A Randomized, Placebo-Controlled, Double-Blind, Phase 3 Study Evaluating Safety and Efficacy of the Addition of Veliparib Plus Carboplatin Versus the Addition of Carboplatin to Standard Neoadjuvant Chemotherapy Versus Standard Neoadjuvant Chemotherapy in Subjects with Early Stage Triple Negative Breast Cancer (TNBC).

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The primary objective of the study is to assess the incidence of pathological complete response (pCR) in breast and ipsilateral axillary tissue after daily treatment with veliparib in combination with neoadjuvant carboplatin and paclitaxel followed...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON47540

Source
ToetsingOnline

Brief title
M14-011

Condition

- Miscellaneous and site unspecified neoplasms benign
- Breast disorders

Synonym
Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie Deutschland GmbH & Co. KG
Source(s) of monetary or material Support: Industry

Intervention

Keyword: Breast Cancer, Triple Negative, Veliparib

Outcome measures

Primary outcome

Pathological Complete Response (pCR) will be defined by the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and any resected lymph node tissue following completion of neoadjuvant systemic therapy (i.e., ypT0/Tis ypN0 per AJCC staging system). The co-primary efficacy analyses are defined by comparing pCR in two pairwise comparisons of Arm A versus Arm B and Arm A versus Arm C. The percentage of subjects with pCR will be calculated for each treatment arm and will be compared between the active arm (Arm A) and each of the two control arms (Arm B and C) by two pairwise comparisons (Arm A versus Arm B and Arm A versus Arm C) using the Cochran-Mantel-Haenszel (CMH) test stratified by the stratification factors (BRCA status, lymph node stage and planned schedule of doxorubicin/cyclophosphamide administration) at the alpha = 0.05 significance

level. Both comparisons in the co-primary analyses need to be statistically significant to claim efficacy of veliparib.

Secondary outcome

Event Free Survival (EFS):

Event Free Survival (EFS) will be defined as the time from random assignment to documentation of the first of the following events: discontinuation of study therapy due to protocol-defined progression prior to surgery; local, regional, or distant invasive recurrence of breast cancer following curative surgery; a new breast cancer; a new onset malignancy; or death as a result of any cause. If a subject has not experienced above events, then the subject will be censored at date of last available disease assessment. At the completion of the study, EFS will be compared between the treatment arms by the two pairwise comparison (Arm A versus Arm B and Arm A versus Arm C) using the log rank test, stratified by the stratification factors, at the alpha = 0.05 significance level. Only descriptive statistics will be calculated for EFS when the analysis for the primary endpoint (pCR) is performed.

Overall Survival (OS):

Overall Survival (OS) will be defined as the number of days from the day the subject is randomized to the date of the subject's death. All events of death will be included, regardless of whether the event occurs while the subject is still taking study drug, or after the subject discontinues study drug. If a subject has not died, then the data will be censored at the date when the subject is last known to be alive. At the completion of the study, OS will be

compared between the treatment arms by the two pairwise (Arm A versus Arm B and Arm A versus Arm C) using the log rank test, stratified by the stratification factors, at the alpha = 0.05 significance level. Only descriptive statistics will be calculated for OS when the analysis for the primary endpoint (pCR) is performed.

Breast Conservation Rate (BCR):

Breast Conservation Rate (BCR) will be defined as the rate at which subjects are eligible for breast conservation after neoadjuvant therapy among subjects for whom mastectomy was planned at diagnosis. The Breast Conservation Rate at the pre-operative visit will be calculated for each treatment arm and will be compared between the active arm (Arm A) and each of the two control arms (Arms B and C) by two pairwise comparisons (Arm A versus Arm B and Arm A versus Arm C) using the Cochran-Mantel-Haenszel (CMH) test stratified by the stratification factors (BRCA status, lymph node stage and planned schedule of doxorubicin/cyclophosphamide administration) at the alpha = 0.05 significance level.

Study description

Background summary

Breast cancer is the most common cancer in women worldwide with approximately 1,380,000 new cases and 460,000 deaths estimated in 2008. Survival for early invasive breast cancer is improved with the addition of chemotherapy and/or radiotherapy to surgery for all but small, localized tumors. According to global breast cancer care guidelines, neoadjuvant chemotherapy should contain anthracyclines and taxanes. In breast cancer, administration of carboplatin to

previously untreated patients with metastatic disease results in response rates of 20% to 50%. Paclitaxel in combination with carboplatin is also highly active in breast cancer, with response rates of approximately 39% to 62% for first-line treatment of metastatic disease. Consistent with the observation that PARP activity may act as a resistance factor in some tumors, PARP inhibitors have been shown in preclinical models to sensitize tumors to a variety of DNA-damaging agents, including cross-linking chemotherapy agents such as carboplatin and to ionizing radiation therapy. Veliparib is a potent PARP inhibitor that delays the repair of DNA damage induced by chemotherapeutics. Veliparib increases sensitivity of tumor cells to DNA-damaging agents in vitro and in vivo, and inhibits PARP in murine tumors in vivo, human peripheral blood mononuclear cells (PBMCs) ex vivo, and human tumors ex vivo.

Study objective

The primary objective of the study is to assess the incidence of pathological complete response (pCR) in breast and ipsilateral axillary tissue after daily treatment with veliparib in combination with neoadjuvant carboplatin and paclitaxel followed by doxorubicin + cyclophosphamide compared to two neoadjuvant chemotherapy regimens (paclitaxel followed by doxorubicin + cyclophosphamide; carboplatin and paclitaxel followed by doxorubicin + cyclophosphamide) with matching placebo in subjects with triple negative breast cancer.
The secondary objective of the study is to assess event free survival (EFS), overall survival (OS) and the rate of eligibility for breast conservation after therapy (BCR).
The tertiary objectives are to assess clinical response rate (CRR) at 12 weeks, incidence of pCR plus minimal residual disease (defined as residual cancer burden [RCB] class I), Eastern Cooperative Oncology Group (ECOG) performance status, and breast cancer related quality of life (QoL).

Study design

This is a Phase 3, randomized, placebo-controlled, double-blinded, multinational, multicenter study to evaluate the safety and efficacy of the addition of veliparib and carboplatin in combination with standard neoadjuvant chemotherapy compared to carboplatin in combination with standard neoadjuvant chemotherapy compared to standard neoadjuvant chemotherapy in subjects with previously untreated triple negative breast cancers who are candidates for potentially curative surgery. Subjects will be stratified by BRCA status (deleterious mutation in BRCA1 and/or BRCA2 gene; no BRCA mutation; or unknown), lymph node stage (N0 versus N1-2) and planned schedule of doxorubicin/cyclophosphamide administration (q2 weeks, also known as dose dense, versus q3 weeks). Subjects with mutations of uncertain clinical significance according to core laboratory testing will be

considered to have no BRCA gene mutation, and subjects with deleterious mutations or suspected deleterious mutation according to core laboratory testing will be considered to have a BRCA gene mutation.

Intervention

Approximately six hundred twenty-four (624) subjects will be randomized in a 2:1:1 ratio to one of the following three treatment arms:
Arm A) paclitaxel + carboplatin + veliparib followed by doxorubicin/cyclophosphamide
Arm B) paclitaxel + carboplatin followed by doxorubicin/cyclophosphamide
Arm C) paclitaxel followed by doxorubicin/cyclophosphamide

Study burden and risks

From the I-SPY 2 study, a benefit of 20% absolute increase in pathologic complete response (pCR) rate with veliparib combination therapy is assumed for the design of the current trial. analysis demonstrated that in breast cancer subgroups considered to have highly proliferating tumors, the pCR rate can accurately discriminate between patients with good and poor prognosis. The prognostic impact of the pCR rate was highest in triple negative and in HER2-positive (nonluminal) tumors, with 3-year disease-free survival rates in patients achieving pCR approximating 90%. The prognosis in patients without pCR was comparable to that in patients receiving systemic treatment after surgery, with 3-year disease-free survival rates approximating 55%. The long-term outcome of these patients suggests that a 20% increase in the pCR rate may lead to an improvement in disease-free survival of approximately 47% (HR ~ 0.68), or an absolute improvement in the recurrence-free survival rate of ~ 9.8% at 5 years.

Risks in this study include toxicity from the addition of veliparib and/or carboplatin to standard therapy. Preliminary safety data for veliparib show the most common AEs in the clinical studies evaluating veliparib in drug combination studies were hematological toxicities, gastrointestinal events, and other toxicities commonly associated with those known for each background therapy. Standard clinical practices to manage these toxicities are well established. Patients receiving veliparib in this study will also receive carboplatin, and additional toxicity from the combination must be considered versus the standard of care comparator paclitaxel followed by AC. Limited published data suggest that carboplatin adds little severe toxicity (increase in grade 3/4 anemia by 5% to 10%, low incidence of grade 3/4 thrombocytopenia) to a regimen containing taxane and doxorubicin in patients with basal type breast cancer.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Women >= 18 years of age.
2. Histologically confirmed invasive breast cancer by core needle or incisional biopsy (excisional
biopsy is not allowed). Clinical stage T2-3 N0-2 or T1 N1-2 by physical exam or radiologic studies.
At the time of presentation, subjects must be candidates for potentially curative surgery by surgeon's
assessment. Inflammatory breast cancer or neuroendocrine carcinoma is not allowed. If multiple
(up to 2) suspicious lesions are present, each must be biopsied to evaluate for invasive disease, and
all invasive lesions in the same breast must be triple-negative as defined below. Subjects

with
synchronous bilateral invasive breast cancers are not eligible.
3. Documented BRCA germline mutation testing. All subjects regardless of BRCA mutation status
(i.e., wildtype BRCA or germline BRCA mutation) are eligible for study participation. If testing has
been performed by a laboratory other than the Sponsor core laboratory, subjects may be enrolled but must be re-tested by Sponsor core laboratory for confirmation of BRCA1 and/or BRCA2 germline mutation. Subjects who complete informed consent and screening procedures will not be denied protocol therapy due to delays in BRCA testing results. For those subjects who meet other enrollment criteria but have not received BRCA germline mutation testing results at the completion
of the screening period, randomization to a treatment group based on other stratification factors will
be permitted upon Sponsor approval. Subjects will be analyzed according to results of BRCA testing as described in the statistical methods.
4. ER-, PR-, and HER2-negative (triple-negative) cancer of the breast. Randomization based on local results will be permitted, and all results will be confirmed by central pathology reading.
Triple-negative tumors are defined as:
* For ER- and PR-negative: less than or equal to 1% tumor staining by immunohistochemistry (IHC).
* HER2-negative disease, defined as IHC 0 - 1+ OR HER2-neu negative according to ASCO-CAP guideline recommendations.
5. ECOG Performance status of 0 to 1.
6. Adequate organ function as follows:
* Bone Marrow: Absolute neutrophil count (ANC) >= 1500/mm3 (1.5 × 109/L); Platelets >= 100,000/mm3 (100 × 109/L); Hemoglobin >= 9.5 g/dL (5.6 mmol/L); Leukocytes > 3,000/mm3;
* Renal Function: Calculated creatinine clearance >= 50 mL/min/1.73 m2 by the Cockroft-Gault
formula;
* Hepatic Function: Aspartate aminotransferase (AST) or alanine transaminase (ALT) <= 2.5 × upper limit of normal (ULN); bilirubin <= 1.5 × ULN. Subjects with Gilbert's syndrome
may have a bilirubin > 1.5 × ULN, if no evidence of biliary obstruction exists;
* Activated Partial Thromboplastin Time (APTT) must be <= 1.5 × ULN and international normalized ratio (INR) < 1.5 × ULN. Subjects on anticoagulant therapy will have an appropriate APTT and INR as determined by the Investigator;
* Adequate cardiopulmonary reserve to undergo surgery with general anesthesia;
* Left ventricular ejection fraction greater than or equal to 50% by MUGA or echocardiogram.
7. Women must be determined to be not of childbearing potential (surgically sterile, or postmenopausal
defined as amenorrheic for at least 12 months) by the Investigator OR they must have a negative
serum pregnancy test prior to randomization. Women of childbearing potential must agree to use

adequate contraception (one of the following listed below) prior to study entry, while receiving
study treatment, and for 6 months (or per local labels) following completion of therapy:
* Total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable;
* Sexual intercourse with only vasectomized partner;
* Double-barrier method (condoms, contraceptive sponge, diaphragm or vaginal ring with spermicidal jellies or cream);
* Intra-Uterine Device (IUD).
8. Capability of understanding and complying with parameters as outlined in the protocol and able to sign and date the informed consent, approved by an Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to initiation of any screening or study-specific procedures.
9. Capability of taking oral medication.

Exclusion criteria

1. Previous anti-cancer treatment (cytotoxic chemotherapy, immunotherapy, biologic therapy,
radiotherapy or investigational agents) with therapeutic intent for current breast cancer.
2. Previous treatment with carboplatin, paclitaxel, doxorubicin, or cyclophosphamide.
3. Prior therapy with a Poly-(ADP-ribose)-Polymerase (PARP) inhibitor.
4. Concurrent treatment with an ovarian hormonal replacement therapy or with hormonal agents such
as raloxifene, tamoxifen or other selective estrogen receptor modulator (SERM). Subjects must
have discontinued use of such agents prior to beginning study treatment.
5. A history of seizure within 12 months prior to study entry.
6. Pre-existing neuropathy from any cause in excess of Grade 1.
7. Known history of allergic reactions to cremophor-containing medications, including Polyoxyl 35
Castor Oil.
8. Clinically significant uncontrolled condition(s) including but not limited to the following:
* Active infection;
* Symptomatic congestive heart failure;
* Unstable angina pectoris or cardiac arrhythmia;
* Myocardial infarction within last 6 months;
* Contraindications to surgery with general anesthetic or regional radiotherapy;
* Psychiatric illness/social situations that would limit compliance with study requirements;
* Hemorrhagic cystitis;
* Uncontrolled hypertension despite optimal medical management;
* Major surgery or significant traumatic injury, within 4 weeks of starting study treatment;
* History of Hepatitis B (HBV) or Hepatitis C (HCV) infection. Subjects with positive history of HBV or HCV may undergo confirmatory testing if not performed within 3 months prior to initiation of study treatment. Tested subjects with positive HBcAb or positive HCV RNA are

excluded; or
* Any medical condition which in the opinion of the Investigator places the subject at an unacceptably high risk for toxicities.
9. A previous or concurrent cancer that is distinct in primary site or histology from the cancer under
study, except cervical carcinoma in situ, non-melanoma carcinoma of the skin, or in situ carcinoma
of the bladder. Any cancer curatively treated greater than 3 years prior to entry is permitted.
10. Pregnant or breastfeeding.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-11-2015
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Cyclophosphamide

Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxorubicin
Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Veliparib
Generic name:	Veliparib

Ethics review

Approved WMO Date:	19-05-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-11-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-02-2016
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-08-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2018
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-12-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-07-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-002377-21-NL
CCMO	NL48946.029.14

Study results

Results posted: 15-10-2021

First publication
13-10-2021