Multicenter, randomized, open label study evaluating a poly(ADP-ribose) polymerase-1(PARP-1) inhibitor, SAR240550 (BSI-201), administered twice weekly or weekly, in combination with gemcitabine/carboplatin, in patients with metastatic Triple Negative Breast Cancer (mTNBC)

Published: 19-03-2010
Last updated: 04-05-2024

The primary objective of this study is to assess the objective response rate (ORR, the percentage of treated patients in whom the tumor significantly reduces in size or becomes non-detectable) of SAR240550 administered as a 60min intravenous...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON34839

Source
ToetsingOnline

Brief title
TCD11418

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, metastatic triple negative breast neoplasm

Research involving
Human

Sponsors and support

Primary sponsor: Sanofi-aventis
Source(s) of monetary or material Support: sponsor: sanofi-aventis

Intervention

Keyword: Breast cancer, Poly(ADP-ribose) Polymerase inhibitor, SAR240550

Outcome measures

Primary outcome

Objective response rate. The ORR will be evaluated every second cycle.

Secondary outcome

Efficacy

- Clinical benefit rate (CBR): the percentage treated patients of whom the

tumor is stable, decreases in size or becomes undetectable for >=24 weeks.

- Progression-free survival and total survival.

Safety

Safety will be assessed by standard clinical and laboratory tests (hematology,

serum chemistry). Toxicity grade is defined by the NCI CTC AE v 4.0.

Molecular-biological properties and pharmacokinetics

In a substudiy which is optional for the patients the following evaluations

will be performed:

-Pharmacogenetic properties of the tumor (including BRCA1 and BRCA2) <=1 month

before the first treatment and at the end of the first cycle. For this purpose

tumor biopsies will be performed.

-Pharmacodynamics; by means of blood sampling (in the first 6 weeks of

treatment) the amount of PAR (poly-(ADP-ribose)) will be analyzed.

-Pharmacokinetics; by means of blood sampling (in the first 6 weeks of

treatment) the pharmacokinetic profile of SAR240550 will be determined.

Study description

Background summary

Breast cancer remains the most common malignancy in women worldwide with more than 1.2
million cases diagnosed every year and 500 000 deaths per year. Routine assessment of three cellular receptors (estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor 2 [HER2]) are biomarkers that are being used for predicting patient response to therapies.
However, up to 20% of breast cancers are negative for expression of all three receptors. Despite best available therapy, TNBC continues to be associated with poorer outcomes when compared to other breast cancer subtypes, and is associated with a higher chance on metastases. No treatment has been registered specifically for TNBC.
SAR240550 is a first-in-class investigational targeted therapy designed to inhibit poly-(ADPribose)
polymerase (PARP1). PARP1 is an enzyme involved in DNA damage repair, and inhibition of this enzyme can prevent tumor cells from recovering from DNA-damage. This can cause the tumor cells to die by apoptosis or make them more vulnerable to chemotherapy.

Study objective

The primary objective of this study is to assess the objective response rate (ORR, the percentage of treated patients in whom the tumor significantly reduces in size or becomes non-detectable) of SAR240550 administered as a 60min intravenous infusion twice weekly (arm A) or weekly (arm B), in combination with gemcitabine/carboplatin chemotherapy regimen in patients with metastasized TNBC. Secundary objective are the safety profile and (in a subset of the patients) the molecular biological profile of the tumor and the pharmacokinetic

profile of SAR240550.

Study design

This is an open label, randomised study.

Intervention

Patients will be randomly assigned in one of the two treatment arms.
Arm A: Each treatment cycle of 3 weeks the patient will receive a 60-minut intravenous treatment of 5,6 mg/kg SAR240550 on day 1, 4, 8, and 11.
Arm B: Each treatment cycle of 3 weeks the patient will receive a 60-minut intravenous treatment of 11.2 mg/kg SAR240550 on day 1, and 8.
In both treatment arms the patients will receive treatment with gemcitabine and carboplatin on day 1 and 8. Treatment will continue every 3 weeks in the absence of disease progression or unacceptable toxicity.

Depending on the treatment arm the patient will receive intravenous treatment in the hospital 2-4 times per 3-week cycle. From all patients blood samples will be taken on days 1 and 8 of each cycle for standard hematological and biochemical analysis. Every 6 weeks a CT-imaging will be performed to determine the status of the tumor(s).

Study burden and risks

The adverse events of gemcitabine (Gemzar®) and carboplatine (Carbosin®) are well known since these products have been registered for the treatment of several types of tumors for a number of years now.
So far SAR240550 (BS201) has been administered as single agent to about 37 patients and as a combination therapy to about 238 patients. From the latter group about 60 patients had TNBC and were treated in combination with gemcatibine and carboplatin.
Safety data provided to date demonstrates that the addition of SAR240550 to gemcitabine/carboplatin did not potentiate toxicities of gemcitabine/carboplatin alone.

Depending on the treatment arm the patient will receive intravenous treatment in the hospital 2-4 times per 3-week cycle. From all patients blood samples will be taken on days 1 and 8 of each cycle for standard hematological and biochemical analysis. Every 6 weeks a CT-imaging will be performed to determine the status of the tumor(s).

If the patient chooses to participate in the substudy, she may be asked to stay overnight twice during the first cycle. For this substudy 26 (arm A) or 22 (arm B) extra bloodsamples are required. The total amount of blood is 78 (arm A) or

66(arm B) milliliters.

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

* Histologically documented breast cancer that is ER- negative, PR-negative, and HER2 non-overexpressing with metastases measurable by RECIST 1.1 criteria
* Prior treatment that includes:
- never having received anticancer therapy for metastatic disease OR
- having received 1 or 2 prior chemotherapy regimens in the metastatic setting;
* Eastern Cooperative Oncology Group (ECOG) performance status of 0-1;
* Good organ and marrow function (see protocol page 32 for laboratory values)
* Radiation therapy completed at least 7 days before study dosing on day 1;
*Central nervous system (CNS) metastases allowed under certain conditions (see protocol

page 32)
* No other diagnosis of malignancy (with exception of non-melanoma skin cancer or a malignancy diagnosed and curatively treated >5 years ago)

Exclusion criteria

*Systemic anticancer therapy within 14 days of the first dose of study drug;
*Prior treatment with gemcitabine, carboplatin, cisplatin or any PARP inhibitor;
*Has not recovered to grade 1 from AEs per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.0;
*Bone metastasis or skin metastasis only;
*Major medical conditions that might affect study participation (e.g., uncontrolled pulmonary, renal, or hepatic dysfunction, uncontrolled infection, cardiac disease);
*Concurrent radiation therapy intended to treat primary tumor not permitted throughout the course of the study; palliative radiation is acceptable;
* Leptomeningeal disease or brain metastases requiring steroids or other therapeutic intervention;

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-05-2010
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	Carbosin
Generic name:	carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Gemzar
Generic name:	gemcitabine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-03-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-05-2010
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	30-06-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-08-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	27-08-2010
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-02-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-06-2011
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2009-016091-80-NL
CCMO	NL30484.078.09
Other	Zie sectie J