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Carboplatin with or without ZD4054 in patients with metastatic breast cancer

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Registration date 18/05/2010	**Overall study status** Stopped	
Last Edited 01/05/2012	**Condition category** Cancer	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01134497

Secondary identifying numbers
SPON804-10

Study information

Scientific Title
A randomised Phase II study of carboplatin with or without the addition of the ETAR inhibitor ZD4054 as treatment for patients with metastatic breast cancer

Acronym
PLANET

Study objectives
Metastatic breast cancer (MBC) remains incurable and there has been little change in long term outcomes. Chemotherapy is used to improve symptoms and prolong survival in patients with advanced breast cancer. Nevertheless, most tumours inevitably progress and the clinical response rates to subsequent chemotherapy agents are disappointing. There is, therefore, a need for continued clinical research into new strategies to enhance the effectiveness of currently available chemotherapy agents to improve survival.

The endothelin pathway has been implicated in a number of oncogenic pathways. ET-1 and ETAR are frequently over-expressed in breast cancers and are prognostic for poor outcome. Inhibition of the endothelin pathway enhances cytotoxicity when combined with chemotherapy agents such as carboplatin in pre-clinical models. ZD4054 is a specific inhibitor of ETAR and represents a novel therapeutic target in breast cancer.

This study investigates whether ZD4054, an oral endothelin A receptor (ETAR) inhibitor, in combination with carboplatin chemotherapy, has sufficient activity to warrant a future Phase III trial in patients with advanced/metastatic breast cancer.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Protocol approval will be sought from a Multi-Centre Research Ethics Committee (MREC). Each participating centre will be approved through a Regional Ethics Committee (REC) prior to patient recruitment.

Study design
Mmulticentre phase II parallel group double blind randomised controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Metastatic breast cancer

Interventions
1. Stage 1
Patients will receive carboplatin (AUC4 or AUC5 q21d as below) + ZD4054 (10mg daily). Dose limiting toxicity (DLT) and safety assessments will be performed during cycle 1. Patients may receive up to 6 cycles.
1.1. Dose Level 1 (carboplatin - AUC4 q21d + ZD4054 10mg once daily [OD])
Three patients will receive carboplatin AUC4 intravenously [IV] over 30mins on day 1 plus ZD4054 (10mg daily) orally (PO) on days 1-21 of a 21 day cycle. Patients will be assessed at day 1, 8, 15 and 22 for toxicity.
1.1.1. If Dose Level 1 is tolerable (i.e. none of the initial 3 patients experience DLT as per Section 8.2), six patients will be treated at Dose Level 2.
1.1.2. If one of the initial 3 patients does not tolerate Dose Level 1 (i.e. they experience DLT) a further 3 patients will be treated at this dose level. If no further patient experiences DLT the study will proceed to Dose Level 2. If Dose Level 1 is not tolerable (i.e. ≥ 2 patients experience DLT), at Dose Level 1 the study will not proceed further.
1.2. Dose Level 2 (carboplatin - AUC5 q21d + ZD4054 10mg OD)
Six patients will receive carboplatin AUC5 IV over 30mins on day 1 plus ZD4054 (10mg daily) PO on days 1-21 of a 21 day cycle. They will be assessed for toxicity at day 1, 8, 15 and 22.
1.2.1. If Dose Level 2 IS tolerable (i.e. < 2 of 6 patients experience DLT),the study will proceed to Stage 2
1.2.2. If Dose Level 2 is NOT tolerable (i.e. ≥ 2 DLTs in 6 patients within the same dose level) then the study will not proceed to stage 2.
1.2.3. If a patient in Dose Level 2 experiences DLT then that patient may receive a de-escalated dose of carboplatin (AUC4) with ZD4054 on subsequent cycles.

2. Stage 2
Recruitment to Stage 2 will commence after 6 patients in Dose Level 2 of Stage 1 have completed at least 1 cycle of therapy with < 2 patients experiencing DLT. Patients will be randomised to one of two arms:
2.1. Arm A (control arm): carboplatin + placebo
The control arm will consist of up to 6 cycles of carboplatin (AUC5 q21d for 6 cycles) IV over 30 minutes on day 1, plus placebo PO on days 1-21 of a 21 day cycle.
2.2. Arm B (experimental arm): carboplatin + ZD4054
The experimental arm will consist of up to 6 cycles of carboplatin (AUC5 q21d for 6 cycles) IV over 30 minutes on day 1, plus ZD4054 (10mg daily) OD PO on days 1-21 of a 21 day cycle.

3. Assessments on treatment
3.1. Stage 1
3.1.1. Cycles 1 Days 8 and 15 and 22
3.1.1.1. Physical examination (to include Eastern Cooperative Oncology Group Performance Status Scale [ECOG PS])
3.1.1.2. Full Blood Count (FBC)
3.1.1.3. Urea and Electrolytes
3.1.1.4. Liver Function Test (LFT) (including aspartate aminotransferase [AST], alanine

aminotransferase [ALT], bilirubin, alkaline phosphatase)
3.1.1.5. Optional blood sample for separate translational sub-study (may be obtained at any point between consent and second treatment)
3.1.1.6. Toxicity assessment according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE v4)
3.1.1.7. Concomitant medication
3.1.2. Cycles 2-6 Day 1 of each cycle
3.1.2.1. Physical examination (to include ECOG PS)
3.1.2.2. FBC
3.1.2.3. Urea and Electrolytes
3.1.2.4. Liver Function Test (LFT) (including AST, ALT, Bilirubin, alkaline phosphatase)
3.1.2.5. Toxicity assessment according to NCI CTCAE v4
3.1.2.6. Concomitant medication
3.1.3. Weeks 6, 12 and 18 while on treatment
3.1.3.1. Computed Tomography [CT] chest/abdomen/pelvis
3.2. Stage 2
3.2.1. Day 1 of each cycle 1
3.2.1.1. Physical examination to include ECOG
3.2.1.2. Full blood count
3.2.1.3. Urea and Electrolytes
3.2.1.4. Liver Function Test (LFT) (including AST, ALT, Bilirubin, alkaline phosphatase)
3.2.1.5. Optional blood for separate translational sub-study (may be obtained at any point between first and second treatments)
3.2.1.6. Toxicity assessment according to NCI CTCAE v4
3.2.1.7. Concomitant medication
3.2.2. Weeks 6, 12 and 18 while on treatment
3.2.2.1. CT chest/abdomen/pelvis
3.3. Post-Treatment
On completion of chemotherapy, patients may continue ZD4054/placebo, and will have clinical follow up assessments performed every 9 weeks to disease progression. Each follow up assessment will include assessments of disease response/progressionincluding radiological assessments, late toxicity assessment and assessment of performance status. Patients will be asked to consent to NHS Information Centre Flagging so that the date and cause of death can be collected without longer term follow up. We have adopted a more rigorous scanning schedule to ensure that our estimate of progression-free survival is accurate.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
ZD4054; carboplatin

Primary outcome measure
Progression Free Survival (PFS) (time to event) based on Response Evaluation Criteria in Solid Tumours (RECIST v1.1).
Time from enrolment to any progression and/or death. Those progression-free and alive will be censored at time of last follow-up visit.

Secondary outcome measures
1. Safety, tolerability (side effects) and feasibility of use (number of participants requiring dose delays or reductions and/or treatment withdrawal).
2. Objective response rate as assessed by RECIST v1.1.

Overall study start date
01/06/2010

Completion date
31/05/2013

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. Patients aged ≥ 18
2. Histological or cytological diagnosis of breast cancer
3. Metastatic disease
4. No more than 2 prior lines of chemotherapy treatment for metastatic breast cancer
5. Life expectancy greater than 3 months
6. Patients must have previously received or be ineligible for a taxane
7. Informed consent
8. Adequate haematological, renal and hepatic function.
9. At least one measurable lesion on Computed Tomography (CT) scanning

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
A maximum of 12 in stage 1, 126 in stage 2

Key exclusion criteria
1. Previous treatment with platinum based chemotherapy
2. Known brain or leptomeningeal metastases
3. Any co-existing medical condition that, in the investigators judgement, may substantially increase the risk associated with the patients participation in the study or potentially hamper compliance with the study protocol and follow-up schedule
4. Concomitant medication unsuitable for combination with trial medication
5. Concomitant administration of potent CYP3A inhibitors, specifically:

5.1. Protease inhibitors (atanazavir, indinavir, nelfinavir, ritonavir, saquinavir)
5.2. Macrolide antibiotics (clarithromycin, telithromycin)
5.3. Azole antifungals (ketoconazole, itraconazole, voriconazole)
5.4. Nefazodone

Date of first enrolment
01/06/2010

Date of final enrolment
31/05/2013

Locations

Countries of recruitment
Northern Ireland

United Kingdom

Study participating centre
Centre for Cancer Research and Cell Biology
Belfast
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Sponsor information

Organisation
Cardiff University (UK)

Sponsor details
Research and Commercial Division (RACD)
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CF24 ODE

Sponsor type
University/education

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
University/education

Funder Name
Cardiff University, Wales Cancer Trials Unit (WCTU) (UK)

Funder Name
Cancer Research UK (CRUK) (UK) - provide core funding for WCTU

Funder Name
Astra Zeneca (UK) - providing study drug and covering distribution costs

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration