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Vandetanib in non-cisplatin fit patients with urothelial cancers

Submission date 03/06/2009	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 20/07/2009	**Overall study status** Completed	
Last Edited 26/10/2022	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-carboplatin-gemcitabine-vandetanib-treat-advanced-transitional-cell-cancer-spread

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01191892

Secondary identifying numbers

SPON672-09

Study information

Scientific Title
A randomised phase II Trial of carboplatin and gemcitabine +/- vandetanib in first line treatment Of advanced Urothelial cell Cancer in patients who are not suitable to receive cisplatin

Acronym
TOUCAN

Study objectives
Gemcitabine and cisplatin (GP) is the only licensed chemotherapy regimen for advanced urothelial cancer; however around 40% of patients in the UK are not suitable for GP and many receive a combination of gemcitabine plus carboplatin. There are currently no trials targeting this population.

Vandetanib (ZD6474; Zactima) is an oral tyrosine kinase inhibitor selective for vascular endothelial growth factor receptor-1 (VEGFR-1), VEGFR-2, VEGFR-3 and epidermal growth factor receptor (EGFR). EGFR and VEGFRs are expressed in bladder cancer and over expression of VEGF is associated with poor outcome. Vandetanib has demonstrated additive clinical efficacy in combination with docetaxel chemotherapy in a second line phase III setting in non-small cell lung carcinoma and it has also been shown to enhance cytotoxicity when combined pre-clinically with platinum-based chemotherapy (e.g. cisplatin and carboplatin).

In this study, we hypothesize that it may be possible to increase the anti-tumour efficacy of GP by combining it with vandetanib.

Ethics approval required
Old ethics approval format

Ethics approval(s)
West of Scotland Research Ethics Committee, 02/09/2009, ref: 09/S0703/98

Study design
Multicentre 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 the contact details below to request a patient information sheet.

Health condition(s) or problem(s) studied
Locally advanced and/or metastatic transitional cell carcinoma of the urothelium

Interventions
Participants will be recruited from 20 UK centres over an 18 month period. All participants will receive 6 cycles of chemotherapy, each of 21 days. Each cycle will consist of:

Arm A - control arm:
Carboplatin (30 minutes intravenous [IV] infusion, day 1) with a dose corresponding to AUC = 4.5 using Calvert formula, gemcitabine (30 minutes IV infusion, day 1 and 8) with a dose 1000 mg /m^2 plus a placebo oral tablet once daily.

Arm B - experimental arm:
Carboplatin (30 minutes IV infusion, day 1) with a dose corresponding to AUC = 4.5 using Calvert formula; gemcitabine (30 minutes IV infusion, day 1 and 8) with a dose 1000 mg/m^2 plus 100 mg of vandetanib taken orally in tablet form once daily.

Dose modifications or discontinuation of treatment due to toxicity will be implemented according to the NCI CTCAE v3.0.

The following trial assessment will be performed:
Baseline (inclusive of eligibility screening collected after patient consent)
1. Computerised axial tomography (CT) scan of chest, abdomen and pelvis
2. Physical examination including height, weight and blood pressure
3. Estimation of glomerular filtration rate (GFR) by Cockcroft and Gault calculation, or measured, or isotope clearance (in accordance with local practice)
4. Serum biochemistry including renal, liver, and bone profiles, serum magnesium, serum albumin, plasma glucose and lactate dehydrogenase (LDH)
5. ECOG performance status
6. Electrocardiogram (ECG)
7. Haematology including full blood count and clotting
8. Toxicity assessment
9. Pregnancy test (only for females of child bearing potential)
10. Medical history
11. Optional blood, urine and tissue sample for separate translational sub-study to be collected before treatment

Day 1 (within 3 days prior to treatment) of each 21 day cycle
1. Physical examination to include ECOG
2. Concomitant medication
3. Full blood count (FBC)
4. Urea and electrolytes
5. ECG
6. Liver function test (LFT)
7. Serum biochemistry
8. Toxicity assessment
9. Optional blood, urine and tissue sample for separate translational sub-study (may be obtained at any point between consent and first treatment)

Day 8 (with 1 day prior to treatment) of each 21 day cycle
1. FBC
2. Concomitant medication
3. Toxicity assessment

Between cycle 3 day 14 and cycle 4 day 1
CT abdomen and pelvis, CT or x-ray of chest

Cycle 6 day 14 - 28
CT abdomen and pelvis, CT or x-ray of chest

Weeks 26, 39 and 52 (+/-14 days) (if no prior progression)
1. ECOG performance status
2. Disease evaluation including CT abdomen and pelvis and CT or x-ray of chest as appropriate
3. Late toxicity assessment
4. Optional translational blood and urine samples (weeks 26 and 52 only)

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Carboplatin, gemcitabine, vandetanib

Primary outcome measure
Progression-free survival (PFS) at 26 weeks based on RECIST v1.1

Secondary outcome measures
1. PFS (time-to-event). Time from enrolment to any progression (based on RECIST v1.1) and/or death. Those progression-free and alive will be censored at time last seen
2. Tolerability (side effects) and feasibility of use (number of participants requiring dose delays or reductions and/or treatment withdrawal)
3. Objective response rate as assessed by RECIST v1.1
4. Overall survival (OS). Time from enrolment to death. Those still alive will be censored at time last seen.
5. Change of sum of measurable lesions 9 weeks after start of chemotherapy (using Waterfall plots) (measurements according to RECIST v1.1)
6. Toxicity, during and after treatment using NCI CTCAE v4.0. Serious adverse events (SAEs) will be collected in real time. N.B. NCI CTCAE v3.0

Overall study start date
01/09/2009

Completion date
05/09/2016

Eligibility

Key inclusion criteria

1. Male or female
2. Aged greater than or equal to 16 years
3. Histologically confirmed transitional cell carcinoma (pure or mixed histology) of urothelium (upper or lower urinary tract). Cancers with other pathologies are permitted, provided that the dominant morphology is transitional cell carcinoma.
4. Radiologically measurable (Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), locally advanced/and/or metastatic disease not amenable to curative treatment with surgery or radiotherapy not suitable for cisplatin, defined as one or more of the following:
4.1. Creatinine clearance less than 60 ml/min estimated by Cockcroft and Gault formula or measured by 24-hour urine collection or isotope clearance (N.B. patients are excluded if creatinine clearance is less than 30 ml/min)
4.2. Eastern Cooperative Oncology Group (ECOG) performance status 2. N.B. patients are excluded if PS is 3 or worse.
4.3. Clinically significant ischaemic heart disease (myocardial infarction [MI] or unstable angina 3 - 12 months prior to date of randomisation, or symptomatic angina 0 - 3 months prior to date of randomisation). N.B. See section 4 of exclusion criteria.
4.4. Prior intolerance of cisplatin
4.5. Aged greater than 75 years
4.6. Any other factor, which, in the opinion of the investigator indicates that cisplatin is not suitable for this patient
5. The patient has provided written informed consent

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
102

Total final enrolment
82

Key exclusion criteria
1. Laboratory results rendering the patient unsuitable for trial treatment:
1.1. Serum bilirubin greater than 1.5 x the upper limit of reference range (ULRR)
1.2. Creatinine clearance less than or equal to 30 ml/min (calculated by Cockcroft-Gault formula)
1.3. Potassium, less than 4.0 mmol/L despite supplementation; or above the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) grade 1 upper limit
1.4. Magnesium below the normal range despite supplementation, or above the NCI CTCAE grade 1 upper limit
1.5. Serum calcium above the NCI CTCAE grade 1 upper limit. In cases where the serum calcium is below the normal range, the calcium adjusted for albumin is to be obtained and substituted for the measured serum value. Exclusion is to then be based on the adjusted for albumin values falling below the normal limit.
1.6. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2.5 times ULRR or alkaline phosphatase (ALP) greater than 2.5 x ULRR, or greater than 5 times ULRR if

judged by the investigator to be related to liver metastases
2. Evidence of severe or uncontrolled systemic disease or any concurrent condition which in the investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol
3. PS (ECOG) 3 or worse
4. Clinically significant cardiovascular event (e.g., myocardial infarction, superior vena cava syndrome (SVC), New York Heart Association (NYHA) classification of heart disease greater than or equal to 2 within 3 months before entry; or presence of cardiac disease that, in the opinion of the investigator, increases the risk of ventricular arrhythmia bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) which is symptomatic or requires treatment (NCI CTCAE grade 3) or asymptomatic sustained ventricular tachycardia. Atrial fibrillation, controlled on medication is not exclusionary.
5. QTc prolongation with other medications that required discontinuation of that medication
6. Congenital long QT syndrome, or first degree relative with unexplained sudden death under 40 years of age
7. Presence of left bundle branch block (LBBB)
8. QTc with Bazett's correction that is unmeasurable, or greater than or equal 480 msec on screening electrocardiogram (ECG). (Note: If a subject has a QTc interval greater than or equal to 480 msec on screening ECG, the screen ECG may be repeated twice [at least 24 hours apart]. The average QTc from the three screening ECGs must be less than 480 msec in order for the subject to be eligible for the study.) Patients who are receiving a drug that has a risk of QTc prolongation are excluded if QTc is greater than or equal to 460 msec.
9. Concomitant medication which has known adverse interaction with vandetanib, including:
9.1. Any medication that may cause QTc prolongation or induce Torsades de Pointes
9.2. Potent inducers of CYP3A4 function (e.g. rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital and St. John's Wort)
10. Hypertension not controlled by medical therapy (systolic blood pressure greater than 160 mmHg or diastolic blood pressure greater than 100 mmHg)
11. Currently active diarrhoea that may affect the ability of the patient to absorb the vandetanib or tolerate diarrhoea
12. Women who are currently pregnant or breast feeding. (Women of child bearing potential must have a negative urine or serum pregnancy test within 7 days prior to the start of trial therapy.)
13. Patients who are not prepared to practice method(s) of birth control of established efficacy
14. Previous or current malignancies of other histologies within the last 5 years, with the exception of cervical carcinoma in situ, adequately treated basal cell or squamous cell carcinoma of the skin and prostate cancer
15. Receipt of any investigational agents within 30 days prior to commencing study treatment
16. Major surgery within 4 weeks before starting study therapy
17. Prior chemotherapy (unless delivered perioperatively and completed greater than 12 months prior to first presentation of recurrent disease)

Date of first enrolment
20/07/2010

Date of final enrolment
16/12/2014

Locations

Countries of recruitment

Scotland

United Kingdom

Study participating centre
Beatson West of Scotland Cancer Centre
Glasgow
United Kingdom
G120YN

Study participating centre
20 other recruiting centres
United Kingdom
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Sponsor information

Organisation
Cardiff University (UK)

Sponsor details
Research and Commercial Division (RACD)
7th Floor
30-36 Newport Road
Cardiff
Wales
United Kingdom
CF24 ODE

Sponsor type
University/education

Website
http://www.cf.ac.uk/racdv/index.html

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Charity

Funder Name
AstraZeneca (UK) - provided vandetanib and its distribution costs free-of-charge, as an educational grant (subject to contract)

Funder Name
Cancer Research UK (CRUK) (UK) - WCTU is core funded by CRUK. WCTU core resources will be used to support this trial.

Results and Publications

Publication and dissemination plan
Single final paper will be submitted for publicationi in peer-reviewed journal.
Participant data will be made available on request: a specific request for release data form needs to be filled in and signed by applicant, data custodian, TSC chair, and sponsor.

Intention to publish date

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results	results	10/01/2016	16/04/2019	No	No
Plain English results			26/10/2022	No	Yes
HRA research summary			28/06/2023	No	No