

# MUK Nine b: OPTIMUM

<b>Submission date</b> 24/04/2017	<b>Recruitment status</b> No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
<b>Registration date</b> 08/05/2017	<b>Overall study status</b> Ongoing	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
<b>Last Edited</b> 16/06/2025	<b>Condition category</b> Cancer	<input type="checkbox"/> Individual participant data

## 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

### Contact name

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### Contact details

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## Additional identifiers

### EudraCT/CTIS number

2016-002670-12

### IRAS number

215490

### ClinicalTrials.gov number

NCT03188172

### Secondary identifying numbers

## 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; londonsear.ethics@hra.nhs.uk), ref: 17/LO/0023

### Study design

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

### 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, please use the contact details below to request a patient information sheet

### 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/m<sup>2</sup> 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/m<sup>2</sup>, (12 hours post Melphalan) bortezomib 1.3 mg/m<sup>2</sup>, day +5, +14, weekly

#### Consolidation part 1 (6 cycles):

Bortezomib 1.3 mg/m<sup>2</sup> 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/m<sup>2</sup> 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 measure

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.

### Secondary outcome measures

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

### **Overall study start date**

01/10/2014

### **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  $\geq 5\text{g/L}$  or  $\geq 0.5\text{ g/L}$  for IgD subtypes
  - 3.2. Serum-free kappa or lambda light chains  $\geq 100\text{ mg/L}$  with abnormal ratio (for light chain only myeloma).
  - 3.3. Urinary Bence Jones protein  $\geq 200\text{ mg/L}$
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  $\leq 2$
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  $\geq 30\text{mL/min}$  (using Cockcroft-Gault formula)
10. ALT and/or AST  $\leq 2.5$  times upper limit of normal (ULN)
11. Bilirubin  $\leq 2.0 \times \text{ULN}$ , except in participants with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin  $\leq 2.0$  times ULN
12. Platelet count  $\geq 75 \times 10^9/\text{L}$ . ( $\geq 50 \times 10^9/\text{L}$  if myeloma involvement in the bone marrow is  $>50\%$ ). Platelet support is permitted.

13. Absolute neutrophil count (ANC)  $\geq 1.0 \times 10^9/\text{L}$ . Growth factor support is permitted.
14. Haemoglobin  $\geq 80 \text{ g/L}$ . (Participants may be receiving red blood cell (RBC) transfusions in accordance with institutional guidelines.
15. Corrected serum calcium  $\leq 3.5 \text{ mmol/L}$

#### **Inclusion Criteria for ASCT**

1. Minimum stem cell harvest of  $2 \times 10^6 \text{ CD34+ cells/kg body weight}$
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  $100 \text{ mg/m}^2$  Melphalan in order to proceed with consolidation)
2. Neutrophils  $\geq 1.0 \times 10^9/\text{L}$ . Growth factor support is permitted
3. Platelet count  $\geq 75 \times 10^9/\text{L}$ . 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  $\geq 1.0 \times 10^9/\text{L}$ . Growth factor support is permitted
3. Platelet count  $\geq 75 \times 10^9/\text{L}$ . Platelet support is permitted

#### **Inclusion Criteria for Maintenance (RD)**

1. Received 12 cycles of Consolidation Part 2 (VRD)
2. Neutrophils  $\geq 1.0 \times 10^9/\text{L}$ . Growth factor support is permitted
3. Platelet count  $\geq 75 \times 10^9/\text{L}$ . Platelet support is permitted

#### **Participant type(s)**

Patient

#### **Age group**

Adult

#### **Lower age limit**

18 Years

#### **Sex**

Both

#### **Target number of participants**

Planned Sample Size: 95; UK Sample Size: 95

#### **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  $\geq 2$ ) 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**

England

Scotland

United Kingdom

**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

Leicester

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**  
Marlborough Street  
Bristol  
United Kingdom  
BS1 3NU

**Study participating centre**

**University Hospital Birmingham NHS Foundation Trust**  
Trust HQ  
PO box 9551  
Queen Elizabeth Medical Centre  
Edgbaston  
Birmingham  
United Kingdom  
B15 2TH

**Study participating centre**

**Heart of England NHS Foundation Trust Birmingham**  
Heartlands Hospital  
Bordesley Green East  
Birmingham  
United Kingdom  
B9 5ST

**Study participating centre**

**Nottingham University Hospitals NHS Trust**  
Trust Headquarters  
QMC Campus  
Derby Road  
Nottingham  
United Kingdom  
NG7 2UH



**Study participating centre**

**Central Manchester University Hospitals NHS Foundation Trust**

Trust Headquarters,  
Cobbett House  
Manchester Royal Infirmary  
Oxford Road  
Manchester  
United Kingdom  
M13 9WL

**Study participating centre**

**NHS Tayside**

Department of Haematology  
Ninewells Hospital  
Dundee  
United Kingdom  
DD2 1UB

**Study participating centre**

**Beatson West of Scotland Cancer Centre**

Department of Haematology  
1053 Great Western Road  
Glasgow  
United Kingdom  
G12 0YN

**Study participating centre**

**Oxford Radcliffe Hospitals NHS Trust**

John Radcliffe Hospital  
Headley way  
Headington  
Oxford  
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**

**The Christie NHS Foundation Trust**

550 Wilmslow Road  
Withington  
Manchester  
United Kingdom  
M20 4BX

**Study participating centre**

**Freeman Hospital**

Freeman Road  
High Heaton  
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**

Glossop Road  
Sheffield  
United Kingdom  
S10 2JF

**Study participating centre****Royal Bournemouth General Hospital**

Castle Lane East  
Bournemouth  
United Kingdom  
BH7 7DW

**Study participating centre****East Yorkshire Hospitals NHS Trust (head Office)**

Castle Hill Hospital  
Castle Road  
Cottingham  
United Kingdom  
HU16 5JQ

## **Sponsor information**

**Organisation**

University of Leeds

**Sponsor details**

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**Sponsor type**

University/education

**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

## Publication and dissemination plan

Planned publication in a high-impact peer reviewed journal

## Intention to publish date

10/08/2025

## 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](mailto: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?
<a href="#">Abstract results</a>	Early results	28/05/2021	25/04/2023	No	No
<a href="#">Abstract results</a>	Molecular stratification of participants		25/04/2023	No	No
<a href="#">Protocol article</a>		24/03/2021	25/04/2023	Yes	No
<a href="#">HRA research summary</a>			28/06/2023	No	No
<a href="#">Results article</a>		10/08/2023	14/05/2024	Yes	No