pCR rate of 65% in arm A of cohort 2 (Schmidt, Cortez et al 2022), a sample size of 908 patients, 454 in each arm, is required to have 80% power to detect the same relative effect (OR=1.51) using a two-sided Chi-squared test with the significance level set at 5%. The expected pCR rate for arm A is 62.7% which is a weighted average of 80 patients (18%) with rate 52% (cohort 1) and 374 patients (82%) with rate 65% (cohort 2). To account for an expected low fraction of non-evaluated patients, the sample size is set at 920. Patients that are included in the study and receive study treatment, but do not undergo surgery will be evaluated as having a non-pCR.

Primary translational aim: To investigate if the effects of the treatments depend on HRD-status. More specifically, the aim is to test for differential effect of the two treatments on pCR for HRD-negative (HRD low and intermediate by oncoscan) and HRD-positive (HRD high by oncoscan) patients.

Assuming that 59% of the patients are HRD-positive (implying that 41% are HRD-negative) and that the overall pCR rate is 52% in treatment arm A, the pCR rate in HRD- is given by (0.52 – 0.59*p)/0.41, where p is the pCR rate in HRD+ for treatment A. Hence, this pCR rate can be calculated for a series of reasonable values of p: for example, a pCR rate in HRD+ of 63% implying a pCR rate of 36% in HRD- corresponding to an OR for HRD+ vs HRD- in treatment A of 3.0. or an even larger effect, e.g., 67% vs 30% implying an OR of 4.6. If we, furthermore, assume the same effect of the treatments A and B in HRD+ (OR 1.0) and that the overall pCR rate is 62% in treatment arm B, the pCR rate in HRD- in arm A is given by (0.62-0.59*p)/0.41. Hence, the OR for treatment B vs A can be calculated. To sum up, the set of assumptions:

- 59/41 ratio HRD+/HRD-
- 52% pCR in arm A
- 62% pCR in arm B
- OR = 1.0 for pCR when comparing B vs A in HRD+

Imply that the OR for pCR when comparing B vs A in HRD- can be calculated for each possible value of the pCR rate in e.g. HRD+ for treatment A.

Holding the sample size fixed at approximately 800 patients in total for the two groups, the power to detect differential effect of B vs A on pCR in HRD+ and HRD- using a two-sided test of interaction at the 5% significance level can be calculated. Below follows two examples:

- 63% pCR in HRD+ (for both arms) implies 36.2% pCR in HRD- for arm A and 60.6% pCR in HRD- for arm B corresponding to an OR of 2.71 for B vs A in HRD-, an effect which can be detected with 92% power with the chosen sample size
- 67% pCR in HRD+ (for both arms) implies 30.4% pCR in HRD- for arm A and 54.8% pCR in HRD- for arm B corresponding to an OR of 2.77 for B vs A in HRD-, an effect which also can be detected with 92% power with the chosen sample size

10.2 Randomization

Randomization will be performed 1 : 1 between the two treatment arms A and B, with stratification for the following factors:

1) Clinical T stage. Comment: If several imaging modalities are available, these should be considered in the following order: MRI followed by ultrasound and mammography. T4 inflammatory disease is evaluated based on clinical appearance.

2) Clinical N stage, Comment: the cN0 stratum includes patients without imaging-based signs of nodal involvement that undergo a sentinel node biopsy irrespective of the result of the pathological assessment of the sentinel node. Comment: This is in order to allow for randomization also in the event that the pathological evaluation of the SN is not yet available at time of randomization.

3) Country

4) Pembrolizumab planned, yes/no.

11 STUDY MANAGEMENT

11.1 Investigator Delegation Procedure

The principal investigator is responsible for making and updating a “delegation of tasks” listing all the involved co-workers and their role in the project. Performing tasks according to clinical praxis does not define that particular individual as a ”co-worker” in the project, e.g., chemotherapy administration. The PI will ensure that appropriate training relevant to the study is given to all co-workers in the study, and that any new information of relevance to the performance of this study is forwarded to the staff involved.

11.2 Protocol Adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations.
All significant protocol deviations will be recorded and reported in the Clinical Study Report (CSR).

11.3 Study Amendments

If it is necessary for the study protocol to be amended, the amendment and/or a new version of the study protocol (Amended Protocol) must be notified to and approved by the Competent Authority and the Ethics Committee according to EU and national regulations.

11.4 Audit and Inspections

Authorized representatives of a Competent Authority may visit the center to perform inspections, including source data verification. Likewise, the representatives from sponsor may visit the center to perform an audit. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (ICH GCP), and any applicable regulatory requirements. The principal investigator will ensure that the inspectors and auditors will be provided with access to source data/documents.

12 ETHICAL AND REGULATORY REQUIREMENTS

The study will be conducted according to the Declaration of Helsinki and ICH-GCP and all applicable regulatory requirements. Registration of patient data will be carried out in accordance with national personal data laws.

12.1 Ethics Committee Approval

The study protocol, including the patient information and informed consent form to be used, will be approved by the ethics committee in each participating country before enrolment of any patients into the study.

The coordinating investigator in each country is responsible for informing the ethics committee of any serious and unexpected adverse events and/or major amendments to the protocol.

12.2 Other Regulatory Approvals

The protocol will be submitted and approved by the Medical Product Agency in each country before commencement of the study.

The protocol will also be registered in www.clinicaltrials.gov before inclusion of the first patient.

12.3 Informed Consent Procedure

The investigator is responsible for giving the patients verbal and written information about the nature, purpose, possible risk, and benefit of the study. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever she/he wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered in the study. This will be done in accordance with the national and local regulatory requirements. The investigator is responsible for obtaining signed informed consent.

A copy of the patient information and consent will be given to the patients. The signed and dated patient consent forms will be filed in the Investigator Site File binder.

12.4 Subject Identification

The investigator is responsible for keeping a list of all patients (who have received study treatment or undergone any study specific procedure) including patient's date of birth and personal identification number and full names.

The patients will be identified in the eCRFs by patient number and year and month of birth.

12.5 Risk-benefit analysis

Treatment arm A includes dose-dense EC, a treatment that has been extensively studied in clinical trials, and that is proven more effective in a recent meta-analysis compared with conventionally scheduled regimens. In treatment arm B, the oral agent capecitabine is added to the EC treatment. Due to the anticipated toxicity profile, capecitabine and EC will be given with an interval of three weeks, keeping in mind that the oral capecitabine per se is a dose dense treatment given twice daily for two out of three weeks. After four treatment cycles, both study arms contain a combined carboplatin-taxane part, consisting of iv carboplatin AUC 5 three-weekly in parallel with weekly paclitaxel x 12. The decision to include carboplatin in the comparator arm was made since a recent metaanalysis comparing preoperative treatment in approximately 2000 patients with TNBC with and without the addition of carboplatin has shown a significant and relevant improvement in the rate of patients that experience an optimal response to preoperative chemotherapy with the addition of carboplatin. There is a substantial experience in the clinic from this type of treatment that is expected to result in an increased hematological toxicity during the treatment period, in comparison with a non-carboplatin containing arm. The carboplatinum containing treatment arm, has been and is being investigated in several other studies, including treatment studies in metastatic breast cancer. Also the CEX treatment has been extensively evaluated in previous studies.

Several measures are taken in order to minimize the risk of inadequate treatment toxicities in any of the study arms. 1) a rigorous dose adjustment scheme is included in the protocol, allowing for dose adjustments based on experienced individual toxicity in the different study arms. 2) An interim analysis focusing on treatment toxicity after 60 treated patients, whereafter potential adjustment in the study regimens will be made with the aim of reasonable and equivalent toxicity between the study arms. 3) After the addition of pembrolizumab to study treatment, a second interim analysis will be performed in order to monitor treatment related toxicities and the outcome in terms of pCR rate irrespective of treatment allocation among the first 60 patients.

Two general ethical issues may be seen in a study of this design; undertreatment and overtreatment. Boths problems are relevant, but largely unavoidable in curative medical treatment in breast cancer, where a fraction of patients will recur despite intense treatment efforts, and others would not have had a recurrence even if they would not have had any medical treatment at all. This is applicable even in the adverse subset of TNBCs. Undertreatment might primarily be an issue in the comparator arm. We have delt with this using an optimal and modern treatment regimen including a dose dense treatment step, and with the addition of carboplatin, which we consider to be a tolerable regimen given the seriousness of the disease. It is our judgement that the carboplatin based treatment arm meets current standards of a modern adjuvant treatment regimen in early TNBC. Overtreatment, i.e., excessively toxic treatment, may be an issue in both treatment arms, just as it is in any adjuvant medical treatment in breast cancer where a fraction of patients would in fact be cured by surgery alone. However, the problem of over treatment is not associated to the study itself but is equal in the population of patients treated outside of this trial. All patients would receive treatment even outside of the study. Still, if the study is negative, the added toxicity of capecitabine, would occur without benefit to the individual patients. Given the fact that this added toxicity is generally reversible, we consider this risk ethically acceptable.

13 END-OF-STUDY

Recruitment will stop after the enrollment of 920 patients. The study will be formally closed when the last patient has finished the last follow-up, 10 years after start of treatment according to table 6. The actual

time-point depends on when the last patient will actually be included in the study. The study may be prematurely discontinued at the discretion of the sponsor as described in section 6.5.3. A Declaration of End-of-Trial Notification will be sent to the competent authorities within 90 days from the End-of-Study. Safety and efficacy data will be reported to the EudraCT database within 12 months from the End-of-Study date.

14 TRIAL SPONSORSHIP

Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital is the sponsor of the trial.

15 TRIAL INSURANCE

Swedish patients treated within this trial are covered by patientskadeförsäkringen.

Danish patients treated within this trial are covered by patienterstatningen (www.pebl.dk).

Finnish patients treated within the trial are covered by the national patient insurance (Potilasvahinkovakuutus).

Icelandic patients treated within this trial are covered by insurance held by Landspitali and the Ministry of Health.

16 PUBLICATION POLICY

Upon study completion and finalization of the study report the results of this study will either be submitted for publication and/or posted in a publicly assessable database of clinical study results. Results from the feasibility analysis, the neoadjuvant part and interim analysis will be reported on international meetings and could be submitted for publication.

The results of this study will also be submitted to the Competent Authority and the Ethics Committee according to EU and national regulations.

All personnel who have contributed significantly with the planning and performance of the study (Vancouver convention 1988) may be included in the list of authors.

17 REFERENCES

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Appendix A – List of participating centers

21 sites in Sweden:

- Region Skåne SUS (Malmö, Kristianstad)
- Region Halland (Halmstad)
- Region Blekinge (Blekingesjukhuset)
- Region Kronoberg (Växjö)
- Region Väst (Gothenburg, Borås, Uddevalla, Skaraborg)
- Region Stockholm (Södersjukhuset, Capio St Görans sjukhus, Karolinska Universitetssjukhuset)
- Region Uppsala-Örebro (Uppsala, Örebro, Gävle, Västerås, Karlstad)
- Region Sydost (Jönköping)
- Region Norr (Umeå, Sundsvall)
- Region Sörmland (Eskilstuna)

10 sites in Denmark

- Rigshospitalet, Köpenhamn
- KAS Herlev
- Regionsjälland Nästved
- Universitetshospital J.B. Odense
- Hilleröd Hospital
- Vejle Sygehus
- AUH Aarhus
- Sönderborg Sygehus
- Aalborg Sygehus Syd
- Esbjergs Sydvestjysk Sygehus

2 sites in Finland

1 site in Iceland

- Landshospitali Reykjavik

APPENDIX B – CHARLSON COMORBIDITY INDEX

(REF CHARLSON ET AL 1987)

Age	<50 years	0
	50-59 years	+1
	60-69 years	+2
	70-79 years	+3
	≥80 years	+4
Diabetes Mellitus	None	0
	Uncomplicated	+1
	End-organ damage	+2
Liver disease	None	0
	Mild	+1
	Moderate-severe	+3
Malignancy (not applicable in this study)	None	0
	Any leukemia, lymphoma or localized solid tumor	+2
	Metastatic solid tumor	+6
AIDS	No	0
	Yes	+6
Moderate to severe Chronic Kidney Disease	No	0
	Yes	+2
Congestive Heart Failure	No	0
	Yes	+1
Myocardial Infarction	No	0
	Yes	+1
Chronic Obstructive Pulmonary Disease	No	0
	Yes	+1
Peripheral Vascular Disease	No	0
	Yes	+1
Cardiovascular Accident or TIA	No	0
	Yes	+1
Dementia	No	0
	Yes	+1
Hemiplegia	No	0
	Yes	+2
Connective Tissue Disease	No	0
	Yes	+1
Peptic Ulcer Disease	No	0
	Yes	+1

APPENDIX C – Summary of Product Characteristics (SPC)

Capecitabine: https://www.ema.europa.eu/documents/product-information/capecitabine-accord-epar-product-information_en.pdf

Carboplatin:
https://docetp.mpa.se/LMF/Carboplatin%20Accord%20concentrate%20for%20solution%20for%20infusion%20SmPC_09001be68022e1b3.pdf

Cyclophosphamid:
https://docetp.mpa.se/LMF/Sendoxan%20powder%20for%20solution%20for%20injection%20SmPC_09001be680015ef6.pdf

Epirubicin:
https://docetp.mpa.se/LMF/Epirubicin%20Teva%20solution%20for%20injection%20or%20infusion%20SmPC_09001be68022da56.pdf

Paclitaxel:
https://docetp.mpa.se/LMF/Pacligen%20concentrate%20for%20solution%20for%20infusion%20SmPC_09001be68028cde7.pdf

Appendix D – Common Terminology Criteria for Adverse Events (CTCAE) Version 5-0:

Published: November 27 2017, US department of Health and Human Services, National Institute of Health, National Cancer Institute,
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf

Appendix E – WHO performance status:

Grade	Explanation of activity
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 or sedentary nature, e.g., light housework, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix F – Resist criteria and adoption for clinical response evaluation in NordicTrip

https://project.eortc.org/recist/wp-content/uploads/sites/4/2015/03/RECISTGuidelines.pdf

Clinical response will be based on breast imaging and will be classified and recorded according to the following principles: Clinical response (ClinR), Stable disease (SD), and Progressive disease (PD). This assessment is meant to correspond to RECIST 1.1 criteria (Eisenhauer et al.), although RECIST is not defined primarily for mammography and ultrasound of breast tumors. ClinR will be used for a situation corresponding to complete response and partial response according to RECIST 1.1).

Appendix G – Statistical analysis plan

STATISTICAL ANALYSIS PLAN

The primary objective of the study is to compare pathologic complete response (pCR) rates in the two treatment groups. The intention-to-treat (ITT) principle will be followed and a one-degree-of-freedom chi-square test with significance threshold α set to 0.05 will be used to determine significance. The pCR rates will be reported as well as the absolute difference between these rates with 95% confidence interval (CI). Furthermore, the relative risk of non-pCR, with 95% CI will be estimated using a univariable generalized linear model (glm) with log-link.

The primary translational objective, which is to determine if the relative treatment effect varies with Homologous Repair Deficiency (HRD) status (positive vs negative/intermediate), will also be evaluated in a glm with log-link. This model will include main effects for the dichotomous variables randomization group and HRD status and the interaction between these two variables. Statistically significant differential treatment effect by HRD status will be claimed if the p-value for the interaction term is below 0.05.

pCR rates will also be compared in subgroups of patients, for example by HRD-status, PDL1-status and in subgroups defined by BRCA-status: germline BRCA-mutation, somatic BRCA-mutation, promoter methylated BRCA and no BRCA-aberration.

The above mentioned analyses will be carried out as soon as possible after trial has been closed for inclusion and the data on pathological outcome at the time of radical surgery is available, ie at the earliest time about 6 months after the inclusion of the last patient.

The secondary objectives related to long-term survival (invasive disease free, breast cancer specific, distant recurrence free and overall survival) will be evaluated in relation to randomization group, again adhering to the ITT principle. Standard methods for survival analysis will be used, i.e. Kaplan-Meier estimates, log-rank tests and Cox-regression analysis. Focus will be on estimated relative effects with 95% CI from Cox-regression analyses and not on p-values. We foresee a problem with interpretation of the analyses of treatment effects on long term survival due to an expected clinical use of postoperative adjuvant therapy after evaluation of pCR among patients not achieving a pathological complete response. We have reason to believe that future clinical guidelines will suggest postoperative capecitabine treatment as an option in triple negative breast cancer patients not having achieved a pathologic complete response at radical surgery, following preoperative chemotherapy. We cannot estimate the extent of such additional treatment in the study cohort, but it will most probably be restricted to patients not having a pathological complete response. Sensitivity analyses will be carried to investigate the magnitude of this problem, e.g. by ignoring postoperative adjuvant chemotherapy (ITT) or by censoring the follow-up at the date of starting postoperative chemotherapy.

The timing of the survival analyses depends on the event rates. Simulation show that, assuming uniform inclusion of 2x410 patients over three years, exponentially distributed survival times in both randomization groups and a 5-year survival of 70% for the treatment with the poorest survival, 300 events is necessary to have 80% power to detect a hazard ratio of 0.70 for the other group relative to the chosen reference group with a log-rank test with significance level set to 0.05. But, again, focus will not be on p-values in these analyses, but on relative effects with 95% CI:s. Over the 1000 simulations, under these assumptions mentioned above, the timing of event number 300 varied from 3 to 6 years after inclusion of the last patient.

Pär-Ola Bendahl Niklas Loman

APPENDIX H – SPECIAL PROTOCOL CONDITIONS IN DENMARK

NordicTrip, a Collaborative Group Trial

NordicTrip is an academic group trial that was conceived and planned by a group of collaborative clinical researchers affiliated with Swedish Breast group (SweBCG), Swedish Association of Breast Oncologists (SABO), Danish Breast Cancer Group (DBCG), Finnish Breast Cancer group (FBCG), and Icelandic Breast Cancer Group (IBCG). The trial is managed and sponsored by Dr. Niclas Loman on behalf of the Department of Hematology, Oncology and Radiation Physics, Skåne University Hospital.

The trial is funded by research grants in 2017 from Nordic Cancer Union to dr. Henrik Lindman (30.000 €); in 2019-2021 from Swedish Research Council to dr. Niklas Loman (19.6MM SEK); in 2020 from Bröstcancer Förbundet i Sverige to dr. Niklas Loman (200.000 SEK); and in 2019-2022 Fru Berta Kamprads Stiftelse för Utforskning och Bekämpning af Cancersjukdomar (1.6MM SEK).

The involved researches have no relevant financial or non-financial competing interests in relation to the sponsors or the outcome of the trial. Payment or compensation is nor offered to participants or investigators. All decisions concerning use of data generated by the trial will be taken jointly by the Trail Management Group consisting of the coordinating investigator from the participating countries, the trial pathologist and statistician.

Additional funding

If additional funding is obtained, then this will be communicated to participating patients and the Ethics Committee.

Participants from Denmark

In total 250 eligible Danish women are expected to participate.

Internal registration

A log specifying name and civic registration number of participants from the institution will be kept within double locks at the treating institution.

Identification of potential Danish paticipants

When a person is diagnosed in Denmark with invasive breast cancer a strategy for further diagnostic evaluations and and treatment will be settled at a multidisciplinary team (MDT) meeting at the responsible institution with participation of at least a breast radiologist, a breast pathologist, a breast surgeon, and a clinical oncologist. If neoadjuvant chemotherapy is advised, then the patients will be reffered to the department of clinical oncology and the oncologist who participated in the MDT will write a note in the medical record. Toogether with the appointment the patient is invited to include an observer. At the first visit at the department of oncology the patient will be informed about the diagnosis, results of the preceding investigations and the treatment strategy suggested at the MDT will be proposed. Both the patient and the observer are secured good opportunity to pose questions. If the patient's characteristics comply with the in- and exclusion criteria of the NordicTrip trial the patient will subsequently be offered participation in the trial. The patient and observer will be given verbal and written information about the nature, purpose, possible risk and benefit of the study in a separate and private interview room located in a quiet environment and will be given enough time for questions. If the patient has not brought an observer and want to include one or if the patient wishes to postpone the information about the trial, then a new appointment will be squeduled. After receiving the information, the patient will be giving the possibility of at least 24 hours for reflection before deciding about participation.

Capture from the electronic health record (EHR)

The following data will be captured in the patient's electronic health record (EHR) or automatically transferred from the treatment database allready established in DBCG.

1. Consent, Inclusion, and Randomization

Consent (y/n), date of consent, consent retraction (y/n), date of retraction, comments about retraction. In- and exclusion criterias (y/n). Treatment allocation/randomization (regime A /regime B), date of randomization. Stratification (country, N-status, T-status, Pembrolizumab yes/no).

2. Baseline
   Date of diagnosis, laterality (right/left), Clinical T-size (mm), Mammography date, Mammography T-size (mm), UL date, UL T-size (mm), MRI date, MRI (mm), Imaging based T stage (cT0, cT1, cT2, cT3, cT4, cTx). UL nodal status (normal, enlarged, suspect), FNA axilla (ND, negative, positive), FNA N3 (ND, negative, positive), N-stage (N0/N+), Clinival M-stage (M0/M1/Mx).
   SN performed (Y/N), Date of SN, Number of SN, Number of non-SN, Metastatic nodes, Micrometastatic nodes, Largest affected node (mm), ITC (Y/N).
   ER (%), PgR (%), Ki67 (%), HER2 (0/1+/2+/3+/NE), HER2 ish (ND/amplified/non-amplified), Histologic type, RBC (0/I/II/III).
   Results of germline testing (class) including BRCA1 (1,2,3,4, or 5), BRCA2 (1,2,3,4, or 5), PALB2 (1,2,3,4, or 5), other high-penetrance genes according to institutional praxis.

3. Chemotherapy
   To be registered directly in the eCRF of the NordicTrip trial.

4. Adverse events, SAE and SUSAR
   To be registered directly in the eCRF of the NordicTrip trial.

5. Surgical treatment
   Date of breast surgery, type (BCR/mastectomy), Radical (Y/N), Contralateral surgery (Y/N) and type (risk reducing/oncoplastic/other), Primary surgery (Y/N), Final breast surgery (BCR/mastectomy).
   Axillary procedure (none/SN/ALND/SN+ALND) and date. SN performed (Y/N), Date of SN, Number of SN, Number of non-SN, Metastatic nodes, Micrometastatic nodes, Largest affected node (mm), ITC (Y/N).
   Residual invasive cancer (Y/N/no surgery), ypT (mm), ypTcis (mm), ypT-stage, ER (%), PgR (%), Ki67 (%), HER2 (0/1+/2+/3+/NE), HER2 ish (ND/amplified/non-amplified), Histologic type, RBC (0/I/II/III).

6. Follow-up
   To be registered directly in the eCRF of the NordicTrip trial.

Participants in the trial will allow direct access to relevant health information in their EHR records by the person responsible for the trial, sponsor and his/her representative, including the monitor and a DBCG employee, the Danish Medicines Agency, the Science Ethics Committee and the Data Protection Agency for up to 15 years after the trial ends (cf Health Act of June 24th 2005, Act 546).

Informed consent

Patients will be provided at least 24 hours for consideration before signing the informed consent.

Risks, side effects and sequela

Just about all treatments for breast cancer cause some type of side effects and the majority will suffer side effects from chemotherapy. Although chemotherapy is demanding for the person being treated very serious or even deadly side effects are rare. Most people can be physically active during treatment with chemotherapy and many are working during treatment, others need to be on sick leave during their treatment and in the time after.

Patients allocated to regime A will receive chemotherapy identical to chemotherapy given off trial and they will have the risks of side effects that chemotherapy generally leads to, including but not restricted to:

- Hair loss
- General malaise and sometimes nausea.
- Temporaly affection of white blood cells and platelets
- Fatigue. Fatigue may worsen after several treatments and sometimes only month after stopping treatment.
- Earlier menopause and reduced fertility in premenopausal women

Patientes allocated to regime B will receive experimentel treatment with capecitabine and may suffer diarrhea, which is a frequent side effect to capecitabine. In most cases the side effects will be mild, but in some cases severe (at least four times per day or during night). Capecitabine may also cause "Hand and foot disease" with redness, swelling and sometimes blisters on palms and soles of the feet. Hand and feet syndrome may lead to dose reduction and discontinuation with treatment.

Participation in the NordicTrip trial may be associated with disadvantages in form of additional blood and tissue samples, filling in questionnaires and thus also an increased time of consumption. Treatment with capecitabine leads to the prolongation of chemotherapy by three weeks and may also cause additional side effects as described above.

Only patients accepting germline genetic testing will in Denmark be eligible for participating in the NordicTrip trial and this in contrast to Sweden were germ-line testing may be performed as a consequence of participation in NordicTrip. Information about hereditary dispositions will to Danish patients consequently be given as part of general practice but information on germline mutations will be recorded in the database of the trial.

Medical imaging is a key to neoadjuvant chemotherapy and for participants in NordicTrip imaging will be performed according to standard practice outside the trial. As most of these procedure expose patients to ionizing radiation we have below made an evaluation of the amount ionizing radiation patients are exposed to by neoadjuvant chemotherapy, even though exposure would be the same outside the trial.

Procedure	Average dose	Examinations	Total dose	Dose by natural background
Mammography	0.4 mSv	3	1.2 mSv	4.8 mo
SN	>0.1 mSv	1	>0.1 mSv	1 mo
Breast MRI	None	3	none	-
PET-CT	22 mSv	1	22 mSv	7.3 years

Genetics germ-line testing

Participation in Nordic Trip is conditional upon consent to germ-line genetic testing (bullit 7 of the inclusion criteria) including BRCA1, BRCA2 and other genes defined by the institutional gene panel. Danish women with ER and HER2 negative breast cancer are offered germ-line testing as part of standard practice in Denmark. The result of germ-line genetic testing will be recorded in patients case record form.

Biobank and future research

NordicTrip is a translational clinical trial and biospecimens will be collected as specified below for blood and tissue samples.

Blood samples (in addition to germ-line testing) will be collected:

1. Blood sample at baseline entry for study specific analysis of germline alterations to enable comparison with alterations detected in tumor tissue. The sample will be forwarded to the Nordic Trip Lab, Medicon Village 404: B3, Scheelevägen 2, 223 81 Lund. Findings will not be reported to participants.
2. Blood sample after chemotherapy cycle 2 for immunoprofiling. The sample will be forwarded to the Nordic Trip Lab, Medicon Village 404: B3, Scheelevägen 2, 223 81 Lund. Findings will not be reported to participants.
3. Blood samples at baseline, after cycle 2, before surgery, after surgery, 1 year after baseline and potentially at recurrence for circulating tumor DNA (ctDNA) and circulating tumor markers. Samples will be forwarded to the Barbro Linderholm, Sahlhrenska cancer Center, Medicinaregatan 1G, vån 5, 413 90 Göteborg. Findings will not be reported to participants.

Formalin fixed paraffin embedded (FFPE) tumour tissue

4. Two to four tumor core biopsies at baseline), a representative piece from residual tumor tissue or from the tumor bed in case of pCR at surgery plus normal tissue outside the tumor bed. Samples will be forwarded to Anne-Vibeke Lænkholm, Department of Pathology, Roskilde Hospital, Zealand University Hospital, Sygehusvej 9, 4000 Roskilde. Findings will not be reported to participants.

After final analyzes by 2036 at the latest, residual tissue, RNA, or DNA from blood samples and residual tissue RNA, or DNA from the formalin-fixed paraffin-embedded tissue will be returned to the DBCGs biobank no. RH-2015-122 (i-suite 03903) with a view to future research projects.

Any research not specified by the current study protocol will require the approval of the Scientific Ethics Committee, and as a rule a new consent from the participant. The Scientific Ethics Committee may in some cases waiver claim of consent. The Data protection rules will apply to future research and all researh will be compliant to the General Data Protection Regulation (GPDR) as specified by the Danish Data Protection Authority.

Safety monitoring and reporting
SUSARS will be reported to the sponsor using the CIOMS-form by the site and to the Danish Medicines Agency by the site using the e-Form Indberetning af mistænkte uventede og alvorlige bivirkninger (SUSAR) set i kliniske forsøg. SUSARs will be reported immediately to the Danish Medicines Agency and in accordance with the definitions and time frames specified in protocol and in the Danish executive order on clinical trials (no. 295 of 26 April 2004) and EU directive 2001/20/EC.

Annual safety report
The sponsor will provide the Danish Medicines Agency with a yearly report which includes all serious adverse reactions (SARs) from the entire trial on the trial subjects' safety. This will include expected as well as unexpected serious adverse reactions (SARs and SUSARs).

Quality assurance and data monitoring
The Danish sites are monitored by the DBCG (responsible for the Nordic Trip Trial in Denmark as defined below) and the Study Monitor will perform two types of action:

1. Site visits or remote monitoring by video/phone contact in a secure environment (prohibiting unauthorized persons and recording) will be performed in order to:
    - Conduct a Nationwide Danish Initiation Meeting
    - Conduct Initiation Visits at all sites including review of study specific procedures and passing sites files
    - Secure availability of CV's from investigators and research nurses. Ensure that authorization-, screening-, delegation-, site visit- and training logs, DEKS certificates all are up to date
    - Check of Informed Consents from all participants
    - Check of identity using the Danish civic registration number (CPR) and protocol Identification number
    - Cross check of inclusion and exclusion criteria using data reported to the clinical DBCG database from independent data sources e.g surgical and pathology departments
    - Check of AEs
    - Calification in the case of inconsistancies, through check of patient file by contacting research nurses at the center
    - Communication with PI and research nurses at all Danish centers on an on-going basis both during treatment and follow-up period
    - Ensure that all necessary approvement are available
    - Monitor the recruitment of patients
    - Ensure timely reporting of data
    - Ensure that participating sites are compliant with the study protocol during both the treatment period and follow-up
    - Check of SUSARs (see Safety monitoring and reporting)
    - Extend monitoring at specific sites whenever needed e.g. sites in need of help, with slow recruitment, or in case of incomplete and deficient data entry
    - Participate in quarterly meetings of the DBCG Scientific Committee for Medical Therapy
    - Close out visit at "End of trial"and related task
2. By linking to four national registries using the Danish civic registration number (CPR) as identification. Note that Sponsor has only the patient number (identification in Nordic Trip), however DBCG as a national register, also knows the civic registration number.

- Every three months a linkage is done to the National Pathology Registry (NPR), Danish Patobank, for identification of diagnosis of new breast cancer and/or recurrences
- Every three months a linkage is done to the Danish National Patient Registry (LPR) for identification of Late adverse events or other events defined by admission to a hospital
- Yearly a linkage to the Danish Cancer Registry (CR) to find any second malignancies
- Every three months a linkage is done to the the Central Population Registry in order to get the patients vital status

Publication of study results

Results will be published and preferable in a peer-reviewed scientific journal irrespective of whether these results may be positive, negative or inconclusive. Results will also be published in clinicaltrials.gov.

Appendix I – List of participating Principal Investigators in Denmark

Center	Principal Investigator
Onkologisk Afd., afs. 5073 Rigshospitalet Blegdamsvej 9 2100 København Ø	**Ulla Brix Tange** ulla.brix.tange@regionh.dk Tlf.: 35 45 0463 Fax: 3545 4449
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Onkologisk og Palliativ Afdeling Nordsjællands Hospital Hillerød, Dyrehavevej 29 3400 Hillerød	**Karin Peschardt** karin.peschardt@regionh.dk Tlf. 48 29 32 35
Onkologisk Afdeling Vejle Sygehus Beriderbakken 4 7100 Vejle	**Lone Volmer** Lone.volmer@rsyd.dk Sygehuset: 79 40 50 00

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Appendix J – Quality of Life Assessment in NordicTrip

Rational

One of the secondary aims of this study is to compare patients' health related quality of life (HRQoL) between the randomization arms during the course of treatment and at the one- and two-year follow-up. The differences in HRQoL between the two regimens will be evaluated.

Knowledge about differences in HRQoL between the randomization arms is valuable but is also important in relation to the results for main outcome, complete response at surgery. The information gained can be used in patient information in the treatment decision situation.

Material and methods

Patients
All patients in Sweden included in the Nordic Trip Trial will be asked to participate in the HRQoL study, starting 1st of September 2022. The aim is to include 250 patients in this subset.

Points of assessment
HRQoL will be measured at five time points during the first two years after randomization.

The first point of assessment is after informed consent has been obtained, but before randomization. Information to the patient about which treatment arm the patient has been randomized to might have an impact on the HRQoL. Thus, it is important that the patient is unaware of the result of randomization when responding to the QoL-questionnaires. This point of assessment provides HRQoL estimates unaffected by side effects of treatment. It should be kept in mind, however, that the included patients have recently been informed about their breast cancer diagnosis. Thus, their HRQoL cannot be regarded as a true "baseline" assessment. This point of assessment will give a measure of HRQoL that allows for detection of potential differences in HRQoL between the treatment arms at inclusion. If there are differences in HRQoL at the first point of assessment, these can be adjusted for when analyzing the variations in HRQoL during the course of treatment. In addition, biased results due to selective attrition during the study period may also be analyzed by comparing those who participate with those who are lost at subsequent points of assessment.

The subsequent four time points of assessment are: Before start of Paclitaxel-Carboplatin treatment (to compare the ddEC and CEX regimens), before surgery (the compare the effects of the various neo-adjuvant treatments), and at one and two years after randomization (to evaluate the HRQoL when treatment has been terminated. At some of the timepoints patients will be faced with information about the efficacy of the treatment. This information might affect their HRQoL, positively for those who respond and negatively for those who do not. To minimize this impact, it is important that the QoL questionnaires are filled in before the actual visit starts.

Instruments
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30, version 3.0 (EORTC QLQ-C30) is a HRQoL instrument developed to be multidimensional in structure and self-administrative to be used in cancer clinical trials (Aaronson et al., 1993). It includes nine multi-item scales and six single item variables. The five functional scales consist of physical- (PF), role- (RF), emotional- (EF), social- (SE), and cognitive functioning (CF). Fatigue (FA), nausea/vomiting (NV) and pain (PA) comprise the three multi-item symptom scales. Additional symptoms are assessed by single items: dyspnoea (DY), sleep disturbances (SL), appetite loss (AP), constipation (CO), and diahorrea (DI). One single item scale concern financial problems related to disease and treatment. Most items are responded to on a four-point scale ranging from 1 (not at all) to 4 (very much). The two items assessing global health and overall quality of life are responded to in seven categories ranging from 1 (very poor) to 7 (excellent).

The EORTC QLQ Breast Cancer Module (QLQBR-23) is a breast cancer specific questionnaire developed for use among patients varying in disease stage and treatment modality (Sprangers et al., 1996). It comprises 23 items divided into four functioning scales: body image (BRBI), sexual functioning (BRSEF), sexual satisfaction/enjoyment (BROSE), and future perspective (BRFU); and four symptom scales: systemic therapy side effects (BRST), breast symptoms (BRBS), arm symptoms (BRAS), and being upset by hair loss (BRHL). The questionnaire has been validated in an international study (Sprangers et al., 1996). Completion of the questionnaire takes about 10–20 min. The items are responded to in the same four categories as most items in the EORTC QLQ-C30.

Procedure
First questionnaire: After inclusion in the study and informed consent is given, the patient is informed orally and in writing about the HRQoL assessment. The physician who includes the patient into the NordicTrip Trial, or a research nurse, gives the patient the first questionnaire and an envelope. The questionnaires should be marked with the Patient ID generated from the eCRF. The first questionnaire is completed at the ward or at the out-patient clinic before information is conveyed about to which arm the patient has been randomized. Patients should be informed to answer all questions and then put all forms in the envelope, seal the envelope and return it to the site personnel. The treating physicians and nurses have no access to the HRQoL-forms. This procedure should be conveyed to the patients.

At all the following time points of assessment, questionnaires marked with Patient ID and return envelopes are handed out by a research nurse at the defined clinical visits. All HRQoL-forms should be completed before any other procedures and before information from response evaluations and surgery are reveled to the patient.

Once a month all sites will send unopened envelopes to the sponsor.

Data analysis
In this study HRQoL is a secondary endpoint. Data for the EORTC QLQ-C30/BR23 will be scored according to the algorithm described in the EORTC QLQ-C30 scoring manual (Fayers et al., 2001). All scales and single items are scored on categorical scales and linearly transformed to 0-100 scales where:
- a high score for a symptom scale or item represents a high level of symptoms or problems
- a high score for a functional scale represents a high or healthy level of functioning
- a high score for the global health status/QoL represents high QoL.

Compliance with completing QoL questionnaires will be investigated at each time point to evaluate the procedure for data collection and the feasibility of the questionnaires.

The effect of treatment on each of the scale scores at the different time points will be evaluated using linear regression models including both treatment and baseline values for the studied scales. Considering multiple testing, the results from the regression analysis will be presented as mean differences together with 99% confidence intervals. Linear mixed-models will be used to study treatment, time, and the treatment-time interaction using all available longitudinal data.

In the interpretation of the QLQ-C30 and BR-23 scores, a difference of $\geq$5 points on the 0–100 scales will be considered clinically important. Differences of 5–9 points are considered small, those of 10–20 as moderate, and those ≥20 as large (Osoba et al., 1998).

Due to multiple testing, the level of statistical significance will be set to 0.01 to avoid type I errors. All analyses will be performed according to the ‘‘intention-to-treat’’ principle.

References

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