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Trial of temsirolimus for advanced urothelial cancer

Submission date 11/03/2008	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 25/04/2008	**Overall study status** Completed	
Last Edited 16/01/2025	**Condition category** Cancer	

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

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2007-007615-82

ClinicalTrials.gov (NCT)
NCT01090466

Protocol serial number
SPON 417-07; C7838/A9346

Study information

Scientific Title
A phase I/II single-arm trial to evaluate the combination of cisplatin and gemcitabine with the mTOR inhibitor temsirolimus for first-line treatment of patients with advanced transitional carcinoma of the urothelium

Acronym
TOTEM

Study objectives
The prognosis for patients with advanced urothelial cancer (predominantly bladder) is poor and approximately 4,700 patients in the United Kingdom (UK) die each year from the disease. Approximately 50% of patients who are fit enough to undergo cisplatin-based chemotherapy will respond to treatment. Median progression-free survival for such patients is approximately 8 months and median overall survival 14 months. Despite a recent increase in our understanding of the molecular basis of bladder cancer, there have been few clinical studies using molecularly-targeted compounds in advanced urothelial cancer.

Temsirolimus (Torisel®) is a treatment which prevents the growth of tumours and has recently been demonstrated to improve survival in advanced renal cancer. Further studies suggest that temsirolimus may also have activity against urothelial cancer.

This trial will assess whether adding temsirolimus to the standard cisplatin/gemcitabine based chemotherapy in the treatment of advanced urothelial cancer is safe and effective and improves outcome of patients with advanced urothelial disease.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 16/09/2009, Research Ethics Committee for Wales (Churchill House, Fourth Floor, 17 Churchill Way, Cardiff, CF10 2TW, United Kingdom; +44 (0)29 2037 6829; corinne.scott@bsc.wales.nhs.uk), ref: 09/MRE09/30

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

Study design
Early phase I/II single-arm non-randomised open-label multicentre trial

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions

Patients will be recruited over approximately 18 months. All patients will receive a maximum of six 21-day cycles of cisplatin and gemcitabine chemotherapy in combination with temsirolimus. All three drugs will be administered intravenously.

The starting doses of cisplatin and gemcitabine will be fixed (70 mg/m^2, day one and 1000 mg /m^2 days one and eight, respectively); the optimum dose for temsirolimus will be determined in the phase I stage of the trial by dose-escalation in successive cohorts of three to six patients, until the maximum tolerated dose (MTD) is met. Intra-patient dose escalation will not be permitted. The recommended phase II dose will then be given to an expanded group of patients in the phase II stage.

A maximum of 18 patients will participate in phase I. In phase II, additional patients will be treated up to a total of 63 evaluable patients. Three or six patients treated at the MTD in phase I will be included in this total. The maximum number of patients that will be treated in the entire trial is therefore 78 patients.

Assessments will be performed at baseline, at specified times during trial treatment, and at 6 and 12 months from date of enrolment, as per timelines specified in the trial protocol, and including:

1. Diagnostic biopsy (in absence of previous histological diagnosis only)
2. Cross-sectional imaging (CT scan of chest, abdomen and pelvis)
3. Physical exam (including height and weight)
4. WHO performance status
5. Haematology (including full blood count and blood clotting)
6. Biochemical profile (including renal, liver, bone profile, serum magnesium, human chorionic gonadotropin [hCG], glucose and lactate dehydrogenase)
7. Serum triglycerides and cholesterol
8. Isotopic estimation and calculated GFR
9. Isotope bone scintigram (if clinically relevant)
10. Electrocardiogram
11. Plain film chest x-ray
12. Toxicity and late toxicity*
13. Pregnancy test (females of child bearing potential only)
14. Optional blood samples**

* Assessment of toxicity will be performed during and at the end of each cycle, but the safety assessment period for dose limiting toxicities (DLTs) in the phase I stage of the trial will be until the commencement of cycle two or (if only one cycle is given) 36 days.

** Additional blood samples will be requested for pharmacokinetic, pharmacodynamic and translational studies for patients participating in the optional translational sub-study. Permission will also be sought to retrospectively analyse sections of previous histological specimens. Analyses will be performed as part of a future translational study that will be submitted for separate funding and addressed by separate questions on the patient consent form.

Disease response/progression and performance status will be assessed by cross-sectional imaging at baseline, after cycle three of treatment (week 9) and 6 and 12 months after date of enrolment. If results confirm sufficient activity of the three-drug chemotherapy, the combination treatment will be taken forward into a randomised phase III setting.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Temsirolimus (Torisel®), cisplatin, gemcitabine

Primary outcome(s)
Phase I:
1. Safety: dose-limiting toxicities and maximum tolerated dose (MTD)
2. Determination of recommended dose for phase II

Phase II:
Activity: progression-free survival at six months after date of enrolment.

Key secondary outcome(s))
Phase II:
1. Tolerability and feasibility of use: determined as the number of patients requiring dose delays or reduction and/or treatment withdrawal and will be determined at the end of phase I if the trial does not progress to phase I, otherwise after all patients have completed phase II treatment
2. Objective response rate: determined relative to baseline prior to treatment cycle four (week nine) and at 6 and 12 months from date of completion of treatment
3. Progression-free-survival, time-to-event: calculated as the time from enrolment to any disease progression and/or death patients after all patients have completed at least six months follow-up. Where there is no evidence of progression, patients will be censored at the date last seen.
4. Overall survival: calculated at the end of the study duration (2.5 years) based on the time of enrolment to date of death or date censored (date last known to be alive)
5. Toxicity, during and after treatment: measured at baseline (less than or equal to one week before treatment) and every 21 days whilst on treatment to coincide with the beginning of each new treatment cycle. Late toxicity will be measured at the end of treatment, and at 6 and 12 months from date of enrolment. Serious adverse events (SAEs) will be collected in real time.

Completion date
15/03/2017

Eligibility

Key inclusion criteria
1. Aged greater than or equal to 18 years, either sex
2. Histologically confirmed transitional cell carcinoma (pure or mixed histology) of urothelium (upper or lower urinary tract)
3. Radiologically evaluable locally advanced and/or metastatic disease (T4b Nany Many, Tany N2-3 Many or Tany Nany M1)
4. Not amenable to curative treatment with surgery or radiotherapy. Patients enrolled in the phase II stage of the trial must have radiologically measurable disease
5. Estimated life expectancy greater than three months
6. World Health Organization (WHO) performance status 0 - 2
7. Fit to receive cisplatin-containing combination chemotherapy
8. No prior systemic therapy for locally advanced or metastatic disease - patients who have

received prior neoadjuvant or adjuvant chemotherapy for urothelial cancer (up to four cycles), completed at least six months prior to first documented disease progression will remain eligible)
9. No prior radiotherapy within one month prior to registration or involving more than 30% of total bone marrow volume
10. No investigational drug within one month prior to registration
11. Adequate renal function (glomerular filtration rate [GFR] greater than 60 ml/min, uncorrected for surface area and measured by isotopic means)
12. Adequate bone marrow function (absolute neutrophil count greater than or equal to 1.5 x 10^9/l; platelets greater than or equal to 100 x 10^9/l at baseline)
13. Adequate liver function (bilirubin less than or equal to 1.5 x upper limit of normal [ULN]; alanine aminotransferase [ALT] and alkaline phosphatase [ALP] less than or equal to 2.5 ULN at baseline)
14. Prothrombin time (PT) or International normalised ratio (INR) less than or equal to 1.5 x ULN
15. Written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
15

Key exclusion criteria
1. Considered with a view to possible cure
2. Previous malignancy other than non-melanoma skin cancer, cervical carcinoma in situ or incidental localised prostate cancer
3. Previously-identified central nervous system (CNS) metastases - routine baseline computed tomography (CT) scanning of the head is not a requirement for trial entry and should only be performed if clinically indicated
4. Women who are pregnant or breast feeding. Woman of childbearing potential must have a negative pregnancy test performed within seven days prior to the start of trial therapy.
5. Men and women not prepared to practice method(s) of birth control of established efficacy
6. Known infection with human immunodeficiency virus (HIV) or chronic hepatitis B or C
7. Uncontrolled hypertension
8. Symptomatic coronary artery disease, myocardial infarction within the last six months, congestive cardiac failure greater than New York Heart Association (NYHA) class II, uncontrolled or symptomatic cardiac arrhythmia
9. Clinically significant bacterial or fungal infection
10. Concurrent anticoagulant therapy with warfarin or un-fractionated heparin - patients requiring anti-coagulation may be entered after successful conversion to low molecular weight

heparin (LMWH)
11. Concomitant medication which have adverse interactions with temsirolimus

Date of first enrolment
01/07/2008

Date of final enrolment
31/08/2015

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St. James's University Hospital
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Sponsor information

Organisation
Cardiff University (UK)

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (CRUK) (UK) (ref: C7838/A9346) - grant funded by the Feasibility Study Committee (FSC)

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Wyeth Pharmaceuticals (UK) - provided temsirolimus and its distribution costs free-of-charge (subject to contract)

Funder Name
The Wales Cancer Trials Unit (WCTU) is core funded by CRUK and WCTU core resources will be used to support this trial.

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results	abstract	20/05/2016		No	No
Basic results			20/05/2019	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes