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ImmuniCell® in patients with advanced cancers

Submission date 20/01/2016	**Recruitment status** Stopped	[ ] Prospectively registered [ ] Protocol
Registration date 03/02/2016	**Overall study status** Stopped	[ ] Statistical analysis plan [ ] Results
Last Edited 15/01/2019	**Condition category** Cancer	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-gamma-delta-t-cells-for-advanced-melanoma-renal-cell-kidney-cancer-or-non-small-cell-lung-cancer

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2015-000402-19

IRAS number

ClinicalTrials.gov number
NCT02459067

Secondary identifying numbers
TCB-101-001

Study information

Scientific Title
Adaptive study of the safety, tolerability & efficacy of autologous γδ T lymphocyte therapy (ImmuniCell®) in patients with advanced cancers refractory to current treatment or have indolent disease for which immunotherapy may be beneficial

Study objectives
To determine the safety, tolerability, maximum tolerated dose (MTD) and efficacy of ImmuniCell® in patients with melanoma, renal cell cancer (RCC) or non-small cell lung cancer (NSCLC). The study is an adaptive design that has 3 stages:
1. Stage 1 - dose escalation
2. Stage 2 - efficacy
3. Stage 3 - confirm efficacy in one of the tumor types

Ethics approval required
Old ethics approval format

Ethics approval(s)
Scottish A Research Ethics Committee, 06/12/2015, ref: 15-SS-0150

Study design
Interventional non-randomized study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format or downloadable format

Health condition(s) or problem(s) studied
Non small-cell lung cancer, renal cell carcinoma and malignant melanoma

Interventions
Stage 1: The study will adopt an intra-patient dose escalation stage to define the maximum tolerated dose (MTD) for future stages of the study using the 3+3 design, that is 3 patients will initially be enrolled and treated as follows:
1. Patient 1 will receive their first dose
2. Patient 2 will receive their first dose after patient 1 completes the first cycle without any dose limiting toxicities (DLTs) or unresolved grade 2 serious adverse event (SAE) which lasts more

than 7 days between cycle/dose
3. Patient 3 will receive their first dose after patient 2 completes the first cycle without any DLTs or unresolved grade 2 SAE which lasts more than 7 days between cycle/dose
Should any one patient experience a DLT at any dose, and additional cohort of 3 patients will be enrolled at that dose, then if 1 out of 6 has a DLT then MTD has been achieved.
If 2 out of 3 patients at any dose have a DLT, escalation will stop and an additional 3 patients will be treated at the previous dose level
If 10 x 109 is reached and no DLTs, that will be MTD.
(Added 29/01/2018: Stage 1 complete).

Stage 2 will explore efficacy in the 3 tumour types:

Patients will have CT scans every 6 weeks over the course of the study to assess their disease. Overall response is assessed using the immune-related response criteria (irRC):
The overall response according to the irRC will be derived from time-point response assessments (based on tumour burden) as follows:
1. irCR: complete disappearance of all lesions (whether measurable or not, and no new lesions) - confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented
2. irPR: decrease in tumour burden ≥50% relative to baseline - confirmed by a consecutive assessment at least 4 weeks after first documentation
3. irSD: not meeting criteria for irCR or irPR, in absence of irPD
4. irPD: increase in tumour burden ≥25% relative to nadir (minimum recorded tumour burden) - confirmation by a repeat, consecutive assessment no less than 4 weeks from the date first documented.
5.The investigator will assess the overall response rate (ORR) (CR and PR) at each tumour time point assessment. However, the primary assessment of ORR will be as adjudicated by the IRRP.
6. The Disease Control rate (CR, PR or SD) and total tumour burden will also be calculated at each tumour time point assessment.

T lymphocyte proliferation assay: 14 days prior to patient enrolment into the trial, proliferative capacity screening will be performed by TC BioPharm. 10ml of whole blood will yield 1-5x107 PBMC's of which 0.5-5% of the leukocyte population will be γδ T lymphocytes. To assess proliferative capacity of the γδ T lymphocyte population, an immunophenotypic assay using the panel of antibodies below will be measured using the BD Accuri C6 flow cytometer. A minimum of 5 x105 PBMC's are required. The PBMC's will be stained with antibodies to CD45-PE, CD3-APC and anti-TCR Vγ9-FITC. The percentage of γδ T lymphocyte will be measured after PBMC isolation to determine the initial percentage of γδ T lymphocytes within the starting sample. PBMC's will be grown in culture for 48-96 hours and immunophenotyping performed using the above antibodies. The increase of γδ T lymphocytes will be measured to determine the proliferative capacity of the γδ T lymphocytes. Acceptance criteria will be set at a population doubling of γδ T lymphocytes ≥ 1.0 between 48-96 hours in culture.

Immune response assessment: Blood samples (10ml in sodium citrate tubes) will be collected for the analysis of an effect of ImmuniCell® in boosting the immune system – an indication that cytokine levels are increased and that the γδ T lymphocytes are of effector memory phenotype capable of tumour cell killing. Phenotypic analysis will be conducted at baseline and at the end of each treatment cycle by flow cytometry to measure the proportion of γδ T lymphocytes in the total T-cell population and the proportion of γδ T lymphocytes of the effector memory phenotype (CD45RA- CD27-). TNF-α, IFN-γ and IL-2 will be measured by ELISA assay at baseline and at the end of each treatment cycle as a measure of up-regulation of the immune system elicited by ImmuniCell® infusion.

miRNA profiling: miRNA levels in plasma will be measured with the aim of identifying an miRNA profile which can be used as a biomarker of clinical response to treatment. Blood samples (10ml in EDTA tubes) will be taken at baseline and at the end of each treatment cycle and centrifuged immediately to separate the plasma. The blood samples will be processed at the study site in order to isolate high quality plasma samples essential for miRNA analysis, ideally processing will commence within 1 hour of blood draw. Briefly, tubes containing freshly drawn blood will be centrifuged at 1200g for 15mins to separate the plasma from the cellular components. Following centrifugation, the top (plasma-containing) layer will be removed, taking care not to disturb the lower (cell containing) layers. The plasma will be transferred to a clean 15ml tube and mixed gently by inversion. The plasma will then be pipetted into 1ml aliquots in 4-5 cryovials as appropriate and immediately frozen at -15oC to -25oC. Plasma samples will transported to TC BioPharm, for the analysis of miRNA profiles by PCR.

Stage 3 will confirm the efficacy results.

Intervention Type
Biological/Vaccine

Primary outcome measure
Stage 1
1. Proportion of patients with DLTs. Dose limiting toxicity will be assessed after each treatment with ImmuniCell and since a toxicity can occur at any time, patients will be advised to report any changes to the site staff immediately. In addition, blood samples will be analysed at screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48; vital signs (heart rate, blood pressure, temperature, height & weight) will be measured at screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48; an ECG will be performed at screening, before the first infusion, the day after the first infusion, week 2, week 4, week 6, week 8, week 10 and week 12; and a clinical examination will be performed screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48.
2. Number, type and severity of AEs and SAEs and their relationship to treatment. Adverse events (untoward medical event) and serious adverse events will be assessed on an ongoing basis throughout the trial. In addition, patients will be asked at every trial visit if there has been any medical event since their previous visit. In addition, blood samples will be analysed at screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48; vital signs (heart rate, blood pressure, temperature, height & weight) will be measured at screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48; an ECG will be performed at screening, before the first infusion, the day after the first infusion, week 2, week 4, week 6, week 8, week 10 and week 12; and a clinical examination will be performed screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48.
3. Full blood count and clinical chemistry (FBC, U&Es, LFTs, LDH). Blood samples will be analysed at screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48.

Stage 2
1. Tumour response (CR or PR) by irRC. Tumour measurements will be assessed during screening then again every 6 weeks for a year by CT scan (or MRI or PET scan).
2. Number, type and severity of AEs and SAEs and their relationship to treatment. Adverse events (untoward medical event) and serious adverse events will be assessed on an ongoing basis throughout the trial. In addition, patients will be asked at every trial visit if there has been

any medical event since their previous visit. In addition, blood samples will be analysed at screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48; vital signs (heart rate, blood pressure, temperature, height & weight) will be measured at screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48; an ECG will be performed at screening, before the first infusion, the day after the first infusion, week 2, week 4, week 6, week 8, week 10 and week 12; and a clinical examination will be performed screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48.
3. Full blood count and clinical chemistry (FBC, U&Es, LFTs, LDH). Blood samples will be analysed at screening, before the first infusion, the day after the first infusion, weekly for 12 weeks, then at week 16, 18, 24, 36 and 48

Stage 3
To be decided upon completion and outcome of stage 2 by Data Review Committee

Secondary outcome measures

Stage 1
1. Progression Free Survival. This is assessed from the tumour measurements every 6 weeks and is the length of time during and after treatment that a patient lives with the disease and the tumour does not increase in size
2. Overall Survival. This the length of time from the start of treatment that the patient is still alive and is assessed from a date of death, should it occur during the study or in the follow up every 3 months (and all patients will be followed until death)
3. DC (CR, PR or SD) and total tumour burden by irRC. These are all outcomes from the tumour measurements and are assessed every 6 weeks – complete response means the tumour has disappeared, PR means the tumour has decreased in size and SD means the tumour has stabilised and not changed in size.

Stage 2
1. Disease Control rate (CR, PR or SD) and total tumour burden by irRC. These are all outcomes from the tumour measurements and are assessed every 6 weeks – complete response means the tumour has disappeared, PR means the tumour has decreased in size and SD means the tumour has stabilised and not changed in size.
2. Changes in peripheral T lymphocyte counts, phenotype and markers of immune response (IFN-γ, TNF-α and IL-2) before the first and subsequent ImmuniCell® infusions. These are assessed by blood samples taken day 1, weeks 2, 4, 6, 8 10 and 12 after treatment (treatment is administered on day 0, weeks 2, 4, 6, 8 and 10).
3. Progression free survival up to 12 months from start of treatment. This is assessed from the tumour measurements every 6 weeks and is the length of time during and after treatment that a patient lives with the disease and the tumour does not increase in size, and the cut off time is 12 months.
4. 12-month overall survival. This the length of time from the start of treatment that the patient is still alive until 12 months after the start of treatment
5. Overall survival. This the length of time from the start of treatment that the patient is still alive and is assessed from a date of death, should it occur during the study or in the follow up every 3 months (and all patients will be followed until death).
6. MicroRNA (miRNA) profiling in plasma pre- and post-ImmuniCell® treatment. This is assessed from blood samples taken at Day 1, weeks 2, 4, 6, 8 and 10.

Stage 3
To be decided after stage 2

Overall study start date
04/12/2015

Completion date
31/07/2019

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. Male or female patients aged ≥18 years
2. Performance status ECOG 0 or 1
3. Subjects with histological or cytological confirmation of advanced metastatic melanoma, renal cell carcinoma or NSCLC which are refractory to current standard treatments or who have indolent disease for which immunotherapy may be beneficial
4. Measurable disease according to the irRC criteria
5. Adequate bone marrow, liver and renal function as assessed by the following laboratory requirements to be conducted <2 weeks prior to Cycle 1:
5.1. Creatinine ≤ 1.5 x upper limit of normal (ULN) OR a calculated creatinine clearance ≥ 50 ml /min
5.2. Total bilirubin ≤ 1.5 x ULN
5.3. Alanine transaminase (ALT) and aspartate transaminase (AST) ≤ 2.5 x ULN or ≤ 5 x ULN with liver metastases
5.4. White blood cell count ≥3.0 x 109/L
5.5. Absolute Neutrophil Count (ANC) ≥1.5 x 109/L
5.6. Platelets ≥100 x 109/L
5.7. Haemoglobin ≥ 10 g/dL
6. Life expectancy of at least 3 months
7. Sufficient evidence of γδ T lymphocytes expansion in the proliferation assay at the first screening visit which will be a population doubling of γδ T lymphocytes ≥ 1.0 between 48-96 hours in culture.
8. Able to give informed, written consent
9. For female patients and female partners of male patients: must be surgically sterile, postmenopausal, or compliant with two forms of contraception (one of which must be a barrier method) during and for 6 months after the treatment period; female patients must have a negative urine pregnancy test at screening and must not be breastfeeding.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
48

Key exclusion criteria
1. Other primary cancers apart from non-melanoma skin cancers, carcinoma – in situ of the cervix, or a prior cancer treated with curative intent more than 5 years ago without any evidence or recurrent disease
2. Uncontrolled systemic infection
3. Systemic steroid therapy or other immunosuppressant's
4. Treatment with bisphosphonates, for instance zoledronate, in the previous 30 days or throughout the trial
5. New York Heart Association (NYHA) functional class ≥3 (Appendix 4) or myocardial infarction within 6 months
6. Clinically significant uncontrolled cardiac arrhythmia other than asymptomatic atrial fibrillation not requiring therapy
7. Ulcerative Colitis / Inflammatory bowel disease, Addison's disease
8. Pregnancy or lactation prior to or during the trial. A urine or serum pregnancy test will be carried out at screening
9. Taking any other IMP or participation in another interventional clinical trial in the previous 30 days
10. Less than 4 weeks since systemic anti-cancer therapy (tyrosine kinase inhibitors, chemotherapy, immunotherapy, hormonal therapy, radiotherapy) and more than 6 weeks since mitomycin C and nitrosureas
11. Substance abuse, medical, psychological or social conditions that may interfere with the subject's participation in the trial or evaluation of the trial results
12. Any other condition considered by a trial physician to be inappropriate for inclusion.
13. Coagulation disorders - Contraindications should also be taken into consideration during the Leukapheresis procedure these include, contraindications to heparin which are: significant thrombocytopenia (platelet count less than 50x109/litre); recent cerebral haemorrhage; peptic ulcer; recent surgery to eye or nervous system; hypersensitivity to heparin; past history of Type II heparin induced thrombocytopenia; past history of significant spontaneous haemorrhage; known haemophilia or other bleeding disorder.

Date of first enrolment
10/12/2015

Date of final enrolment
04/12/2018

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
Beatson West of Scotland Cancer Centre
Level 0
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
University Hospital Southampton NHS Foundation Trust
Somers Cancer Research Building
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Edinburgh Cancer Centre
Western General Hospital
Edinburgh
Edinburgh
United Kingdom
EH4 2XU

Study participating centre
St James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
UCLH
Clinical Research Facility
170 Tottenham Court Road
London
United Kingdom
W1T 7HA

Study participating centre

Velindre Cancer Centre
Clinical Trials Unit
Whitchurch
Cardiff
United Kingdom
CF14 2TL

Study participating centre
Churchill Hospital
Early Phase Clinical Trials Unit
Department of Oncology
Old Road
Oxford
United Kingdom
OX3 7LE

Sponsor information

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Sponsor type
Industry

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ROR
https://ror.org/00kt5rm23

Funder(s)

Funder type

Industry

Funder Name
TC BioPharm

Results and Publications

Publication and dissemination plan
It is planned to present the study results at international conferences (e.g. ASCO and ESMO) and publish in a peer reviewed oncology journal. Preliminary results will be published in 2019 (safety) followed by the complete study results.

Intention to publish date
31/12/2019

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Data sharing statement to be made available at a later date