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MUK Nine b: OPTIMUM

Submission date 24/04/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 08/05/2017	**Overall study status** Ongoing	
Last Edited 16/06/2025	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-new-combination-treatment-newly-diagnosed-high-risk-myeloma-plasma-cell-leukaemia-muk-9-b-optimum

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT03188172

Clinical Trials Information System (CTIS)
2016-002670-12

Integrated Research Application System (IRAS)
215490

Protocol serial number

33205

Study information

Scientific Title
MUK nine b: OPTIMUM. A phase II study evaluating optimised combination of biological therapy in newly diagnosed high-risk multiple myeloma and plasma cell leukaemia

Acronym
OPTIMUM

Study objectives
The aim of this study is to look at whether a combination of bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex) and dexamethasone with cyclophosphamide is active in high-risk patients, to take forward into a phase III trial compared to standard treatment.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 25/01/2017, London- South East Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 (0)207 104 8177; londonsoutheast.rec@hra.nhs.uk), ref: 17/LO/0023

Study design
Non-randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Multiple myeloma and malignant plasma cell neoplasms

Interventions
All participants undergo the following treatment:

Induction (6 cycles):
Cyclophosphamide 500 mg on days 1 and 8, bortezomib 1.3 mg/m2 on days 1, 4, 8 and 11, lenalidomide 25 mg on days 1-14 daratumumab 16 mg/kg on days 1, 8 and 15 (cycles 1& 2) and day 1 only from cycle 3, and dexamethasone 20-40 mg on days 1, 4, 8 and 11

ASCT stem cell harvest:
with bortezomib 1.3 mg/m2, (12 hours post Melphalan) bortezomib 1.3 mg/m2, day +5, +14, weekly

Consolidation part 1 (6 cycles):
Bortezomib 1.3 mg/m2 on days 1, 8, 15 and 22, lenalidomide 25 mg on days 1-21, daratumumab 16 mg/kg on day 1, dexamethasone 20-40 mg on days 1, 8, 15 and 22

Consolidation part 2 (12 cycles):
Bortezomib 1.3 mg/m2 on days 1, 8 and 15, lenalidomide 25 mg on days 1-21, daratumumab 16 mg/kg on day 1

Maintenance (until disease progression):
Lenalidomide 10 mg on days 1-21, daratumumab 16 mg/kg on day 1

Participants will be required to attend a follow-up visit at 3 months post the end of treatment to allow any adverse reactions up to 90 days post the last dose of trial treatment to be documented.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex), dexamethasone, cyclophosphamide

Primary outcome(s)
Whether a combination of four agents bortezomib, lenalidomide, daratumumab & dexamethasone in combination with low-dose cyclophosphamide is sufficiently active in a high-risk population of myeloma patients, to take forward into a phase, as determined during analysis at the end of the recruitment.

Key secondary outcome(s))
1. The safety and toxicity profile will be determined by capturing AEs, ARs, SAEs and SUSARs from registrations to 90 days post treatment discontinuation
2. Clinical activity will be measured by collecting bone marrow samples and measuring response from registration until the end of the trial.
3. Treatment compliance is assessed by reviewing the patient's data at the end of each cycle during the treatment period
4. Overall treatment benefit and a clinician's assessment of treatment benefit is measured on how both the patient and clinicians feel that the patient is doing on treatment. This is captured at the end of induction therapy and 100 days post-ASCT
5. Quality of life will be captured on QOL questionnaires at the end of induction, 100 days post-transplant, at day 1 of consolidation 1 and 2 and at day 1 of maintenance

Completion date
31/05/2029

Eligibility

Key inclusion criteria

1. Confirmation of High Risk status from ICR following bone marrow and blood sample processed through the MUKnine a screening protocol
2. Previously untreated participants, although participants may have received up to 2 cycles of CTD, CVD, CRD or VTD pre-trial induction chemotherapy while awaiting the results of the laboratory analysis from the MUK nine a Screening Protocol. (In addition, non-systemic therapy such as therapeutic plasma exchange, dexamethasone up to a maximum of 160 mg or radiotherapy sufficient to alleviate or control pain or local invasion is permitted)
3. Measurable disease with at least one of the following or willing to undergo further bone marrows for assessment:
3.1. Paraprotein ≥5g/L or ≥0.5 g/L for IgD subtypes
3.2. Serum-free kappa or lambda light chains ≥100 mg/L with abnormal ratio (for light chain only myeloma).
3.3. Urinary Bence Jones protein ≥200 mg/L
4. Non-measurable participants providing they accept a 3-monthly bone marrow during induction and a 6-monthly bone marrow assessment during consolidation and maintenance
5. Aged 18 years or over
6. Fit for intensive chemotherapy and autologous stem cell transplant (at clinician's discretion)
7. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2
8. The Celgene Pregnancy Prevention Plan must be followed and participants must agree to comply with this:
8.1. Females of childbearing potential (FCBP) must agree to utilise two reliable forms of contraception simultaneously or practice complete abstinence for at least for 28 days prior to starting trial treatment, during the trial and for at least 28 days after trial treatment discontinuation, and even in case of dose interruption, and must agree to regular pregnancy testing during this timeframe
8.2. Males must agree to use a latex condom during any sexual contact with FCBP during the trial, including during dose interruptions and for 28 days following discontinuation from this trial even if he has undergone a successful vasectomy o Males must also agree to refrain from donating semen or sperm while on trial treatment including during any dose interruptions and for at least 6 months after discontinuation from this trial
o All participants must agree to refrain from donating blood while on trial drug including during dose interruptions and for 28 days after discontinuation from this trial
9. Calculated creatinine clearance ≥ 30mL/min (using Cockcroft-Gault formula)
10. ALT and/or AST ≤2.5 times upper limit of normal (ULN)
11. Bilirubin ≤2.0 x ULN, except in participants with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 times ULN
12. Platelet count ≥75 x 10(9)/L. (≥50 x 10(9)/L if myeloma involvement in the bone marrow is >50%). Platelet support is permitted.
13. Absolute neutrophil count (ANC) ≥1.0 x 10(9)/L. Growth factor support is permitted.
14. Haemoglobin ≥80 g/L. (Participants may be receiving red blood cell (RBC) transfusions in accordance with institutional guidelines.
15. Corrected serum calcium ≤ 3.5 mmol/L

Inclusion Criteria for ASCT
1. Minimum stem cell harvest of 2 x 106 CD34+ cells/kg body weight
2. Received a minimum of 4, unless CR has been achieved with a lesser number, or a maximum of 6 Induction (CVRDd) cycles
3. Achieved a response of SD or better

Inclusion Criteria for Consolidation Part 1 (VRDd)
1. Undergone autologous transplant with HDM-V conditioning (Participants must have received a minimum of 100 mg/m2 Melphalan in order to proceed with consolidation)

2. Neutrophils ≥1.0 x 10(9)/L. Growth factor support is permitted
3. Platelet count ≥75 x 10(9)/L. Platelet support is permitted

Inclusion Criteria for Consolidation Part 2 (VRD)
1. Received 6 cycles of Consolidation Part 1 (VRDd) or 1 cycle of VRd pre-harvest plus 5 cycles of Consolidation Part 1 (VRDd)
2. Neutrophils ≥1.0 x 10(9)/L. Growth factor support is permitted
3. Platelet count ≥75 x 10(9)/L. Platelet support is permitted

Inclusion Criteria for Maintenance (RD)
1. Received 12 cycles of Consolidation Part 2 (VRD)
2. Neutrophils ≥1.0 x 10(9)/L. Growth factor support is permitted
3. Platelet count ≥75 x 10(9)/L. Platelet support is permitted

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
108

Key exclusion criteria
1. Participants that have progressive disease
2. Solitary bone/solitary extramedullary plasmacytoma
3.Primary diagnosis of amyloidosis, monoclonal gammopathy of undetermined significance or smoldering multiple myeloma or Waldenstrom’s Disease

Medical history and Concurrent disease:
1. Prior or concurrent invasive malignancies except the following:
1.1. Adequately treated basal cell or squamous cell skin cancer
1.2. Incidental finding of low grade (Gleason 3+3 or less) prostate cancer
1.3. Any cancer from which the subject has been disease free for at least 3 years
2. Known/underlying medical conditions that, in the investigator’s opinion, would make the administration of the study drug hazardous (e.g uncontrolled diabetes or uncontrolled coronary artery disease)
3. Any clinically significant cardiac disease, including:
3.1. Myocardial infarction within 1 year before randomization, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV
3.2. Uncontrolled cardiac arrhythmia (National Cancer Institute Common Terminology Criteria

for Adverse Events [NCI CTCAE] Version 4 Grade > = 2) or clinically significant ECG (Electrocardiogram) abnormalities
3.3. Screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) > 470 msec
4. Known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume [FEV] in 1 second < 60% of predicted normal), persistent asthma, or a history of asthma within the last 2 years (intermittent asthma is allowed). Participants with known or suspected COPD or asthma must have a FEV1 test during screening
5. Known to be seropositive for history of human immunodeficiency virus (HIV) or known to have active hepatitis B or hepatitis C
6. Any known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or Investigator's Brochure), or known sensitivity to mammalian-derived products
7. Clinically significant allergies or intolerance to cyclophosphamide, lenalidomide, velcade, daratumumab or dexamethasone
8. Previous treatment with daratumumab or any other anti-CD38 therapies
9. Participants with contraindication to thromboprophylaxis
10. Grade 2 or greater peripheral neuropathy (per NCI-CTCAEv4.0)
11. Participants with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes)
12. Any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study
13. Known or suspected of not being able to comply with the study protocol (e.g. because of alcoholism, drug dependency, or psychological disorder). Participant has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g. compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments
14. Participant is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this trial, 4 months after the last dose of trial treatment. Or, participant is a man who plans to father a child while taking part in this trial, within 4 months after the last dose of trial treatment
15. Major surgery within 2 weeks before treatment protocol registration or has not fully recovered from surgery, or has surgery planned during the time the participant is expected to participate in the study. Kyphoplasty or vertebroplasty is not considered major surgery
16. Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before treatment protocol registration or is currently enrolled in an interventional investigational study

Date of first enrolment
30/05/2017

Date of final enrolment
24/09/2019

Locations

Countries of recruitment
United Kingdom

England

Scotland

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

Study participating centre
University Hospitals of Leicester NHS Trust
Gwendolen House
Gwendolen Road
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United Kingdom
LE5 4QF

Study participating centre
Southampton University Hospitals NHS Trust
Mailpoint 18 s
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
King's College Hospital NHS Foundation Trust
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
University Hospitals Bristol NHS Foundation Trust
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BS1 3NU

Study participating centre
University Hospital Birmingham NHS Foundation Trust
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PO box 9551
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Birmingham
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Study participating centre
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United Kingdom
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Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
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Derby Road
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Study participating centre
Central Manchester University Hospitals NHS Foundation Trust
Trust Headquarters,
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M13 9WL

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

Study participating centre
Oxford Radcliffe Hospitals NHS Trust
John Radcliffe Hospital
Headley way
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United Kingdom
OX3 9DU

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
James Cook University Hospital Laboratory
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
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550 Wilmslow Road
Withington
Manchester

United Kingdom
M20 4BX

Study participating centre
Freeman Hospital
Freeman Road
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Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Norfolk & Norwich University Hospital
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Victoria Hospital (blackpool)
Whinney Heys Road
Blackpool
United Kingdom
FY3 8NR

Study participating centre
Royal Hallamshire Hospital
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S10 2JF

Study participating centre
Royal Bournemouth General Hospital
Castle Lane East
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BH7 7DW

Study participating centre
East Yorkshire Hospitals NHS Trust (head Office)
Castle Hill Hospital
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Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Myeloma UK

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
Current IPD sharing statement as of 18/07/2022:
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds

(contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security) and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets. The conditions of release for aggregate data may differ from those applying to individual
participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree on suitable requirements for release.

Previous IPD sharing statement:
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		10/08/2023	14/05/2024	Yes	No
Protocol article		24/03/2021	25/04/2023	Yes	No
Abstract results	Early results	28/05/2021	25/04/2023	No	No
Abstract results	Molecular stratification of participants		25/04/2023	No	No
HRA research summary			28/06/2023	No	No