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MUK*nine* OPTIMUM protocol: a screening study to identify high-risk patients with multiple myeloma suitable for novel treatment approaches combined with a phase II study evaluating optimised combination of biological therapy in newly diagnosed high-risk multiple myeloma and plasma cell leukaemia

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ABSTRACT

Introduction Multiple myeloma (MM) is a plasma cell tumour with over 5800 new cases each year in the UK. The introduction of biological therapies has improved outcomes for the majority of patients with MM, but in approximately 20% of patients the tumour is characterised by genetic changes which confer a significantly poorer prognosis, generally termed high-risk (HR) MM. It is important to diagnose these genetic changes early and identify more effective first-line treatment options for these patients.

Methods and analysis The Myeloma UK *nine* OPTIMUM trial (MUK*nine*) evaluates novel treatment strategies for patients with HRMM. Patients with suspected or newly diagnosed MM, fit for intensive therapy, are offered participation in a tumour genetic screening protocol (MUK*nine a*), with primary endpoint proportion of patients with molecular screening performed within 8 weeks. Patients identified as molecularly HR are invited into the phase II, single-arm, multicentre trial (MUK*nine b*) investigating an intensive treatment schedule comprising bortezomib, lenalidomide, daratumumab, low-dose cyclophosphamide and dexamethasone, with single high-dose melphalan and autologous stem cell transplantation (ASCT) followed by combination consolidation and maintenance therapy. MUK*nine b* primary endpoints are minimal residual disease (MRD) at day 100 post-ASCT and progression-free survival. Secondary endpoints include response, safety and quality of life. The trial uses a Bayesian decision rule to determine if this treatment strategy is sufficiently active for further study. Patients identified as not having HR disease receive standard treatment and are followed up in a cohort study. Exploratory studies include longitudinal whole-body diffusion-weighted MRI for imaging MRD testing.

Ethics and dissemination Ethics approval London South East Research Ethics Committee (Ref: 17/LO/0022, 17/LO/0023). Results of studies will be submitted for publication in a peer-reviewed journal.

Trial registration number ISRCTN16847817, May 2017; Pre-results.

Strengths and limitations of this study

- This is the first time in the UK that patients with newly diagnosed multiple myeloma may be entered into a clinical trial prospectively according to their genetic risk profile.
- A flexible multiple outcome, multistage Bayesian design is used to enable early stopping for lack of efficacy.
- No concurrent control arm is included due to the availability of near concurrent historical control data from the Myeloma XI trial.

INTRODUCTION

Multiple myeloma (MM) is a clonal disorder of plasma cells which accumulate in the bone marrow leading to cytopenias, bone resorption, renal impairment, infection and the production of a monoclonal protein.[1] MM represents 1.5% of all malignant diseases, with an incidence of 9/100 000 per year accounting for around 5800 new cases each year in the UK (3000 deaths per year).[2] Median age at diagnosis is 69 years but 37% of patients are

diagnosed before the age of 65 (including 15%<55).[3] Median overall survival (OS) of younger patients is approximately 10 years.[4–11] However approximately 20% of patients have a significantly worse prognosis, with estimated survival of <3 years and are characterised as having high-risk (HR) disease.[7 12 13] A number of genetic lesions and gene expression profiles (GEP) have been identified as associated with HR disease,[7] and molecular risk models based on these markers can be used to predict HR disease in a clinical setting. Further research is ongoing to identify additional HR markers and to better understand the mechanisms driving this tumour biology.

Unfortunately, patients with HR disease have, in terms of absolute outcome, benefitted less from the introduction of novel therapies than standard risk (SR) patients.[14–20] It is important to define the optimal way to treat this group of patients given the number of available novel agents with favourable toxicity profiles allowing the use of combination therapy, consolidation and maintenance therapy. Here, we describe the protocol for the MUK*nine* trial, a phase II study evaluating optimised combination of biological therapy in patients with newly diagnosed HRMM and plasma cell leukaemia (PCL), incorporating a screening and observational study for patients with SR disease. The trial has completed recruitment and is currently in follow-up.

Defining HR disease

In a recent meta-analysis of 1905 trial patients from the MRC Myeloma IX and NCRI Myeloma XI trials, recurrent chromosomal translocations t(4;14), t(14;16), t(14;20) and copy number aberrations (CNA) gain(1q) or del(17p) were independently associated with shorter progression-free survival (PFS) and OS. Presence of two or more such HR lesions, also termed double-hit,[7] was associated with particularly adverse outcome and increased specificity of outcome prediction considering individual lesions in isolation. The cosegregation model is exclusively based on molecular features of the tumour cell and contrasts to risk predictors which require inclusion of clinical risk markers (renal function, age, performance status) or their proxies, such as the international staging system.[12] For participants fit to receive intensive therapy, HR can thus be specifically defined by presence of two or more cytogenetically adverse lesions (t(4;14), t(14;16), t(14;20), del(1p32) gain(1q) or del(17p)).

The prognostic relevance of GEP risk signatures, in particular EMC-92, from which the SKY92 MMProfiler diagnostic assay was developed, has been demonstrated in the Myeloma IX trial dataset.[21] A recent analysis including Myeloma IX and Myeloma XI trial patients demonstrated independent association of GEP SKY92 HR and genetic HR markers with adverse outcome in MM.[11 13 21–24] Results suggest that both tests assay different clinically relevant qualities of HR biology. Combining GEP and double-hit genetic risk information identifies about 20%–30% of patients with markedly short PFS and OS.

The exact impact of single nucleotide variants on MM risk status is still under investigation. However, very recent evidence, published after design of MUKnine, seems to confirm that structural aberrations such as translocations and CNA are the dominant markers of HRMM, although detail on their assessment varies.[25–27] The observation of poor prognosis associated with HR disease defined by such molecular criteria is consistent with clinical studies carried out by other trial groups.[5–11 21 22 24 28 29] Clearly, a focused approach to improve the treatment and outcome of this poor performing subgroup of MM patients is essential.

Treatment

Recent data have demonstrated efficacy of the combination of multiple novel agents in HR disease.[30] Until the molecular mechanisms contributing to HR biology can be directly targeted, combinations of multiple novel agents and ongoing therapy to induce and maintain remission are the most efficacious therapeutic principles.[31]

Maximising exposure to novel agents as an alternative to multidrug cytotoxic alkylating chemotherapy is hypothesised to benefit HR patients. Ongoing use of a combination of biological agents with favourable toxicity profiles can potentially minimise the chance of relapse due to sustained multiangled pressure on the MM repopulating cell pool.

Long-term exposure to thalidomide does not benefit HR patients.[32 33] However, lenalidomide maintenance in newly diagnosed HR patients (t(4;14) or del 17p) does have a PFS and OS benefit.[34] There is a substantial body of evidence suggesting that HR patients benefit from long-term exposure to proteasome inhibition such as bortezomib.[35–39]

The combination of bortezomib and lenalidomide as induction and consolidation therapy is safe and deliverable with a number of studies using this approach.[40] Adding cyclophosphamide to this triplicate approach is safe, nevertheless the lenalidomide, cyclophosphamide, bortezomib and dexamethasone combination failed to show any additional benefit to lenalidomide, bortezomib and dexamethasone in the EVOLUTION study.[41] However, this study evaluated all genetic risk groups and it is hypothesised that the addition of low-dose alkylating therapy may present an additional benefit in a HR population with highly proliferative subclones.

Daratumumab is a monoclonal antibody that targets the CD38 molecule and has multiple mechanisms of action against MM cells. It has demonstrated activity in MM as a single agent and in combinations with lenalidomide and dexamethasone where it enhances the potency of other drugs such as lenalidomide offering an interesting alternative to chemotherapy in MM.[42] The addition of daratumumab to standard of care regimens improved outcome and combining with lenalidomide or bortezomib appears to improve the poor outcomes associated with HR disease.[43 44]

While tandem autologous stem cell transplantation (ASCT) may offer prolongation of response in comparison with single procedures, the comparative studies

reported at time of design of MUK*nine* were undertaken in an era in which novel agents were not routinely incorporated in clinical practice.[45] Recent exploratory analyses have suggested the potential advantage of tandem ASCT for patients with HR disease.[46] Depth of response is associated with duration of response and therefore optimising the induction, consolidation and maintenance approach with a single ASCT is an alternative way to achieve minimal residual disease (MRD) negative disease state. Melphalan has been combined with bortezomib in phase II studies demonstrating safety and improvement in complete response (CR) rates compared with conventional high-dose melphalan conditioning.[47] Although a recent report stated no PFS benefit of a Velcade-augmented ASCT in a randomised trial, results for an ultra-HR group such as double-hit MM are unknown.[48] The highly proliferative behaviour of double-hit disease and GEP HR provides rationale for a bridging treatment for the 3 months recovery period post ASCT.

Rapid tumour evolution and associated early relapse are key characteristics of HRMM, even in patients who have achieved deep remission after ASCT.[49] Maintaining multiagent treatment intensity around and long-term after ASCT to limit size of the clonal pool as well as molecular avenues for tumour escape seems currently one of the most promising treatment strategies for HRMM, with the aim of achieving sustained deep responses in at least some patients.[50] Longitudinal MRD monitoring can predict remission status with higher sensitivity than standard biochemical/protein analyses and could be of use in identifying patients with HRMM benefitting most from treatment early. As bone marrow biopsy-based MRD assessment may be biased due to spatial disease heterogeneity, sensitive whole body imaging can be performed in parallel to capture residual disease in other bone marrow or soft tissue areas. Whole body diffusion weighted MRI is a particularly sensitive imaging modality for MM, and standardised image acquisition and interpretation guidelines make implementation in multicentre clinical trials feasible.[51 52]

In line with this, the MUK*nine* OPTIMUM trial has been designed to evaluate the following treatment regimen in patients with HRMM, the full schedule is given in table 1:

- CVRDd (induction)—cyclophosphamide, bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex), dexamethasone
  Based on the EVOLUTION trial.[41] Daratumumab doses are used in ongoing clinical trials.[53]
- Melphalan—bortezomib ASCT
  Melphalan 200 mg/m^2 is standard practice in Europe for induction consolidation treatment.[54 55] The addition of bortezomib in phase II studies demonstrated safety and improvement in CR rates compared with conventional high-dose melphalan conditioning.[47] Velcade weekly monotherapy during the clinical recovery period from ASCT limits very early disease relapse in the HR population.
- VRDd (consolidation 1)—bortezomib, lenaliomide, daratumumab, dexamethasone
  Doses for VRd combination are based on IFM 2008-01[40] and IFM 2009-02/DFCI. Daratumumab doses are used in current clinical trials.[53]
- VRD (consolidation 2)—bortezomib, lenalidomide, daratumumab
  The dose of VRD during consolidation 2 is used to minimise effects of long term corticosteroid use and risks of long-term neuropathy with weekly bortezomib with no break in treatment. Using existing daratumumab dosing schedules it is anticipated this will be a tolerable longer term combination.
- RD (maintenance)—lenalidomide, daratumumab
  The dose of lenalidomide is based on two pivotal studies[34 56] and is the currrent dose used in the Myeloma XI trial.[20] Daratumumab doses are used in current clinical trials.[53]

Current protocols

Current protocols: MUK*nine a*, v2.0, 25/07/2018. MUK*nine b*, v4.0, 14/05/2020.

METHODS AND ANALYSIS

Aims

- To assess whether future trials in this setting are feasible and to determine risk status for participants with MM in order to deliver novel therapy to those deemed HR.
- To determine whether it is possible to improve the outcome of HR patients by using multiple biological agents during induction, ASCT, consolidation and maintenance, and to provide evidence for the future evaluation of these high-cost interventions.

Primary objectives

- Assess whether molecular risk-defining investigations can be turned around within 8 weeks.
- Determine whether the combination of three novel agents bortezomib, lenalidomide and daratumumab in combination with low-dose cyclophosphamide and dexamethasone is sufficiently active in terms of PFS in a HR population to take forward to a phase III trial.

Secondary objectives

Secondary objectives include evaluating safety and toxicity profiles of trial treatment, evaluating additional measures of treatment activity and assessing quality of life. In patients not identified as having HR disease, secondary objectives are to summarise treatment pathways and clinical outcomes in this setting.

Exploratory objectives

To explore novel molecular biomarkers associated with treatment activity, and evaluate germline variability/mutations, genomic instability and clonal evolution.

An exploratory imaging substudy is included to explore the association of imaging MRD status with clinical

Table 1 Treatment schedule

Induction treatment			
Regimen: CVRDd to maximum response (or a maximum of 6 cycles of bortezomib)			**Cycle duration:** 21 days
Drug	**Dose**	**Route**	**Days**
Cyclophosphamide	500 mg	PO	1 and 8
Bortezomib	1.3 mg/m^2	SC	1, 4, 8, 11
Lenalidomide	25 mg	PO	1–14
Daratumumab	16 mg/kg (actual body weight)	IV	1, 8, 15† (cycles 1 and 2) 1 only (cycle 3 onwards)
Dexamethasone*	20–40 mg	PO/IV	1, 4, 8, 11
Autologous stem cell transplant (ASCT) Cyclophosphamide and GCSF mobilisation is recommended			
Regimen: bortezomib HD-MEL+ASCT			
Drug	**Dose**	**Route**	**Days**
Melphalan	200 mg/m^2	IV	–1
Bortezomib	1.3 mg/m^2	SC	–1, (8–18 hours post Melphalan)
Autologous stem cell return	IV		0
Bortezomib	1.3 mg/m^2	SC	+5, +14, then weekly to consolidation 1
Consolidation treatment 1 To begin between 100 and 120 days post ASCT			
Regimen: VRDd×6 cycles*		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Bortezomib	1.3 mg/m^2	SC	1, 8,15, 22
Lenalidomide	25 mg	PO	1–21
Daratumumab	16 mg/kg (actual body weight)	IV	1
Dexamethasone*	20–40mg	PO/IV	1, 8,15†, 22
Consolidation treatment 2			
Regimen: VRD×12 cycles*		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Bortezomib	1.3 mg/m^2	SC	1, 8,15
Lenalidomide	25 mg	PO	1–21
Daratumumab	16 mg/kg (actual body weight)	IV	1
Maintenance treatment			
Regimen: RD until progression		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Lenalidomide	10 mg	PO	1–21

Continued

Table 1 Continued

Daratumumab	16 mg/kg (actual body weight)	IV	1

*On days where participants receive dexamethasone 40 mg at site (i.e. predaratumumab infusion), dexamethasone must not be self-administered at home too.
†On day 15, participants will receive premed as per SPC (eg, methylprednisolone).
CVRDd, cyclophosphamide, bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex), dexamethasone; GCSF, granulyte colony-stimulating factor; HD-MEL, high dose melphalan; IV, intravenous; RD, lenalidomide, daratumumab; SC, subcutaneous; SPC, summary of product characteristics; VRD, bortezomib, lenalidomide, daratumumab; VRDd, bortezomib, lenalidomide, daratumumab, dexamethasone.

Figure 1 MUKnine OPTIMUM trial design.
ASCT, autologous stem cell transplantation; CRD, cyclophosphamide, lenalidomide, dexamethasone; CTD, cyclophosphamide, thalidomide, dexamethasone; CVD, cyclophosphamide, bortezomib, dexamethasone; GCSF, granulyte colony-stimulating factor; HD-MEL, high dose melphalan; VTD, bortezomib, thalidomide, dexamethasone.

outcomes and to assess patterns of disease distribution by whole body diffusion-weighted (DW)-MRI.

Trial design

The MUK*nine* OPTIMUM trial is comprised of two components, MUK*nine a* and MUK*nine b,* as outlined in figure 1. MUK*nine a* is a genetic screening component, where patients with suspected symptomatic MM will be screened to determine their risk status. Patients identified as not having HR disease will receive treatment as standard of care and will have data collected on their treatment and survival. Patients who are identified as having HR disease or PCL are invited to take part in

the second component, MUK*nine b, a* single arm phase II, multicentre trial. MUK*nine b* incorporates interim assessments for futility using a Bayesian strategy for monitoring multiple outcomes proposed by Thall *et al*[57 58] and extended by Thall and Sung.[59] The trial is single arm to ensure a feasible sample size given the availability of molecularly matched individual participant data from currently running trials (Myeloma XI/XI+). This provides a body of almost concurrent control data available for the purpose of exploratory statistical comparison.

Whole-body DW-MRI is a functional method capable of detecting small-volume disease activity in MM,[60 61] being used in standard practice at several academic UK hospitals already, demonstrating excellent performance in guiding therapy on a day-to-day basis. An exploratory substudy is incorporated in MUK*nine* using DW-MRI for disease distribution assessment and imaging MRD in combination with cellular (bone marrow) MRD.

Sample size

Recent data from the Myeloma XI trial demonstrate a median PFS for patients with HR disease in the intensive pathway of 19.7 months (598 patients[12]). With a median PFS of 19–20 months in the control arm, we require 92–94 patients to observe a 25% difference in median PFS (corresponding to a difference of 4.8–5.0 months) in the 85% credible interval. Allowing for slight changes in the actual count data, we require 95 HR patients to be registered.

A sample size re-estimation using individual patient data from Myeloma XI/XI+, when available, allows the number of HR patients required to detect a 25% difference in median PFS to be increased to 105. In order to include 105 HR patients, approximately 620 patients with MM would need to be registered at diagnosis, assuming approximately 10%–15% failed diagnostic tests, and approximately 20% patients identified as HR.

The trial design includes interim analyses after every cohort of 10 MUK*nine b* participants have been followed-up to 120 days post ASCT. Until recruitment is complete, the trial could be terminated early for futility on the basis of MRD status and PFS at 100 days post ASCT.

Consent, eligibility, screening and registration

Participants are recruited from UK National Health Service (NHS) hospitals. Hospital sites delivering the HR treatment are approved sites within the Myeloma UK Early Phase Clinical Trials Network[62] and patients recruited from sites outside of the network sites are referred to receive treatment, to ensure sufficient patient reach to achieve target sample size. The imaging substudy is undertaken at select sites with appropriate radiology capacity. Assenting patients will provide written informed consent and be registered.

Patients presenting who are likely to have symptomatic MM (identified by pretests performed as standard) are approached prior to having a bone marrow biopsy for diagnosis or confirmation of MM. A full list of inclusion and exclusion criteria is in table 2. No age cut-off is incorporated for transplant eligibility, as per Myeloma XI/XI+ and standard practice.

Patients are provided with information about the trial and if agreeable are consented for the bone marrow biopsy to allow samples to be sent to central laboratories and for screening. This consent allows follow-up data to be collected under the MUK*nine a* protocol if the patient is found not to have HR disease. Patients are registered to the trial via a web-based system (provided by University of Leeds) prior to any trial-specific assessments being conducted. Participants can also optionally consent to the imaging substudy. Participants retain the right to withdraw at any time without giving reasons and without their further treatment being prejudiced.

Bone marrow and blood samples are taken as per standard care and sent to the Institute of Cancer Research, London (ICR) by next day postal delivery for genetic molecular risk profiling.

HR status is determined by the presence of one or more of the following, based on the International Myeloma Working Group guidelines,[63] the Myeloma IX trial and the EMC92 GEP model[3 5 10 21 64]:

- Two or more adverse lesions (t(4;14), t(14;16), t(14;20), gain(1q), del(17p), del(1p)).
- GEP—HR score as per EMC92/SKY92 GEP model.
- PCL, defined as the presence of more than 2×10^9/L peripheral blood plasma cells or a plasmacytosis accounting for >20% of the differential white cell count.

Patients identified as having HR disease are provided with a patient information sheet detailing the HR treatment schedule in MUK*nine b* and consented if willing to participate. A further registration documents all patients going on to HR treatment. If the patient does not wish to receive HR treatment they continue with standard treatment and data collected through the MUK*nine a* protocol.

For all patients at screening, bone marrow samples are sent to Haematological Malignancy Diagnostic Service, Leeds, for MRD monitoring. Blood and urine samples are sent to Clinical Immunology Service, University of Birmingham for disease response assessments. A cell-free DNA peripheral blood sample is sent to the ICR.

Interventions

On first consent, treatment with standard local treatment may commence for up to 2 cycles (up to 8 weeks) while central molecular risk profiling is performed. Treatment may be with cyclophosphamide, thalidomide, dexamethasone, cyclophosphamide, lenalidomide, dexamethasone, bortezomib, thalidomide, dexamethasone or cyclophosphamide, bortezomib, dexamethasone to further take part in the MUK*nine* trial. This allows participants to start treatment for MM while awaiting results from risk-defining genetic investigations.

MUK*nine a:* participants not identified as having HR disease continue to receive standard treatment or treatment as directed by their clinician and are followed up

Table 2 Eligibility criteria for trial entry and continuing treatment through each stage

Inclusion criteria	Exclusion criteria
Screening ► Undergoing bone marrow investigation due to suspected symptomatic multiple myeloma or plasma cell leukaemia (PCL) *or* Participants with biopsy-confirmed symptomatic multiple myeloma, willing to undergo a further study bone marrow biopsy for molecular profiling. Participants previously screened but found not to have symptomatic multiple myeloma but now have suspected symptomatic multiple myeloma may be re-screened ► Aged 18 years or over ► Fit for intensive chemotherapy and autologous stem cell transplant (at clinician's discretion) ► Eastern Cooperative Oncology Group (ECOG) score ≤2	► Confirmed solitary bone/solitary extramedullary plasmacytoma. ► Primary diagnosis of Waldenstrom's disease. ► Monoclonal gammopathy of undetermined significance or smouldering multiple myeloma unless progression to symptomatic multiple myeloma is highly suspected or confirmed ► Received therapy for multiple myeloma ► Prior or concurrent invasive malignancies ► Any uncontrolled or severe cardiovascular or pulmonary disease ► Grade 2 or greater peripheral neuropathy (per NCI-CTCAEv4.0) ► Known/underlying medical conditions that, in the investigator's opinion, would make the administration of the study drug hazardous ► Any clinically significant cardiac disease ► Known chronic obstructive pulmonary disease (COPD) ► Known to be seropositive for history of HIV or known to have active hepatitis B or hepatitis C. ► Any known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients or known sensitivity to mammalian-derived products. ► Clinically significant allergies or intolerance to cyclophosphamide, lenalidomide, bortezomib, daratumumab or dexamethasone. ► Previous treatment with daratumumab or any other anti-CD38 therapies. ► Participants with contraindication to thromboprophylaxis. ► Participants with POEMS syndrome ► Any concurrent medical or psychiatric condition or disease ► Known or suspected of not being able to comply with the study protocol ► Participant is a woman who is pregnant, or breast feeding, or planning to become pregnant while enrolled in this trial or within at least 6 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 or within at least 6 months after the last dose of trial treatment. ► 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. ► 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. Imaging substudy Only those taking part in the imaging sub study have these exclusions: ► MRI incompatible metal implant ► Claustrophobia

Continued

Table 2 Continued

Inclusion criteria	Exclusion criteria
Treatment ► Confirmation of high-risk (HR) status from ICR. Participants with confirmed PCL with >20% circulating plasma cells do not need confirmation of HR status from ICR to proceed to treatment. ► Confirmation of receipt of baseline bone marrow at HMDS and, blood and urine samples at the University of Birmingham ► Previously untreated participants, although participants may have received up to 2 cycles of CTD, CVD, CRD or VTD pretrial induction chemotherapy while awaiting the results of the laboratory analysis. ► Measurable disease before starting standard treatment – Paraprotein ≥5 g/L or ≥0.5 g/L for IgD subtypes or Serum free kappa or lambda light chains≥100 mg/L with abnormal ratio (for light chain only myeloma) or Urinary Bence Jones protein ≥200 mg/24 hours. ► Non-measurable participants providing they accept a 3 monthly bone marrow during induction and a 6 monthly bone marrow assessment during consolidation and maintenance. ► Fit for intensive chemotherapy and autologous stem cell transplant (at clinician's discretion). ► ECOG performance status ≤2. ► The Celgene Pregnancy Prevention Plan must be followed and participants must agree to comply with this: ► Females of childbearing potential (FCBP) must agree to use 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. ► 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 ► 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 ► 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. ► Laboratory results ► Calculated creatinine clearance ≥30 mL/min (using Cockcroft-Gault formula). ► ALT or AST ≤2.5 times upper limit of normal (ULN). ► Bilirubin ≤2.0 × ULN, except in participants with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 times ULN ► Platelet count ≥75 × 10^9/L. (≥50 × 10^9/L if multiple myeloma involvement in the bone marrow is >50%). Platelet support is permitted. ► Absolute neutrophil count ≥1.0 × 10^9/L. Growth factor support is permitted. ► Haemoglobin ≥80 g/L. Participants may be receiving red blood cell transfusions in accordance with institutional guidelines. ► Corrected serum calcium ≤3.5 mmol/L	► Solitary bone/solitary extramedullary plasmacytoma. ► Primary diagnosis of amyloidosis, monoclonal gammopathy of undetermined significance or smouldering multiple myeloma or Waldenstrom's disease. ► Prior or concurrent invasive malignancies ► Known/underlying medical conditions that, in the investigator's opinion, would make the administration of the study drug hazardous ► Any clinically significant cardiac disease ► Known COPD ► Known to be seropositive for history of HIV or known to have active hepatitis B or hepatitis C. ► Any known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients or known sensitivity to mammalian-derived products. ► Clinically significant allergies or known intolerance to cyclophosphamide, lenalidomide, bortezomib, daratumumab or dexamethasone. ► Previous treatment with daratumumab or any other anti-CD38 therapies. ► Participants with contraindication to thromboprophylaxis. ► Participants with POEMS syndrome ► Any concurrent medical or psychiatric condition or disease ► Known or suspected of not being able to comply with the study protocol ► Participant is a woman who is pregnant, or breast feeding, or planning to become pregnant while enrolled in this trial or within at least 6 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 or within at least 6 months after the last dose of trial treatment. ► 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. ► 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. Imaging substudy Only those taking part in the imaging sub study have these exclusions: ► MRI incompatible metal implant ► Claustrophobia ► Not received a DW-MRI at baseline
Autologous stem cell transplant ► Minimum stem cell harvest of 2×10^6 CD34+ cells/kg body weight. ► Received a minimum of 4, unless CR has been achieved with a lesser number, or a maximum of 6 induction (CVRDd) cycles (including standard treatment). ► Achieved a response of stable disease or better. ► Dose modifications of any or all individual drugs within induction is permitted including complete stop of no more than one agent due to toxicity as long as the required number of cycles have been received	► Participants that have progressive disease.

Continued

Table 2 Continued

Inclusion criteria	Exclusion criteria
Consolidation part 1 ► Undergone autologous transplant with HDM-V conditioning (participants must have received a minimum of 100 mg/m^2 Melphalan in order to proceed with consolidation). ► Neutrophils≥1.0 × 10^9/L. Growth factor support is permitted. ► Platelet count ≥75 × 10^9/L. Platelet support is permitted. ► Dose modifications because of toxicity including complete stop of weekly bortezomib is permitted	► Participants that have progressive disease.
Consolidation part 2 ► Received 6 cycles of consolidation part 1 (VRDd) ► Neutrophils≥1.0 × 10^9/L. Growth factor support is permitted. ► Platelet count ≥75 × 10^9/L. Platelet support is permitted. ► Dose modification of any or all of the individual drugs in consolidation part 1 is permitted including complete stop of no more than one agent because of toxicity as long as the required number of cycles have been received.	► Participants that have progressive disease.
Maintenance ► Received 12 cycles of consolidation part 2 (VRD). ► Neutrophils≥1.0 × 10^9/L. Growth factor support is permitted. ► Platelet count ≥75 × 10^9/L. Platelet support is permitted. ► Dose modification of any or all of the individual drugs in consolidation part 2 is permitted including complete stop of no more than one agent because of toxicity as long as the required number of cycles have been received.	► Participants that have progressive disease.

ALT, alanine transaminase; AST, aspartate transaminase; CR, complete response; CRD, cyclophosphamide, lenalidomide, dexamethasone; CTCAE, common terminology criteria for adverse events; CTD, cyclophosphamide, thalidomide, dexamethasone; CVD, cyclophosphamide, bortezomib, dexamethasone; CVRDd, Cyclophosphamide, bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex), dexamethasone; DW, diffusion-weighted; HDM-V, high dose mephalan with Velcade; HMDS, Haematological Malignancy Diagnostic Service; ICR, Institute of Cancer Research, London; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes; VRD, bortezomib, lenalidomide, daratumumab; VRDd, bortezomib, lenaliomide, daratumumab, dexamethasone; VTD, bortezomib, thalidomide, dexamethasone.

regularly, with information on their treatment pathway and outcomes collected.

MUK*nine b:* participants identified as having HR disease and who consent to take part in the HR treatment schedule receive treatment as in table 1. Eligibility criteria to continue treatment through each stage of ASCT, consolidation part 1 and 2, and maintenance, are detailed in table 2.

Each individual drug in the schedule may be dose reduced if toxicity is experienced, as deemed necessary by the treating physician and in line with standard reductions used for these treatments (table 3). Dose reductions can be made for grade 1 toxicity (eg, neuropathy) to maximise long-term tolerability and treatment effect in this patient group. Dose reductions from pretrial treatment may be continued at induction treatment. The majority of treatment is delivered in hospital; therefore, adherence is as per protocol. Patients are reminded of treatment scheduling for oral medication at each cycle prescription.

Trial assessments

During treatment

MUK*nine a:* for non-HR participants, a summary of treatment received in each phase of treatment is collected. Central samples are collected at the end of any line of standard treatment for response assessment. For patients participating in the imaging study a DW-MRI scan is performed at 100–120 days and 21 months post ASCT, along with bone marrow, peripheral blood and urine samples for disease assessment.

MUK*nine b:* for HR participants, trial assessments are performed in line with the schedule of assessments in table 4. Data are collected at each cycle of treatment and at the end of each phase of treatment, thus limiting loss to follow-up. All adverse events will be collected for all participants from the first investigational medicinal product (IMP) dose until 90 days after the date of the last dose of study drugs.

Central laboratory investigations include:

- Bone marrow aspirate and peripheral blood for molecular profiling:
  - Multiplex ligation-dependent probe amplification (MLPA) or equivalent platform for CNA (del(17p), gain(1q), del(1p)).[28]
  - Real-Time Quantitative Polymerase Chain Reaction (RQ-PCR) translocation assay or equivalent tool for prediction of HR translocations (t(4;14), t(14;16) and t(14;20)).[65]
  - Gene expression profiling based on Affymetrix HG-*U133* Plus 2.0 or equivalent platform with risk profile determined as per EMC92 model[23]
  - Exploratory molecular analyses to identify potentially targetable mutations

Table 3 Dose modifications

Cyclophosphamide Modifications are at the discretion of the investigator *Renal impairment*—a dose reduction of 50% for creatinine clearance of 10 mL/min is recommended *Hepatic impairment*—a dose reduction to 350 mg is recommended with a serum bilirubin of >2.5 times the upper limit of normal (ULN)

Bortezomib

Induction dose reductions

Regimen: first dose reduction CVRDd	**Cycle duration:** 21 days		
Drug	**Dose**	**Route**	**Days**
Cyclophosphamide	500 mg	PO	1 and 8
Bortezomib	1.3 mg/m^2	SC	1, 8, 15
Lenalidomide	25 mg	PO	1–14
Daratumumab	16 mg/kg (actual body weight)	IV	1, 8, 15 (cycles 1 and 2) 1 only (cycle 3 onwards)
Dexamethasone	20–40 mg	PO/IV	1, 8, 15

Postinduction dose reductions

Bortezomib schedule	**Dose levels**				
	0	–1	–2	–3	–4
Twice weekly schedules	1.3 mg/m^2 d 1, 4, 8, 11	1.3 mg/m^2 d 1, 8, 15	1.0 mg/m^2 d 1, 8, 15	1.3 mg/m^2 d 1, 15	Stop
Once weekly schedules	1.3 mg/m^2 d 1, 8, 15, (22)	1.0 mg/m^2 d 1, 8, 15 (22)	1.0 mg/m^2 d 1, 15	0.7 mg/m^2 d 1, 15,	Stop
Consolidation 1	1.3 mg/m^2 d 1, 8, 15, 22	1.0 mg/m^2 d 1, 8, 15, 22	1.0 mg/m^2 d 1, 15	0.7 mg/m^2 d 1, 15,	Stop
Consolidation 2	1.3 mg/m^2 d 1, 8, 15	1.0 mg/m^2 d 1, 8, 15	1.0 mg/m^2 d 1, 15	0.7 mg/m^2 d 1, 15,	Stop

Neuropathy- CTCAE Grade 1 with pain or grade 2—withhold bortezomib until returns to baseline. Dose reduce 1 level; CTCAE Grade 2 with pain or grade 3—withhold bortezomib until returns to baseline. Dose reduce 2 levels; CTCAE Grade 4—discontinue treatment *Renal impairment*—dose reduce at the discretion of the clinician *Hepatic impairment*—moderate or severe impairment (>1.5–3×ULN) should start on a reduced dose of 0.7 mg/m^2 during the first cycle of treatment and dose escalate to 1.0 mg/m^2 or dose reduce to 0.5 mg/m^2 may be considered *Grade 3 Non-haematological toxicity*—withhold until symptoms of toxicity resolve and reduce one dose. *Grade 4 haematological toxicity*—withhold until symptoms of toxicity resolve and reduce one dose. Support may be given.

Lenalidomide schedule	**Dose levels**					
	0	–1	–2	–3	–4	–5
	25 mg	20 mg	15 mg	10 mg	5 mg	2.5 mg

Thrombocytopenia—<25×10^9/L stop lenalidomide for the remainder of the cycle. Return to ≥50 × 10^9/L decrease by 1 dose level to resume the next cycle. *Neutropenia*—first fall to <0.5×10^9/L omit lenalidomide until a return to ≥0.5 × 10^9/L when neutropenia is the only toxicity. Resume lenalidomide at one dose lower. For each subsequent drop to ≥0.5 × 10^9/L omit lenalidomide, resume lenalidomide decreased by 1 dose level at the next cycle. *Renal impairment*—30–50 mL/min 10 mg daily;<30 mL/min, not requiring dialysis 7.5 mg daily or 15 mg every other day; <30 mL/min, requiring dialysis 5 mg daily administered following dialysis *Other non-haematological toxicities*: CTCAE grade 3 and 4 related to lenalidomide should be stopped and started 1 dose lower when toxicity has resolved to grade 2 at clinicians discretion. Rash—interrupt or discontinue for grade 2 or 3. Grade 4 rash discontinue including angioedema, exfoliative or bullous rash or Steven Johnson syndrome or toxic epidermal necrosis.

Daratumumab schedule	**Frequency**	**Dose held**	**Dosing restart**
Induction cycles 1 and 2	Weekly	>3 days	Next planned weekly dose
Induction cycles 3–6	Monthly	>1 week	Next planned weekly dose
Consolidation 1, Consolidation 2, Maintenance	Monthly	>2 weeks	Next planned weekly dose

Continued

Table 3 Continued

Follow the daratumumab SPC. The daratumumab infusion must be withheld to allow for recovery from toxicity ONLY where any of the following criteria are met and the event cannot be ascribed to lenalidomide or cyclophosphamide. ► Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding. ► Grade 4 neutropenia, if this is the second occurrence despite growth factor support. ► Febrile neutropenia of any grade. ► Neutropenia with infection, of any grade. ► Grade 3 or higher non-haematological toxicities with the following exceptions: – Grade 3 nausea that responds to antiemetic treatment within 8 days. – Grade 3 vomiting that responds to antiemetic treatment within 8 days. – Grade 3 diarrhoea that responds to anti-diarrhoeal treatment within 8 days. – Grade 3 fatigue that was present at baseline or that lasts for<8 days after the previous administration of daratumumab. – Grade 3 asthenia that was present at baseline or that lasts for<8 days after the previous administration of daratumumab.
Dexamethasone Occasionally patients will not be able to tolerate because of corticosteroid effects. Dose reductions from 40 to 20 mg daily. Further dose reductions to 10 mg daily is acceptable followed by the omission of dexamethasone If the bortezomib schedule changes, dexamethasone should change in line with it.
Melphalan Dose may be adjusted based on performance status and clinical judgement in discussion with the Chief Investigator GFR measured by Cockcroft & Gault formula or EDTA—>50 mL/min 200 mg/m^2; 30–50 mL/min 140 mg/m^2;<30 mL/min 100 mg/m^2

CTCAE, common terminology criteria for adverse events; CVRDd, Cyclophosphamide, bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex), dexamethasone; GFR, glomerular filtration rate; IV, intravenous; SC, subcutaneous; SPC, summary of product characteristics.

  - Whole exome or whole genome next-generation sequencing.
  - Gene expression profiling (GEP).
  - Epigenetic analyses.
  - Germline variant analysis.
- Bone marrow aspirate for MRD analyses.
- Peripheral blood for disease assessment
  - Disease parameters, for example, paraprotein, for serum response assessments.
  - Beta-2-microglobulin.
  - Albumin.

Quality of life questionnaires, EQ-5D, QLQ-C30 and QLQ-MY20, are collected from all participants at baseline, and for participants who go on to HR treatment these are completed at:

- End of induction treatment.
- 100 days post ASCT then 3-monthly thereafter until disease progression.

Follow-up

On completion of treatment, patients are followed-up at 3 months, and then 6 monthly during standard of care visits, until second disease progression, death or withdrawal. Assessment via standard of care visits promotes participant retention and complete follow-up.

Imaging assessments

All patients participating in the DW-MRI substudy have whole body DW-MRI scan performed at baseline, 100–120 days post ASCT and at end of consolidation part 2.

Outcomes

Primary endpoint

MUK*nine a:*

The proportion of patients with molecular risk-defining investigations performed within 8 weeks.

MUK*nine b:*

The primary endpoints to determine whether to terminate the trial early for futility are

MRD at 100 days post-ASCT

Progression-free survival at 100 days post-ASCT

The primary endpoint to assess efficacy of HR treatment if the trial is not stopped early for futility is PFS at 18 months post registration to screening.

Secondary endpoints

MUK*nine a:* recruitment rates; PFS; OS; second PFS (PFS2); treatment received; overall response;

MUK*nine b:*

Safety and toxicity (adverse reactions (ARs), serious adverse events, serious ARs and suspected unexpected serious ARs graded by common terminology criteria for adverse events v5.0).

MRD at the end of induction therapy, and postconsolidation part 2.

Overall survival

Maximum and overall response at the end of induction therapy, 100 days post-ASCT and postconsolidation part 2.

Time to progression and time to maximum response.

PFS2

Overall treatment benefit and clinician assessment of treatment benefit at the end of induction therapy and 100 days post ASCT.

Quality of life as assessed by the EQ-5D, EORTC QLQ-C30 and EORTC QLQ-MY20.

Treatment compliance.

Table 4 Trial assessments

	All Patients	Non-HR patients			HR patients								
Investigations	**Screening—all participants**	**Prior to any new line of treatment**	**Post any line of treatment**	**First and second disease progression**	**Before starting MUKnine treatment***	**Prior to each cycle of induction treatment CVRDd†**	**End of induction treatment**	**Autologous stem cell transplant¶**	**100–120 days post transplant**	**Prior to each cycle of consolidation part 1 (VRDd), consolidation part 2 (VRD) and maintenance treatment (RD)**	**End of consolidation part 1 (VRDd), consolidation part 2 (VRD) and maintenance treatment (RD)**	**First and second disease progression**	
Consent	X				X								
Medical history	X				X								
Symptom-directed physical exam (including weight, ECOG)	X	X	X		X	X	X	X	X	X	X		
Haematology and biochemistry test	X	X	X		X	X	X	X	X	X	X		
Disease assessment‡	X	X	X	X	X	X	X	X	X	X	X	X	
DW-MRI Imaging††	X								X		X (Part 2 only)		
ECG					X								
Pregnancy testing as required					X	X	X		X	X	X		
Participant questionnaires	X						X		X	X**	X		
Details of treatment			X			X	X	X	X	X	X		
Clinical assessment of treatment benefit							X		X		X		
Central laboratory samples													
Bone marrow aspirate	X			X			X		X		X	X	
Peripheral blood	X	X		X		X §	X		X	X§, **	X	X	
Urine sample	X	X		X		X §	X		X	X§, **	X	X	

*Treatment must start within 14 days of registration to MUK*nine* treatment.
†All assessments must be performed within 72 hours prior to day 1 of each cycle of treatment.
‡Response assessments must be made in line with the International Myeloma Working Group criteria.
§Cycle 1 day 1 only.
¶ Autologous stem cell transplant will be performed as per local practice with local monitoring of adverse events and haematology tests. Participants will be given weekly bortezomib until 100–120 days post transplant, the assessments will be performed monthly during this time for the trial.
**3 monthly during treatment.
††If site and participant taking part in the imaging substudy.
CVRDd, Cyclophosphamide, bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex); DW, diffusion-weighted; ECOG, Eastern Cooperative Oncology Group; HR, high risk; RD, lenalidomide, daratumumab; VRD, bortezomib, lenalidomide, daratumumab; VRDd, bortezomib, lenaliomide, daratumumab, dexamethasone.

Exploratory endpoints

Genomic instability, mutation rates and clonal evolution.

Imaging substudy

PFS; OS; response; patterns of disease distribution and discreet '3D phenotypes'.

Statistical analysis

The MUK*nine b* trial is designed using a Bayesian approach to enable assessment of multiple outcomes and incorporating multiple interim analyses.

The experimental treatment will be evaluated on an ongoing basis based on assessment of MRD status and PFS. Interim assessments are made after cohorts of 10 participants have been followed up to 100–120 days post ASCT, and data reviewed by an independent Data Monitoring and Ethics Committee (DMEC). The trial may be terminated early for futility on the basis of MRD status and PFS at 100–120 days post ASCT, using initial predefined stopping boundaries based on Myeloma IX data. Following updated prior information becoming available from Myeloma XI/XI+, these stopping boundaries were recalculated to provide updated decision criteria.

If the trial is not terminated early, up to 105 newly diagnosed patients with molecular HR disease will be registered to treatment. With the availability of molecularly matched individual participant data from currently running trials (Myeloma XI/XI+) a body of almost concurrent control data is available to use for the purpose of exploratory statistical comparison.

The experimental treatment arm will be compared with control in terms of PFS at 18 months post registration to screening, expressed as a binary outcome, within the Bayesian framework. Further analyses of PFS at 18 months will be performed outside of the Bayesian framework using Kaplan-Meier estimation.

MUK*nine a* endpoints, and secondary and exploratory endpoints will be analysed using summary statistics alongside confidence intervals where appropriate. All analyses are fully detailed in a statistical analysis plan prior to being undertaken. Full statistical analysis for MUK*nine* is provided in online supplemental file 1, and discussed in the MUK*nine* statistical methods paper (in preparation).

Trial conduct

Data are collected via electronic case report forms. Site monitoring of source data is performed by University of Leeds Clinical Trials Research Unit (CTRU) following the trial monitoring plan. The trial is conducted in accordance with the principles of Good Clinical Practice and in line with the relevant Research Governance Framework within the UK through adherence with CTRU standard operating procedures. All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CTRU. An independent DMEC reviews safety data on a regular basis to identify any safety concerns or trends. An independent Trial Steering Committee periodically reviews safety data and discusses recommendations made by the DMEC.

Statement of indemnity

This trial is sponsored by The University of Leeds and the University of Leeds will be liable for negligent harm caused by the design of the trial. The NHS has a duty of care to participants treated, whether or not the participant is taking part in a clinical trial, and the NHS remains liable for clinical negligence and other negligent harm to participants under this duty of care.

As this is a clinician-led trial, there are no arrangements for no-fault compensation. As this is a clinician-led trial, there are no arrangements for no-fault compensation; however, usual product liability will be covered by the manufacturer under the Consumer Protection Act 1987.

Patient and public involvement

Patients were involved in review and development of trial design, protocol and patient information sheet (model consent form provided in online supplemental file 2).

Ethics and dissemination

The trial has national research ethics approval from the NHS National Research Ethics Service, London South East Research Ethics Committee (Ref: 17/LO/0022, 17/LO/0023). All patients provide written informed consent prior to take part in the trial at the hospital site where they are recruited. Any required protocol amendments will be submitted to ethics and the Medicines and Healthcare products Regulatory Agency (MHRA) (as appropriate), and will be implemented at the relevant sites once approved. Information on amendments will be reported to the DMEC and Trial Steering Committee (TSC).

A manuscript with results of the MUK*nine b* study will be published in a peer-reviewed journal. Separate manuscripts will be written for results of MUK*nine a* and each of the exploratory objectives; these will also be submitted for publication in peer-reviewed journals. Credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributorship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions. Professional writers are not intended to be used. On publication of the final long-term results of the study, requests for use of data may be made to the CTRU and will be reviewed by the Trial Management Group.

DISCUSSION

This is the first time in the UK genetic risk has been used prospectively in MM to identify participants to be treated in an academically-led clinical trial and select treatment based solely on this. It is hoped this trial will bring improved survival and longer term disease control for patients with HRMM in the future by providing an intensive treatment regimen specifically targeted at this difficult to treat disease subgroup. In addition, the trial

will provide important evidence regarding feasibility of multicentre molecular-risk stratified trials in MM at the point of diagnosis, using central molecular tumour investigations.

Intensive treatment in HR patients has been used outside the UK with some promising results but access to drugs in the UK has been challenging. This trial is designed to work within the UK NHS system and provide the best treatment for HR patients. The availability of novel targeted molecular therapies helps in treating the highly heterogeneous disease of MM. Ultimately data generated through this trial aim to support the case for access to combination therapies of expensive agents to patient subgroups with a high unmet need such as HR disease.

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Contributors SB and DS contributed equally as joint first authors. MJ and MK contributed equally as joint last authors. MJ, MK, GP, SB, LF, SH and DS designed the trial. SH, AH, KW and SB developed the statistical analysis plan and are responsible for the ongoing statistical monitoring, analysis and interpretation of data. DS, SH, MK and MJ wrote the manuscript. MJ, MK, CM and GP perform the research and collect data. DS, LF and SR perform trial and data management. All authors reviewed and approved the final manuscript.

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