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A randomised trial of daratumumab to remove myeloma cells from blood stem cells before an autograft for patients with multiple myeloma

Submission date
06/01/2021

Recruitment status
Stopped

Registration date
07/01/2021

Overall study status
Stopped

Last Edited
04/01/2023

Condition category
Cancer

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Despite the introduction of new drugs for the treatment of multiple myeloma (MM), autologous stem cell transplant (ASCT) is still considered the best therapy for a large proportion of all MM patients. Unfortunately, the disease comes back (relapses) in the majority of patients who undergo an SCT due to residual plasma cells (myeloma cells) either in the blood stem cells collected during the separation of cells in preparation for the transplant, or remaining in the bone marrow despite all treatments. Patients will commonly receive stem cells that are contaminated with myeloma cells which can reduce the effect of chemotherapy in destroying the myeloma cells pre-transplant. A few studies have investigated strategies to obtain purified stem cell collections in the past, but due to limitations and the poor quality pre-transplant response these approaches have been ineffective. The goal of this trial is to see if the addition of the drug daratumumab to the stem cell collection process and the stem cell transplant can reduce the level of myeloma cells present in the bone marrow 100 days after the transplant and lead to improved long-term outcomes for MM patients.

Who can participate?
Anyone who has newly diagnosed multiple myeloma with a greater than or equal to partial response following induction therapy and is considered suitable to undergo a stem cell transplant.

What does the study involve?
The study involves you undergoing an autologous stem cell transplant which can help your disease stay away for longer. Autologous means something, in this case cells, that have come from you rather than someone else.
You will undergo induction therapy after which you will undergo the transplant that is done in 4 parts:
1. Mobilisation – treatment is given to encourage stem cells to move from the bone marrow (where they normally live) and into the blood. There are a few different types of treatment that can be used for this; at your transplant centre it is usually cyclophosphamide and G-CSF (explained in more detail below).

2. Collection (sometimes called harvest) – healthy stem cells are filtered from the blood and stored.
3. Chemotherapy - a high dose of chemotherapy, called melphalan, is given.
4. Transplant – the previously collected stem cells are given back to you by a drip.
In this trial you will undergo the same stages but with the addition of a drug called Daratumumab during the mobilisation and chemotherapy stages. You will be carefully followed up throughput the study.

What are the possible benefits and risks of participating?
The treatment the patients will receive is the gold standard myeloma treatment which they would receive whether they are on the trial or not with the addition of the fully licensed drug dartumumab. The risks of these therapies have been individually reviewed and considered to be safe and the addition of the two would pose a minimal risk to the patients in the study. This study has been discussed at the NCRI myeloma subgroup (UK Myeloma Research Alliance; UKMRA) who agreed with this assessment.
There will be an early safety review to minimise any possible risk that daratumumab might have. Treatment with a stem cell transplant is known to be a good way of reducing the amount of myeloma left in the body after chemotherapy and keeping the disease away for longer before treatment is needed again. All patients in the IPANEMA study will receive a transplant. There is a 1 in 2 chance that a patient will be receiving the additional treatment daratumumab, which may be able to improve transplant. However, it is very important to realise that this is not yet known and the aim of this study is to test whether this is true.

Where is the study run from?
The study is run from the Cancer Research Clinical Trials Unit at the University Of Birmingham (UK)

When is the study starting and how long is it expected to run for?
November 2020 to November 2031

Who is funding the study?
Leukaemia UK

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-002147-20

Integrated Research Application System (IRAS)
271709

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 46959, IRAS 271709

Study information

Scientific Title
A randomised, open-label, multicentre, phase III trial of in vivo purging with anti-CD38 (daratumumab) to enhance myeloma autografting

Acronym
IPANEMA

Study objectives
The principal objective is to determine the percentage of patients achieving minimal residual disease (MRD) negativity on bone marrow (BM) at day 100 post-transplant.

The secondary objectives are:
1. To compare safety and toxicity of the addition of daratumumab to the peripheral blood stem cell (PBSC) harvest and autologous stem cell transplant (ASCT) with the control arm
2. To assess the proportion of patients in each arm achieving a greater or equal to 10-fold reduction in disease burden comparing pre-ASCT bone marrow (BM) aspirate and day 100 post-ASCT BM aspirate; to compare progression-free survival (PFS) and PFS-2 (the time from randomization to progression on first subsequent therapy) between the two arms
3. To compare overall survival (OS) between the two arms
4. To measure the effect of anti-CD38

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 27/11/2020, South Central – Hampshire B Research Ethics Committee (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8290; hampshireb.rec@hra.nhs.uk), ref: 20/SC/0341

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Newly diagnosed multiple myeloma

Interventions
A randomised phase III trial has been chosen in order to compare the difference in the proportion of patients who achieve myeloma cell negativity in their day 100 post-transplant bone aspirate and other key secondary objectives between the two treatment arms in an unbiased manner.

ASCT remains the optimal therapy for eligible patients with newly diagnosed multiple myeloma (MM), improving complete response rates and uplifting PFS. However, the majority of patients will relapse and this may arise from contaminating MM cells in the graft, or from residual disease in the bone marrow. Several strategies for harvesting 'clean' grafts have been examined but technical limitations, toxicity and poor disease responses have hindered progress. The availability of a minimally toxic anti-MM monoclonal antibody provides two exciting opportunities to reduce graft contamination and to augment both mobilisation of cells and ASCT targeting residual marrow disease. The experimental arm selected for this study has been based on the use of one such monoclonal antibody.

Up to 22 hospitals have been invited to participate in this trial. Patients who have MM, achieved at least partial remission following induction treatment and have received only first-line induction therapy and meet the disease-specific entry criteria for MM will be invited to participate.

All patients have the opportunity to discuss transplantation and its long-term implications as part of their normal consent process to undergo an NHS clinical procedure. If it is appropriate, investigators will discuss the trial with the patients. Patients will be given time to consider the implications of the trial and if they would like to participate, they will return to sign the consent form and undergo the relevant screening procedure.

As part of their routine care, patients must undergo screening tests prior to transplantation in order to assess overall health and organ function and ensure that they are suitable to undergo the high-risk procedure of transplantation. These tests are conducted as part of routine transplant work-up care and are not required as part of the trial protocol.

A number of trial-specific assessments will be performed as part of the screening process. This includes a pregnancy test for women of childbearing potential, assessment of medical history and demographics, physical examination, height, weight, body surface area, lung function tests, cardiac tests, paraprotein serum free light chain test, extended red cell phenotype/genotype and blood samples for haematology, biochemistry and virology assessments. The patients will also have a bone marrow aspirate to determine the level of disease. These assessments may be performed at any point after patients have consented to enter the trial and prior to their admission to hospital to undergo transplant.

All patients will be randomised prior to stem cell mobilisation, harvest and transplantation and will receive a combination of chemotherapy, growth factors, immunostimulants and monoclonal antibody depending on which treatment arm they are allocated to. During the stem cell mobilisation and collection, the patients will likely be an outpatient but will be monitored on these days.

On Day 1 of the mobilisation and collection phase and Day -14 of the pre-stem cell infusion the patients will have a pregnancy test during their visit. Also on Days 1, 8 and 10 of the mobilisation and collection phase and Days -14 and-7 of the pre-stem cell infusion phase the patients will have blood tests and their vital signs checked. When the high dose of chemotherapy is given prior to the transplant during the pre-stem cell infusion phase (on Day -1) patients will be admitted as inpatients and monitored closely by the clinical team by regular blood tests and monitoring of vital signs. This is in line with routine transplants where patients are admitted for their transplant. All adverse events will also be monitored closely by the clinical team.

After patients have received the high-dose chemotherapy, they will receive their own cells back (Day 0). Patients will continue to be monitored closely while their body begins to make new cells, any symptoms during recovery and severe adverse events will be reported to the Trials Office for up to 100 days after the transplant. Significant adverse events will continue to be reported after this point.

Patients will continue to be monitored in accordance with their local hospitals practice, and trial assessments will be performed at intervals considered appropriate for monitoring the treatment /transplant outcomes as outlined in the protocol. Bone marrow aspirates will be performed during treatment (Day -14) and Day 100 for the purpose of disease monitoring. All bone marrow aspirates will be sent to the Haematological Malignancy Diagnostic Sciences (HMDS) at St James's University Hospital for analysis.

Patients will also have blood tests during treatment and on the day of their transplant, and then day 28, day 100, then at months 6, 12, 18 and 24 post-transplant in order to monitor the longer-term effects of the treatment. These tests are fewer than those required to routine care to minimise the burden to patients.

Patients will be followed-up in the transplant centre for a minimum of 100 days from the date of transplant, and then for a minimum of 10 years by virtual follow-up (remote review at 6-month intervals collecting cumulative prior blood results). The end of the trial will be 12 months after the last patient has completed trial therapy. This will allow sufficient time for the completion of protocol procedures, data collection and data input. For the purposes of the main REC approval, the trial end date is deemed to be the date of last data capture following 10 years of long-term follow-up. All data will be collected and analysed centrally at the Trials Office and the study findings will be reported in a peer reviewed medical journal.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Daratumumab

Primary outcome(s)
Number of patients with MRD-negative bone marrow aspirate (defined as malignant plasma cells <1 in 10(5) total cells) measured by multiparameter flow cytometry at day 100 after autologous stem cell transplant

Key secondary outcome(s))
Safety and toxicity of addition of daratumumab to PBSC harvest and ASCT:
1. Rate of graft failure - measured by blood sample – time point within 28 days of stem cell transplant
2. Time to engraftment - measured by blood sample – time point within 28 days of stem cell transplant
3. Proportion of patients completing treatment as per protocol – measured by review of patient data – time point at day 100 after stem cell transplant
4. Proportion of patients achieving a stem cell harvest yield of ≥4 x 10 to the 6 CD34+ cells/kg – measured by number of cells collected in stem cell harvest and review of patient data were the number of cells is recorded – time point day 10 of the mobilisation and collection phase of the stem cell transplant
5. Toxicity collected accordance with CTCAE criteria 5.0 - measured by review of adverse events collected in the patients records - time point up to day 100 after the admission of the last treatment/transplant
6. Proportion of patients achieving a ≥ 10 fold reduction in disease burden - measured by multiparameter flow cytometry of bone marrow samples and review of patient data were results will be recorded comparing - time point pre-ASCT BM aspirate and day 100 post-ASCT BM aspirate
7. Progression-free survival (PFS) and progression-free survival 2 (PFS2) – measured by review of patient data to determine if there has been a recorded death or disease relapse - time point from time of randomisation to date of death or disease progression for duration of follow-up
7. Time to next treatment - measured by review of patient data to determine if the patient has started a new line of therapy – time point from time of randomisation to date of the start of the next treatment for duration of follow-up
8. Overall survival (OS) – measured by review of patient data to determine if there has been a patient death – time point from time of randomisation to date of death for duration of follow-up
9. Level of residual myeloma in BM pre-and post-ASCT – measured by flow cytometry of bone marrow samples and review of results recorded in patient data – time point before stem cell transplant and day 100 post-transplant

Completion date
30/11/2031

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. Confirmed diagnosis of symptomatic MM, both those with; measurable secretory disease according to IMWG criteria and patients with non-secretory myeloma may enter the trial
2. Received only 1st line induction therapy (i.e., undergoing or completed first line therapy at the time of enrolment)*
3. Induction with either VCD or VTD**
4. Received Bortezomib-containing induction treatment for at least 4 cycles

5. Achieving at least PR following induction treatment
6. Considered suitable for ASCT at the time of entering the trial as clinically judged by the local Investigator
7. ECOG <=2, unless related to myeloma
8. Age >=18
9. Creatinine clearance >=30ml/min
10. Adults of reproductive potential must agree to use effective contraception or maintain abstinence for 6 months after therapy
11. Willing and able to participate in all required evaluations and procedures in this study

*This trial will adopt the general definitions for a cycle of chemotherapy, whereby a line of therapy consists of >=1 complete cycle of a single agent, a regimen consisting of a combination of several drugs, or a planned sequential therapy of various regimens (e.g., 3 - 6 cycles of initial therapy with bortezomib-dexamethasone (VD) followed by stem cell transplantation (SCT), consolidation, and lenalidomide maintenance is considered 1 line). However, since standard practice in many UK centres includes an adaptive approach whereby VCD or VTD is started, but a swap to VTD or VCD respectively is planned depending on response and tolerability, these two combinations (i.e. VCD changing to VTD or VTD changing to VCD) will be considered a single line of therapy and patients will be eligible for this trial.

**This study will recruit patients who have received either VCD or VTD induction therapy. However, since standard practice in many UK centres includes switching from one regimen to the other, we will therefore allow enrollment into the study of patients who have swapped from VCD to VTD or from VTD to VCD.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Previous treatment with daratumumab or other anti-CD38 therapies
2. Demonstrating evidence of progressive disease according to IMWG criteria
3. Peripheral neuropathy above grade 2 as defined by Common Terminology Criteria for Adverse Events (CTCAE) version 5.0
4. Current or prior malignancy within 5 years from enrolment (other than multiple myeloma, adequately treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, or prostate cancer <Gleason Grade 6 with stable Prostate Specific Antigen (PSA))
5. Bilirubin >2 x upper limit of normal (ULN)
6. ALT/AST >3 x ULN
7. Known chronic obstructive pulmonary disease (COPD), persistent asthma or pulmonary

function tests showing Forced Expiratory Volume (FEV1) <60%
8. Known cardiac impairment with Left Ventricular Ejection Fraction (LVEF) <50%
9. Pregnant or breast-feeding women. (Women of child-bearing potential and men who are sexually active will be required to undergo the standard testing prior to chemotherapy, which we will not list here for brevity.)
10. POEMS syndrome, plasma cell leukaemia, amyloidosis (AL), smouldering multiple myeloma, Waldenstrom's macroglobulinaemia.
11. Known or suspected central nervous system (CNS) involvement by myeloma
12. Radiation therapy within 4 weeks of trial entry
13. Participation in an investigational therapeutic study within the 4 weeks prior to first dose of daratumumab
14. Acute active infection requiring systemic antibiotics, antivirals or antifungals within 2 weeks prior to trial entry
15. Known or suspected human immunodeficiency virus (HIV) infection or subjects who are HIV seropositive
16. Active hepatitis A, B (surface antigen or core antibody positive), or C infection (patients with no detectable virus by PCR may be entered into the study with ongoing monitoring and therapy for viral reactivation as per local practice)
17. Serious psychiatric or medical conditions that could, in the investigator’s opinion, interfere with treatment, protocol adherence or a subject's ability to give informed consent

Date of first enrolment
18/01/2021

Date of final enrolment
18/01/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
University College London Hospital
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre
The Royal London Hospital
Barts Health NHS Trust

80 Newark Street
London
United Kingdom
E1 2ES

Study participating centre
The Christie Hospital
Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
Bristol Royal Infirmary
University Hospitals Bristol and Weston NHS Foudnation Trust
Marlborough Street
Bristol
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BS1 3NU

Study participating centre
King's College Hospital
King’s Health Partners Clinical Trials Office
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Gartnavel Royal Hospital
NHS Greater Glasgow and Clyde
J B Russell House
1055 Great Western Road

Glasgow
United Kingdom
G12 0XH

Study participating centre
St Mary's Hospital
Imperial College Healthcare NHS Trust
South Wharf Road
London
United Kingdom
W2 1BL

Study participating centre
Queen Elizabeth Hospital Birmingham
University Hospitals Birmingham NHS Foundation Trust
Mindelsohn Way
Birmingham
United Kingdom
B15 2TH

Study participating centre
St James's Hospital
Leeds Teaching Hospitals NHS Trust
Beckett Street
West Yorkshire
Leeds
United Kingdom
LS9 7TF

Study participating centre
Leicester Royal Infirmary
University Hospitals of Leicester NHS Trust
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
Central Manchester University Hospitals NHS Foundation Trust
Cobbett House
Oxford Road

Manchester
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M13 9WL

Study participating centre
Freeman Hospital
Newcastle Upon Tyne Hospital Trust
Freeman Road
High Heaton
Newcastle
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NE7 7DN

Study participating centre
Queen's Medical Centre
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
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NG7 2UH

Study participating centre
Derriford Hospital
Derriford Road
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United Kingdom
PL6 8DH

Study participating centre
The Royal Marsden NHS Foundation Trust
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Southampton General Hospital
University Hospital Southampton NHS Foundation Trust
Tremona Road
Southampton

United Kingdom
SO16 6YD

Study participating centre
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Sheffield Teaching Hospitals NHS Foundation Trust
Herries Road
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S5 7AU

Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Leukaemia UK

Alternative Name(s)
LUK

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication.

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes