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The MUK*nine* OPTIMUM protocol: A screening study to identify high risk multiple myeloma patients 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 MM patients, but in approximately 20% of patients the tumour is characterised by genetic changes which confer a significantly poorer prognosis, generally termed as 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*) is designed to evaluate novel treatment strategies for patients with HRMM. Patients with suspected or newly diagnosed MM, fit for intensive therapy, are offered participation in a central tumour genetic screening protocol (MUK*nine a*). Patients identified as molecularly HR are invited into the phase II, single-arm, multi-centre trial (MUK*nine b*) investigating an intensive treatment schedule comprising bortezomib (Velcade), lenalidomide (Revlimid), daratumumab (Darzalex), low-dose cyclophosphamide & dexamethasone, with single high dose melphalan and autologous stem cell transplantation followed by combination consolidation and maintenance therapy. 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 will receive standard local treatment and followed up in a cohort study.

Exploratory studies include longitudinal whole body diffusion weighted MRI for imaging Minimal Residual Disease (MRD) testing.

Ethics and dissemination: Ethics approval obtained. Results of study and substudies will be submitted for publication in a peer-reviewed journal.

Trial Registration: ISRCTN16847817, May 2017

Key Words: Newly diagnosed multiple myeloma, daratumumab, phase II, Bayesian, minimal residual disease

Article summary

Strengths and limitations of the study

- This is the first time in the UK that newly diagnosed multiple myeloma patients may be entered into a clinical trial prospectively according to their genetic risk profile
- A flexible multiple outcome, multi-stage 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 standard risk disease. The trial has completed recruitment and is currently in follow-up.

Defining high risk disease

In a recent meta-analysis of 1,905 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 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 co-segregation 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 (ISS)[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 high risk 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 has 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 multi-drug cytotoxic alkylating chemotherapy is hypothesised to benefit HR patients. Ongoing use of a combination of biologic agents with favourable toxicity profiles can potentially minimise the chance of relapse due to sustained multi-angled pressure on the MM re-populating 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 (RCVD) combination failed to show any additional benefit to RVD (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].

Whilst tandem 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 high risk 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 MRD negative disease state. Melphalan has been combined with bortezomib in phase II studies demonstrating safety and improvement in complete response 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-high risk group such as double-hit MM are unknown[48]. The highly proliferative behaviour of

double-hit disease and GEP high risk provides rationale for a bridging treatment for the three 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 multi-agent 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 minimal residual disease monitoring can predict remission status with higher sensitivity than standard biochemical/protein analyses and could be of use in identifying HRMM patients 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 multi-centre 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 salvage treatment [54 55]. The addition of bortezomib in phase II studies demonstrated safety and improvement in complete response (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. Utililsing 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: 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 utilising 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 & daratumumab in combination with low-dose cyclophosphamide & 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 sub-study is included to explore the association of imaging MRD status with clinical outcomes and to assess patterns of disease distribution by whole body 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, multi-centre trial. MUK*nine b* incorporates interim assessments for futility using a Bayesian strategy for monitoring multiple outcomes proposed by Thall, Simon and Estey[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.

Diffusion-weighted whole body MRI (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 sub-study 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 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. The imaging sub-study 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 pre-tests 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 are in Table 2.

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 sub-study. 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 (IMWG) guidelines[63], the Myeloma IX trial and the EMC92 GEP model[3 5 10 21 64]:

- 2 or more adverse lesions [t(4;14), t(14;16), t(14;20), gain(1q), del(17p), del(1p)]
- GEP – high risk score as per EMC92/SKY92 GEP model

- PCL, defined as the presence of more than $2x10^9$/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 (HMDS), 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

Upon first consent, treatment with standard local treatment may commence for up to 2 cycles (up to 8 weeks) whilst central molecular risk profiling is performed. Treatment may be with cyclophosphamide, thalidomide, dexamethasone (CTD), cyclophosphamide, lenalidomide, dexamethasone (CRD), bortezomib, thalidomide, dexamethasone (VTD) or cyclophosphamide, bortezomib, dexamethasone (CVD) 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 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 (e.g. neuropathy) to maximise long-term tolerability and treatment effect in this patient group. Dose reductions from pre-trial treatment may be continued at induction treatment.

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.

Central laboratory investigations include:

- Bone marrow aspirate and peripheral blood for molecular profiling:
  - MLPA or equivalent platform for copy number aberrations [del(17p), gain(1q), del(1p)][28]
  - 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
    - 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, e.g. 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

Upon completion of treatment, patients are followed-up at 3 months, and then six-monthly during standard of care visits, until second disease progression, death or withdrawal

Imaging assessments

All patients participating in the DW-MRI sub-study 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

Minimal residual disease 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 (SAEs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) graded by common terminology criteria for adverse events (CTCAE) v5.0)

MRD at the end of induction therapy, and post- consolidation part 2

OS

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

Exploratory Endpoints

Genomic instability, mutation rates and clonal evolution

Imaging sub-study

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 pre-defined stopping boundaries based on Myeloma IX data. Following updated prior information becoming available from Myeloma XI/XI+, these stopping boundaries were re-calculated 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 to 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 also 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 CTRU following the trial monitoring plan. The trial is conducted in accordance with the principles of Good Clinical Practice (GCP) and in line with the relevant Research Governance Framework within the UK through adherence with University of Leeds CTRU standard operating procedures. 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.

Patient and Public Involvement

Patients were involved in review and development of trial design, protocol and patient information sheet.

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.

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. Upon 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 sub-group. In addition, the trial will provide important evidence regarding feasibility of multi-centre 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 aims to support the case for access to combination therapies of expensive agents to patient subgroups with a high unmet need such as HR disease.

Abbreviations

ADCC	antibody dependant cytotoxicity
ADCP	antibody dependant cell phagocytosis
ALT	Alanine transaminase
ASCT	Autologous stem cell transplant
AST	Aspartate transaminase
CRD	Cyclophosphamide, Lenalidomide (Revlimid®), Dexamethasone
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Cyclophosphamide, thalidomide, dexamethasone
DMEC	Data Monitoring and Ethics Committee
DW-MRI	Diffuse weighted magnetic resonance imaging
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group performance status
^{18}F-FDG PET-CT	18F-fluorodeoxyglucose - Positron emission tomography - computerised tomography
GEP	Gene expression profiling
HDM-V	High dose Melphalan with Velcade (bortezomib)
HR	High risk
IMID	Immunomodulatory drugs
IMWG	International Myeloma Working Group
KCRD	Carfilzomib, Cyclophosphamide, Lenalidomide, Dexamethasone
MM	Multiple Myeloma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
OS	Overall survival
PCL	Plasma Cell Leukaemia
PFS	Progression-free survival
PFS2	Second progression-free survival
RCVD	Lenalidomide, Cyclophosphamide, Bortezomib, Dexamethasone
RVD	Lenalidomide, Bortezomib, Dexamethasone
RD	Lenalidomide, Dexamethasone
VRD	Bortezomib, Lenalidomide, Daratumumab
VRDd	Bortezomib, Lenalidomide, Daratumumab, dexamethasone

Competing interests

SH, DS, LF, SR, AH, KW and SB declare they have no competing interests. MK has served as a consultant and received honoraria from Celgene, Takeda, Amgen, Chugai, BMS, AbbVie and Janssen, and has received research funding from Celgene. GP served as a consultant and received honoraria from Janssen Oncology, Celgene, Amgen, Takeda, Gilead Sciences and Binding Site. MJ has served as a consultant and received honoraria from Celgene, Janssen, Takeda, Amgen, AbbVie and Novartis.

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Author Contributions

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 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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Figure 1. MUK*nine* OPTIMUM trial design

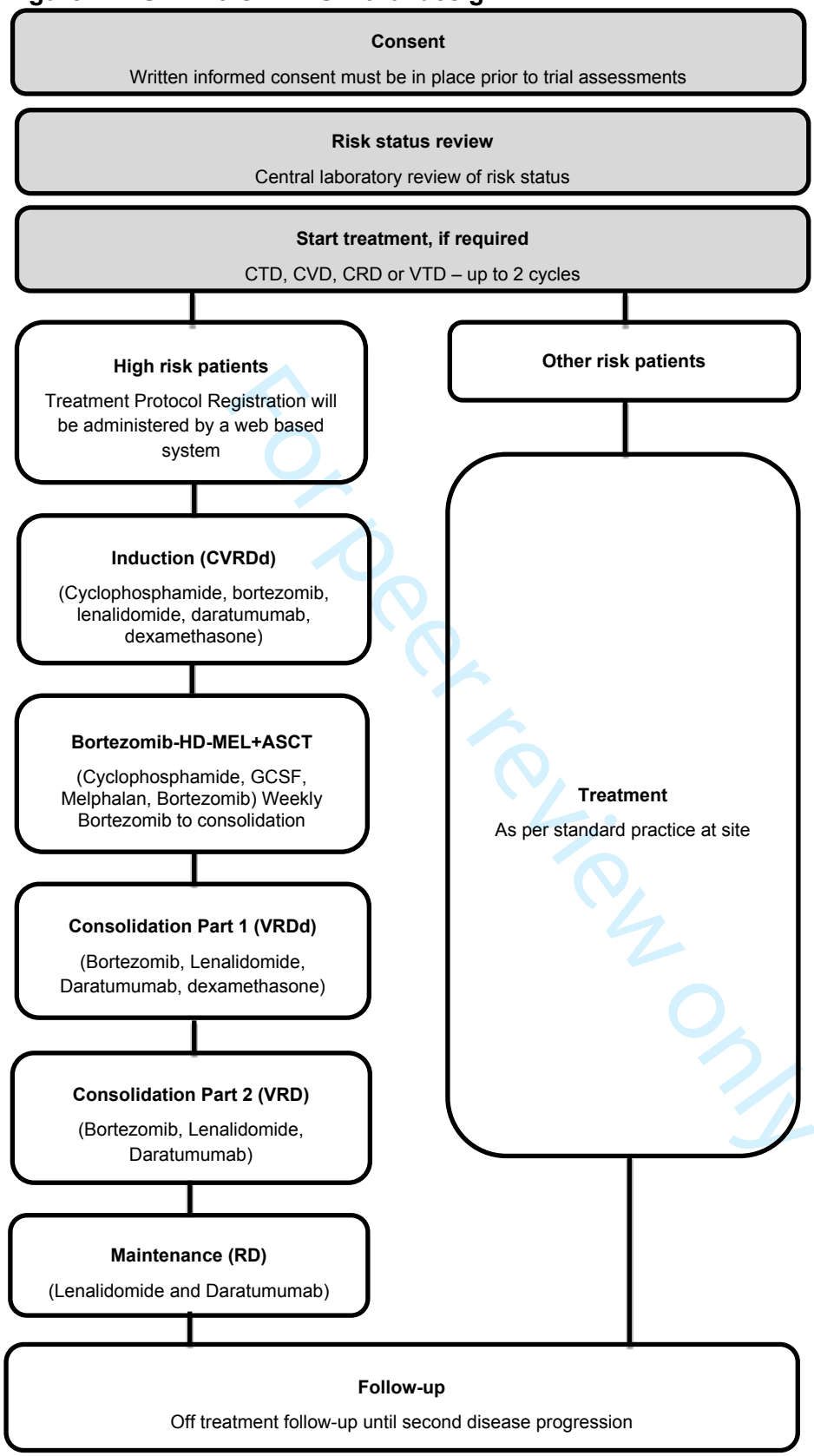

Table 1: Treatment Schedule

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 mg – 40 mg	PO/IV	1, 4, 8, 11
Autologous Stem Cell Transplant			
Cyclophosphamide and GCSF mobilisation is recommended			
Regimen: Bortezomib HD-MEL+ASCT			
Drug	**Dose**	**Route**	**Days**
Melphalan	200 mg/m^2	IV	-1
Bortezomib	1.3mg/m^2	SC	-1, (8-18 hours post Melphalan)
Autologous stem cell return		IV	0
Bortezomib	1.3mg/m^2	SC	+5, +14, then weekly to consolidation 1
Consolidation Treatment 1			
To begin between 100 -120 days post ASCT			
Regimen: VRDd x 6 cycles*		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Bortezomib	1.3mg/m^2	SC	1, 8,15, 22
Lenalidomide	25mg	PO	1 - 21
Daratumumab	16mg/kg (actual body weight)	IV	1
Dexamethasone*	20mg-40mg	PO/IV	1, 8,15**, 22
Consolidation Treatment 2			
Regimen: VRD x 12 cycles*		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Bortezomib	1.3mg/m^2	SC	1, 8,15
Lenalidomide	25mg	PO	1 - 21
Daratumumab	16mg/kg (actual body weight)	IV	1

Maintenance Treatment			
Regimen: RD until progression		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Lenalidomide	10mg	PO	1 - 21
Daratumumab	16mg/kg (actual body weight)	IV	1

** On days where participants receive dexamethasone 40mg at site (i.e. pre Daratumumab infusion), dexamethasone must not be self-administered at home too.*

*** On day 15 participants will receive pre-med as per SPC (e.g. methylprednisolone)*

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 human immunodeficiency virus (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. <u>Imaging sub-study</u> Only those taking part in the imaging sub study have these exclusions: • MRI incompatible metal implant • Claustrophobia
Treatment • Confirmation of High Risk status from ICR. Participants with confirmed plasma cell leukaemia 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 pre-trial induction chemotherapy while awaiting the results of the laboratory analysis. • Measurable disease before starting standard treatment ○ Paraprotein ≥ 5g/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/24h. • 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). • Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2.	• 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 chronic obstructive pulmonary disease (COPD) • Known to be seropositive for history of human immunodeficiency virus (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.

• The Celgene Pregnancy Prevention Plan must be followed and participants must agree to comply with this:
  • 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.
  • 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 ≥ 30mL/min (using Cockcroft-Gault formula).
  • ALT or AST ≤ 2.5 times upper limit of normal (ULN).
  • Bilirubin ≤ 2.0 x ULN, except in participants with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 times ULN
  • Platelet count ≥ 75 x 10^9/L. (≥ 50 x 10^9/L if multiple myeloma involvement in the bone marrow is >50%). Platelet support is permitted.
  • Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L. Growth factor support is permitted.
  • Haemoglobin ≥ 80 g/L. (Participants may be receiving red blood cell (RBC) transfusions in accordance with institutional guidelines.
  • Corrected serum calcium ≤ 3.5 mmol/L
	• 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.
	
	<u>Imaging sub-study</u>
	
	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 x 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 (SD_ 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	• Participants that have progressive disease.

long as the required number of cycles have been received	
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 x 10^9/L. Growth factor support is permitted. • Platelet count ≥ 75 x 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 x 10^9/L. Growth factor support is permitted. • Platelet count ≥ 75 x 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 x 10^9/L. Growth factor support is permitted. • Platelet count ≥ 75 x 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.

Table 3: Dose Modifications

Cyclophosphamide
Modifications are at the discretion of the investigator
Renal Impairment - A dose reduction of 50% for creatinine clearance of 10ml/min is recommended
Hepatic Impairment - A dose reduction to 350mg is recommended with a serum bilirubin of >2.5 times the upper limit of normal

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 mg – 40 mg	PO/IV	1, 8, 15

Post induction 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 – 3x ULN) should start on a reduced dose of 0.7mg/m^2 during the first cycle of treatment and dose escalate to 1.0 mg/m^2 or dose reduce to 0.5mg/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
	25mg	20mg	15mg	10mg	5mg	2.5 mg

Thrombocytopenia - <25 x 10^9/L stop lenalidomide for the remainder of the cycle. Return to ≥50 x 10^9/L decrease by 1 dose level to resume the next cycle.
Neutropenia – first fall to <0.5 x 10^9/L omit lenalidomide until a return to ≥0.5 x 10^9/L when neutropenia is the only toxicity. Resume lenalidomide at one dose lower. For each subsequent drop to ≥0.5 x 10^9/L omit lenalidomide, resume lenalidomide decreased by 1 dose level at the next cycle.
Renal impairment – 30- 50 mL/min 10mg daily; < 30 mL/min, not requiring dialysis 7.5mg daily or 15mg every other day; < 30 mL/min, requiring dialysis 5mg daily administered following dialysis
Other non haematological toxicities: CTCAE grade 3 & 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

Follow the daratumumab SmPC. 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 20mg daily. Further dose reductions to 10mg 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 judgment in discussion with the Chief Investigator
GFR measured by Cockcroft & Gault formula or EDTA - >50ml/min 200mg/m2; 30-50ml/min 140mg/m^2; <30ml/min 100mg/m^2

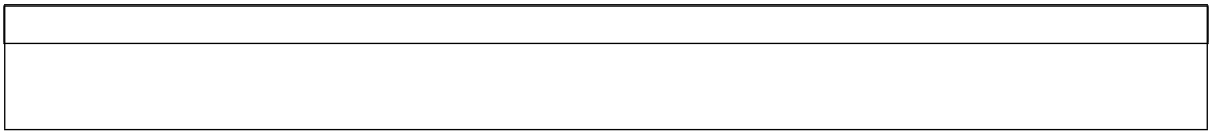

Table 4: Trial Assessments

	All Patients	Non HR Patients			HR Patients							
Investigations	**All – Screening participants**	**Prior to any new line of treatment**	**Post any line of treatment**	**First and second disease progression**	**Before starting MUKnine treatment [1]**	**Prior to each cycle of induction CVRDd [2]**	**End of induction treatment**	**Autologous stem cell transplant [5]**	**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 & biochemistry test	X	X	X		X	X	X	X	X	X	X	
Disease assessment [3]	X	X	X	X	X	X	X	X	X	X	X	X
DW-MRI Imaging [7]	X								X		X (Part 2 only)	
ECG					X							
Pregnancy testing as required					X	X	X		X	X	X	
Participant questionnaires	X						X		X	X [6]	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 [4]	X		X	X [4, 6]	X	X
Urine sample	X	X		X		X [4]	X		X	X [4, 6]	X	X

1 Treatment must start within 14 days of registration to MUK*nine* treatment

2 All assessments must be performed within 72 hours prior to day 1 of each cycle of treatment

3 Response assessments must be made in line with the IMWG criteria

4 Cycle 1 day 1 only

5 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.

6 3 monthly during treatment

7 if site and participant taking part in the imaging sub-study

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1, 2, 4-9, 11-15, Tables 1 and 2
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	14, 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,14
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14, 15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12, 13, 14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-7
	6b	Explanation for choice of comparators	3, 8, 12
Objectives	7	Specific objectives or hypotheses	7, 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8, 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9, 10 and Table 3
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Detailed in main protocol
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Table 2, Table 3

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11, 12, further detail in MUK nine statistical methods paper and statistical analysis plan
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-11, Figure 1, Table 4
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8, 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Detailed in main protocol
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA, not randomised
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA, not randomised
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA, not randomised
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA, not randomised or blinded

	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA, not randomised or blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-13, Table 4
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Detailed in main protocol
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13, 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Detailed in MUK nine statistical methods paper and statistical analysis plan
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Detailed in MUK nine statistical methods paper and statistical analysis plan

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Detailed in MUK nine statistical methods paper and statistical analysis plan
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12, 13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9, 12
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10, 11, 27. Further detail in main protocol
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Detailed in main protocol
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-10, 13. Further detail in main protocol

	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9, 10. Further detail in main protocol
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Detailed in main protocol
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	13, 14. Further detail in main protocol
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	Detailed in main protocol
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 13
	31b	Authorship eligibility guidelines and any intended use of professional writers	Detailed in main protocol
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Detailed in main protocol
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Detailed in main protocol
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9, 10, Table 4. Further detail in main protocol

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The MUKnine OPTIMUM protocol: A screening study to identify high risk multiple myeloma patients 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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The MUK*nine* OPTIMUM protocol: A screening study to identify high risk multiple myeloma patients 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 MM patients, 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, multi-centre trial (MUK*nine b*) investigating an intensive treatment schedule comprising bortezomib, lenalidomide, daratumumab, low-dose cyclophosphamide & 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 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: ISRCTN16847817, May 2017

Key Words: Newly diagnosed multiple myeloma, daratumumab, phase II, Bayesian, minimal residual disease

Article summary

Strengths and limitations of the study

- This is the first time in the UK that newly diagnosed multiple myeloma patients may be entered into a clinical trial prospectively according to their genetic risk profile
- A flexible multiple outcome, multi-stage 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 standard risk disease. The trial has completed recruitment and is currently in follow-up.

Defining high risk disease

In a recent meta-analysis of 1,905 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 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 co-segregation 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 (ISS)[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 high risk 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 has 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 multi-drug cytotoxic alkylating chemotherapy is hypothesised to benefit HR patients. Ongoing use of a combination of biologic agents with favourable toxicity profiles can potentially minimise the chance of relapse due to sustained multi-angled pressure on the MM re-populating 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 (RCVD) combination failed to show any additional benefit to RVD (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].

Whilst tandem 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 high risk 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 MRD negative disease state. Melphalan has been combined with bortezomib in phase II studies demonstrating safety and improvement in complete response 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-high risk group such as double-hit MM are unknown[48]. The highly proliferative behaviour of

double-hit disease and GEP high risk provides rationale for a bridging treatment for the three 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 multi-agent 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 minimal residual disease monitoring can predict remission status with higher sensitivity than standard biochemical/protein analyses and could be of use in identifying HRMM patients 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 multi-centre 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 complete response (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. Utililsing 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: 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 utilising 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 & daratumumab in combination with low-dose cyclophosphamide & 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 sub-study is included to explore the association of imaging MRD status with clinical outcomes and to assess patterns of disease distribution by whole body 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, multi-centre trial. MUK*nine b* incorporates interim assessments for futility using a Bayesian strategy for monitoring multiple outcomes proposed by Thall, Simon and Estey[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.

Diffusion-weighted whole body MRI (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 sub-study 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 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 sub-study 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 pre-tests 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 are 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 sub-study. 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 (IMWG) guidelines[63], the Myeloma IX trial and the EMC92 GEP model[3 5 10 21 64]:

- 2 or more adverse lesions [t(4;14), t(14;16), t(14;20), gain(1q), del(17p), del(1p)]
- GEP – high risk score as per EMC92/SKY92 GEP model
- PCL, defined as the presence of more than $2x10^9$/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 (HMDS), 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

Upon first consent, treatment with standard local treatment may commence for up to 2 cycles (up to 8 weeks) whilst central molecular risk profiling is performed. Treatment may be with cyclophosphamide, thalidomide, dexamethasone (CTD), cyclophosphamide, lenalidomide, dexamethasone (CRD), bortezomib, thalidomide, dexamethasone (VTD) or cyclophosphamide, bortezomib, dexamethasone (CVD) 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 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 (e.g. neuropathy) to maximise long-term tolerability and treatment effect in this patient group. Dose reductions from pre-trial 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 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:
  - MLPA or equivalent platform for copy number aberrations [del(17p), gain(1q), del(1p)][28]
  - 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
    - 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, e.g. 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

Upon completion of treatment, patients are followed-up at 3 months, and then six-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 sub-study 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

Minimal residual disease 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 (SAEs), serious adverse reactions (SARs) and suspected unexpected serious adverse reactions (SUSARs) graded by common terminology criteria for adverse events (CTCAE) v5.0)

MRD at the end of induction therapy, and post- consolidation part 2

OS

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

Exploratory Endpoints

Genomic instability, mutation rates and clonal evolution

Imaging sub-study

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 pre-defined stopping boundaries based on Myeloma IX data. Following updated prior information becoming available from Myeloma XI/XI+, these stopping boundaries were re-calculated 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 to 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 Supplementary 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 CTRU following the trial monitoring plan. The trial is conducted in accordance with the principles of Good Clinical Practice (GCP) and in line with the relevant Research Governance Framework within the UK through adherence with University of Leeds 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 Supplementary 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 MHRA (as appropriate), and will be implemented at the relevant sites once approved. Information on amendments will be reported to the DMEC and 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. Upon 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 sub-group. In addition, the trial will provide important evidence regarding feasibility of multi-centre 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 aims to support the case for access to combination therapies of expensive agents to patient subgroups with a high unmet need such as HR disease.

Abbreviations

ADCC	antibody dependant cytotoxicity
ADCP	antibody dependant cell phagocytosis
ALT	Alanine transaminase
ASCT	Autologous stem cell transplant
AST	Aspartate transaminase
CRD	Cyclophosphamide, Lenalidomide (Revlimid®), Dexamethasone
CTCAE	Common Terminology Criteria for Adverse Events
CTD	Cyclophosphamide, thalidomide, dexamethasone
DMEC	Data Monitoring and Ethics Committee
DW-MRI	Diffuse weighted magnetic resonance imaging
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group performance status
^{18}F-FDG PET-CT	18F-fluorodeoxyglucose - Positron emission tomography - computerised tomography
GEP	Gene expression profiling
HDM-V	High dose Melphalan with Velcade (bortezomib)
HR	High risk
IMID	Immunomodulatory drugs
IMWG	International Myeloma Working Group
KCRD	Carfilzomib, Cyclophosphamide, Lenalidomide, Dexamethasone
MM	Multiple Myeloma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
OS	Overall survival
PCL	Plasma Cell Leukaemia
PFS	Progression-free survival
PFS2	Second progression-free survival
RCVD	Lenalidomide, Cyclophosphamide, Bortezomib, Dexamethasone
RVD	Lenalidomide, Bortezomib, Dexamethasone
RD	Lenalidomide, Dexamethasone
VRD	Bortezomib, Lenalidomide, Daratumumab
VRDd	Bortezomib, Lenalidomide, Daratumumab, dexamethasone

Competing interests

SH, DS, LF, SR, AH, KW and SB declare they have no competing interests. MK has served as a consultant and received honoraria from Celgene, Takeda, Amgen, Chugai, BMS, AbbVie and Janssen, and has received research funding from Celgene. GP served as a consultant and received honoraria from Janssen Oncology, Celgene, Amgen, Takeda, Gilead Sciences and Binding Site. MJ has served as a consultant and received honoraria from Celgene, Janssen, Takeda, Amgen, AbbVie and Novartis.

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Author Contributions

Sarah Brown & Debbie Sherrat contributed equally as joint first authors. Matthew Jenner & Martin Kaiser 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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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 mg – 40 mg	PO/IV	1, 4, 8, 11
Autologous Stem Cell Transplant			
Cyclophosphamide and GCSF mobilisation is recommended			
Regimen: Bortezomib HD-MEL+ASCT			
Drug	**Dose**	**Route**	**Days**
Melphalan	200 mg/m^2	IV	-1
Bortezomib	1.3mg/m^2	SC	-1, (8-18 hours post Melphalan)
Autologous stem cell return		IV	0
Bortezomib	1.3mg/m^2	SC	+5, +14, then weekly to consolidation 1
Consolidation Treatment 1			
To begin between 100 -120 days post ASCT			
Regimen: VRDd x 6 cycles*		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Bortezomib	1.3mg/m^2	SC	1, 8,15, 22
Lenalidomide	25mg	PO	1 - 21
Daratumumab	16mg/kg (actual body weight)	IV	1
Dexamethasone*	20mg-40mg	PO/IV	1, 8,15**, 22
Consolidation Treatment 2			
Regimen: VRD x 12 cycles*		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Bortezomib	1.3mg/m^2	SC	1, 8,15
Lenalidomide	25mg	PO	1 - 21
Daratumumab	16mg/kg (actual body weight)	IV	1

Maintenance Treatment			
Regimen: RD until progression		**Cycle duration:** 28 days	
Drug	**Dose**	**Route**	**Days**
Lenalidomide	10mg	PO	1 - 21
Daratumumab	16mg/kg (actual body weight)	IV	1

** On days where participants receive dexamethasone 40mg at site (i.e. pre Daratumumab infusion), dexamethasone must not be self-administered at home too.*

*** On day 15 participants will receive pre-med as per SPC (e.g. methylprednisolone)*

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 human immunodeficiency virus (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. <u>Imaging sub-study</u> Only those taking part in the imaging sub study have these exclusions: • MRI incompatible metal implant • Claustrophobia
Treatment • Confirmation of High Risk status from ICR. Participants with confirmed plasma cell leukaemia 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 pre-trial induction chemotherapy while awaiting the results of the laboratory analysis. • Measurable disease before starting standard treatment ○ Paraprotein ≥ 5g/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/24h. • 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). • Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2.	• 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 chronic obstructive pulmonary disease (COPD) • Known to be seropositive for history of human immunodeficiency virus (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.

• The Celgene Pregnancy Prevention Plan must be followed and participants must agree to comply with this:
  • 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.
  • 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 ≥ 30mL/min (using Cockcroft-Gault formula).
  • ALT or AST ≤ 2.5 times upper limit of normal (ULN).
  • Bilirubin ≤ 2.0 x ULN, except in participants with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 times ULN
  • Platelet count ≥ 75 x 10^9/L. (≥ 50 x 10^9/L if multiple myeloma involvement in the bone marrow is >50%). Platelet support is permitted.
  • Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L. Growth factor support is permitted.
  • Haemoglobin ≥ 80 g/L. (Participants may be receiving red blood cell (RBC) transfusions in accordance with institutional guidelines.
  • Corrected serum calcium ≤ 3.5 mmol/L
	• 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.
	
	<u>Imaging sub-study</u>
	
	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 x 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 (SD_ 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	• Participants that have progressive disease.

long as the required number of cycles have been received	
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 x 10^9/L. Growth factor support is permitted. • Platelet count ≥ 75 x 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 x 10^9/L. Growth factor support is permitted. • Platelet count ≥ 75 x 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 x 10^9/L. Growth factor support is permitted. • Platelet count ≥ 75 x 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.

Table 3: Dose Modifications

Cyclophosphamide
Modifications are at the discretion of the investigator
Renal Impairment - A dose reduction of 50% for creatinine clearance of 10ml/min is recommended
Hepatic Impairment - A dose reduction to 350mg is recommended with a serum bilirubin of >2.5 times the upper limit of normal

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 mg – 40 mg	PO/IV	1, 8, 15

Post induction 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 – 3x ULN) should start on a reduced dose of 0.7mg/m^2 during the first cycle of treatment and dose escalate to 1.0 mg/m^2 or dose reduce to 0.5mg/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
	25mg	20mg	15mg	10mg	5mg	2.5 mg

Thrombocytopenia - <25 x 10^9/L stop lenalidomide for the remainder of the cycle. Return to ≥50 x 10^9/L decrease by 1 dose level to resume the next cycle.
Neutropenia – first fall to <0.5 x 10^9/L omit lenalidomide until a return to ≥0.5 x 10^9/L when neutropenia is the only toxicity. Resume lenalidomide at one dose lower. For each subsequent drop to ≥0.5 x 10^9/L omit lenalidomide, resume lenalidomide decreased by 1 dose level at the next cycle.
Renal impairment – 30- 50 mL/min 10mg daily; < 30 mL/min, not requiring dialysis 7.5mg daily or 15mg every other day; < 30 mL/min, requiring dialysis 5mg daily administered following dialysis
Other non haematological toxicities: CTCAE grade 3 & 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

Follow the daratumumab SmPC. 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 20mg daily. Further dose reductions to 10mg 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 judgment in discussion with the Chief Investigator
GFR measured by Cockcroft & Gault formula or EDTA - >50ml/min 200mg/m2; 30-50ml/min 140mg/m^2; <30ml/min 100mg/m^2

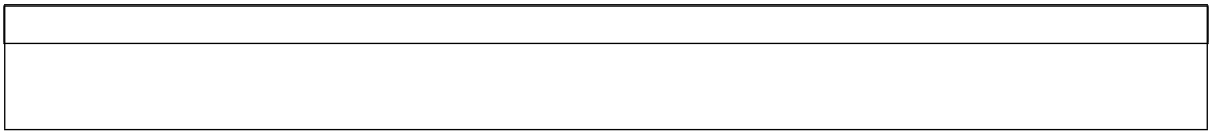

Table 4: Trial Assessments

	All Patients	Non HR Patients			HR Patients							
Investigations	**All – Screening participants**	**Prior to any new line of treatment**	**Post any line of treatment**	**First and second disease progression**	**Before starting MUKnine treatment [1]**	**Prior to each cycle of induction CVRDd [2]**	**End of induction treatment**	**Autologous stem cell transplant [5]**	**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 & biochemistry test	X	X	X		X	X	X	X	X	X	X	
Disease assessment [3]	X	X	X	X	X	X	X	X	X	X	X	X
DW-MRI Imaging [7]	X								X		X (Part 2 only)	
ECG					X							
Pregnancy testing as required					X	X	X		X	X	X	
Participant questionnaires	X						X		X	X [6]	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 [4]	X		X	X [4, 6]	X	X
Urine sample	X	X		X		X [4]	X		X	X [4, 6]	X	X

1 Treatment must start within 14 days of registration to MUK*nine* treatment

2 All assessments must be performed within 72 hours prior to day 1 of each cycle of treatment

3 Response assessments must be made in line with the IMWG criteria

4 Cycle 1 day 1 only

5 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.

6 3 monthly during treatment

7 if site and participant taking part in the imaging sub-study

Figure 1: MUKnine OPTIMUM trial design

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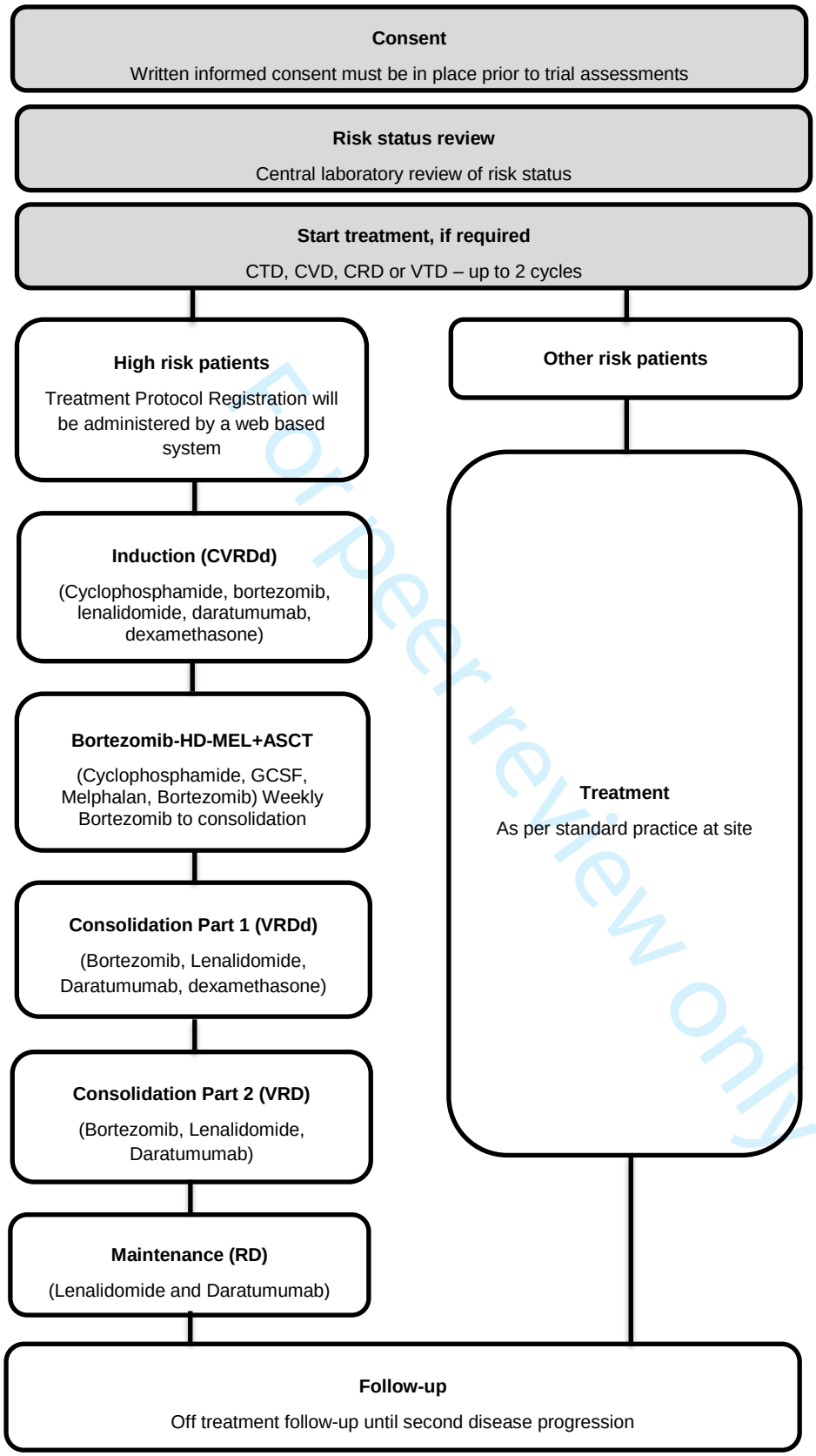

Figure 1. MUK*nine* OPTIMUM trial design

Statistical analysis

MUK*nine a*

Analyses using response and progression data will be performed using the data recorded on the CRF. The data recorded on the CRF may be centrally reviewed to assess the quality of these data.

Screening population

The screening population will include all participants who are registered into MUK *nine a*, regardless of their risk assessment. Participants for whom we do not receive a risk assessment result will be included in this population.

Non-MUK *nine b* population

The Non-MUK nine b population will include all participants who are registered into MUK *nine a*, regardless of their risk assessment, who are not registered into the MUK *nine b* trial. Participants for whom we do not receive a risk assessment result will be included in this population.

Non-MUK *nine* b high risk population

The high risk population will include all participants who are assessed as being high risk, but who are not registered into the MUK *nine b* trial.

Non high risk population

The non-high risk population will include all participants who are assessed as being not high risk. Participants for whom we do not receive a risk assessment result will not be included in this population.

Analyses will be performed for the four populations separately, unless specified.

Imaging study population

The imaging study population will contain all participants who have entered the imaging sub-study and had a diffusion-weighted whole body MRI scan at baseline.

Primary endpoint analysis

The number and proportion of molecular risk-defining investigations performed within 8 weeks will be reported. Summary statistics of the length of time taken to turn around molecular risk-defining investigations will also be reported, including median, mean, standard deviation, inter-quartile range (IQR). This will be summarised for the screening population.

Secondary endpoint analysis

Recruitment rates

The number of participants registered overall and the average rate per month will be reported. The number and proportion of participants identified as high risk (out of both the number of participants registered to MUK *nine* a and the number of participants registered and with a corresponding sample taken for risk definition) overall will also be reported, as well as the number and proportion of participants accepting registration to MUK *nine* b (out of the number identified as high risk). Summaries will be provided overall and by site.

Progression-free survival

Progression-free survival curves will be calculated using the Kaplan-Meier method and the median progression-free survival estimates and progression-free survival estimates at yearly time-points with corresponding 95% confidence intervals will be presented for the Non-MUK *nine b* population, the Non-MUK *nine* b High risk population and the Non high risk population..

The Cox proportional hazards model (if appropriate), adjusting for treatment received first-line, will also be used to summarise progression-free survival for each population. Covariate estimates, standard errors, hazard ratios, 95% confidence intervals, as well as p-values will be presented for all variables incorporated in the model.

The Cox proportional hazards model, adjusting for treatment received first-line and other pre-specified baseline characteristics, may be used to further summarise progression-free survival, after discussion with the MUK *nine* Trial Management Group (TMG). The number of characteristics (and their factors) included in the model will depend on the number of participants in the relevant population.

Second progression-free survival (PFS2)

PFS2 curves will be calculated using the Kaplan-Meier method and the median second progression-free survival estimates and progression-free survival estimates at appropriate time-points with corresponding 95% confidence intervals will be presented for the Non-MUK *nine b* population, the Non-MUK *nine* b High risk population and the Non high risk population..

The Cox proportional hazards model (if appropriate), adjusting for treatment received first and second-line, will also be used to summarise PFS2 within each population. Treatment received second-line will be included using a time-dependant covariate to incorporate timing of treatment. Covariate estimates, standard errors, hazard ratios and 95% confidence intervals, as well as p-values will be presented for all variables incorporated in the model.

The Cox proportional hazards model, adjusting for treatment received first-line and other pre-specified baseline characteristics, may be used to further summarise second progression-free survival, after discussion with the MUK *nine* TMG. The number of characteristics (and their factors) included in the model will depend on the number of participants in the relevant population.

Treatment received first and second-line

Treatment received first and second-line will be summarised in a tabular form, along with reasons for stopping treatment. This will be summarised for the Non-MUK *nine* b population, the Non-MUK *nine* b High risk population and the Non high risk population.

Response to first and second-line treatment

The number and proportion of participants in each response category post first and second-line treatment will be presented with corresponding 95% confidence intervals for each population and type of treatment for the Non-MUK *nine b* population, the Non-MUK *nine* b High risk population and the Non high risk population.

Overall survival

Overall survival curves will be calculated using the Kaplan-Meier method and median overall survival estimates and overall survival estimates at yearly time-points with corresponding 95% confidence intervals will be presented for the Non-MUK *nine b* population, the Non-MUK *nine* b High risk population and the Non high risk population.

The Cox proportional hazards model (if appropriate), adjusting for treatment received first and second-line will also be used to summarise overall survival within each population. Treatment received second-line will be included using a time-dependant covariate to incorporate timing of treatment. Covariate estimates, standard errors, hazard ratios and 95% confidence intervals, as well as p-values will be presented for all variables incorporated in the model.

The Cox proportional hazards model, adjusting for treatment received first-line and other pre-specified baseline characteristics, may be used to further summarise overall survival, after discussion with the MUK *nine* TMG. The number of characteristics (and their factors) included in the model will depend on the number of participants in the relevant population.

MUK*nine b*

Analyses using response and progression data will be performed using both the data recorded on the eCRF, and data from analysis of central samples. Primacy will be given to the central sample assessment of response, and local data recorded on the eCRF will be used

where a central assessment is not available. Differences between the local eCRF data and the central assessment data will be summarised.

Analysis population

The analysis population, as well as the safety population, will include all participants who receive at least one dose of any trial treatment.

Imaging study population

The imaging study population will contain all participants who have entered the imaging sub-study and had a diffusion-weighted whole body MRI scan at baseline.

Interim analyses

Interim assessments will be performed after cohorts of 10 participants have been registered to treatment and followed up to 120 days post-ASCT, until all participants have been recruited and received induction treatment.

The trial may be terminated early for futility based on MRD status at 100 days post-ASCT and PFS at 100 days post-ASCT. If a participant does not receive an ASCT, the 100 days post-ASCT time-point becomes 12 months post registration as this is approximately equivalent.

At each interim analysis, the posterior probabilities of the two events in terms of pre-defined cut-points are calculated in order to determine whether the trial should be stopped for futility.

Primary endpoint analysis

At the end of the study, the experimental treatment arm will be compared to the historical control prior in terms of PFS at 18 months post-registration/randomisation for the MUK *nine* b analysis population. If the proportion of participants who are alive and progression-free at 18 months post-registration is higher in the treatment arm than in the control prior with 85% probability, the treatment arm will be deemed efficacious.

Further analyses of progression-free survival at 18 months post-registration will also be performed outside of the Bayesian framework. PFS curves will be calculated using the Kaplan-Meier method and median progression-free survival estimates and progression-free survival estimates at 6, 12 (corresponding approximately to the 100 days post-ASCT time-point) and 18 months with corresponding 95% confidence intervals will be presented.

At the end of the study, the experimental arm will be independently compared to historical control data using molecularly matched individual participant data (IPD) from Myeloma XI/XI+ and assessed for superiority in terms of progression-free survival (PFS) at 18 months post-registration/randomisation in an exploratory analysis.

Secondary endpoint analysis

Although not an endpoint, baseline characteristics will be summarised for participants in the analysis population. All MUK nine b secondary endpoint analyses will be performed for the MUK nine b analysis/safety population.

Safety

The number of SAEs will be summarised and presented by MedDRA system organ class. In addition, information will be given on the number of SAEs per participant, together with details on the causality, expectedness and outcome of each SAE experienced. Summaries of SARs and SUSARs will also be presented.

Toxicity

Summaries will be produced to show the proportion of participants experiencing each grade of toxicity overall, presented overall and by other groupings, such as stage of treatment, as necessary.

Progression-free survival at 100 days post-ASCT

Progression-free survival at 100 days post-ASCT is used to determine whether the trial should be stopped for futility, as detailed above. The 100 days post-ASCT time-point is approximately equivalent to 12 months post-registration, and progression-free survival estimates at this time-point are presented as part of the primary endpoint, detailed above.

Minimal residual disease (MRD) at the end of induction therapy, 100 days post-ASCT and post-consolidation part 2

MRD status will be assessed at the end of induction therapy, 100 days post-ASCT and 1 year post-ASCT for all participants, regardless of their categorical paraprotein response.

MRD status will be summarised at each time-point. These summaries will be obtained using multi-level repeated measures models accounting for data at all time-points, regardless of timing of sample for the time-point not of interest, assuming missing data at random [MAR], allowing for time and adjusting for pre-specified clinically important baseline characteristics [all fixed effects] and for participant and participant-time interaction [random effects] where appropriate.

Data will also be summarised descriptively using plots of proportion of participants with MRD negative disease over time and summary tables. Missing data patterns will be examined carefully and sensitivity analyses using different missing data assumptions will be performed if appropriate.

Sensitivity analyses may be carried out using methods such as multiple imputation or pattern-mixture multi-level models categorising participants into strata based on clinical information which is believed to represent the reasons for missing data (assuming MAR data conditional upon participants' clinical data).

Overall survival

Overall survival curves will be calculated using the Kaplan-Meier method and median overall survival estimates and overall survival estimates at 12, 24 and 36 months with corresponding 95% confidence intervals will be presented by treatment group.

The Cox proportional hazards model (if appropriate), adjusting for pre-specified baseline characteristics, may be used to further summarise overall survival, after discussion with the MUK *nine* TMG. The number of characteristics (and their factors) included in the model will depend on the number of participants in the analysis population.

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

The number and proportion of participants in each maximum response category will be presented with corresponding 95% confidence intervals at each time-point. Participants who do not achieve a maximum response will be summarised as 'no maximum response'.

Overall response at the end of induction therapy, 100 days post-ASCT and post-consolidation part 2

The proportion of participants achieving at least PR will be summarised with corresponding 95% confidence intervals, at each time-point.

Time to progression

Time to progression will be summarised using cumulative incidence function curves, and median time to progression estimates with corresponding 95% confidence intervals will be presented.

An assessment based on the number of participants who die with no previous evidence of disease progression (i.e. the number of competing risk events) will be made as to whether time to progression should be summarised using the Kaplan-Meier method (i.e. not incorporating competing risks).

Time to maximum response

Time to maximum response curves will be calculated using the Kaplan-Meier method, and the median time to maximum response estimates with corresponding 95% confidence intervals will be presented.

As maximum response is defined as SD or better, the number of participants who progress or die without achieving a maximum response is expected to be small. This will be monitored on an ongoing basis via DMEC reports and an assessment will be made as to whether analyses that take into account competing risks (for example cumulative incidence function curves) are required.

Second progression-free survival (PFS2)

PFS2 curves will be calculated using the Kaplan-Meier method and the median second progression-free survival estimates and progression-free survival estimates at appropriate time-points with corresponding 95% confidence intervals will be presented.

The Cox proportional hazards model, adjusting for pre-specified baseline characteristics, may be used to further summarise second progression-free survival, after discussion with the MUK *nine* TMG. The number of characteristics (and their factors) included in the model will depend on the number of participants in the analysis population.

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

The proportion of participants achieving each score for overall treatment benefit, and each response given to the clinician assessment of treatment benefit question, will be summarised with corresponding 95% confidence intervals, at each time-point.

A cross-tabulation of overall treatment benefit and clinician assessment of treatment benefit will be created to compare the two measures.

Quality of life

Quality of life will be summarised at each post-registration time-point, adjusting for baseline mean scores and 95% CIs. These summaries will be obtained using multi-level repeated measures models accounting for data at all post-baseline time points, regardless of time of completion for the time-point not of interest, assuming missing data at random [MAR], allowing for time and adjusting for baseline QoL and pre-specified clinically important baseline characteristics [all fixed effects] and for participant and participant-time interaction [random effects] where appropriate.

Data will also be summarised descriptively using bar charts, box plots, plots of mean QoL over time and summary tables. Missing data patterns will be examined carefully and sensitivity analyses using different missing data assumptions will be performed if appropriate.

Treatment compliance

Information on dose delays, reductions and omissions will be summarised by stage of treatment. Information on the proportion of participants with at least one dose delay, reduction or incidence of missed doses will also be presented overall and by stage of treatment.

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	Principal Investigator:

MUK *nine a*

A phase II study identifying and evaluating high risk (HR) myeloma patients suitable for novel treatment approaches

SAMPLE PARTICIPANT CONSENT FORM

Participant initial after each statement

1. I confirm that I have read and understand the information sheet for the above trial and have had the opportunity to ask questions. .....

2. I understand that taking part in this trial is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above trial, the data and samples and MRI, CT scan and x-ray images collected from me will be used in analysing the results of the trial and in some cases further information about any unwanted effects of my treatment may need to be collected by the trial team. .....

3. I understand that my healthcare records may be looked at by authorised individuals from the trial team, the NHS Trust, regulatory bodies or Sponsor in order to check that the trial is being carried out correctly. .....

4. I agree to allow any information or results arising from this trial to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible. .....

5. I agree to a copy of this Consent Form, detailing my full name, being sent to the Clinical Trials Research Unit (CTRU) at the University of Leeds. .....

6. I agree that my GP, or any other doctor treating me, will be notified of my participation in this trial. .....

7. I agree that samples of blood, urine and bone marrow taken from me during the course of the trial may be used for additional research investigations that form part of this trial and that the samples will be sent to laboratories outside my hospital. .....

8. I understand that some of the research studies using my samples may include genetic research aimed at understanding the genetic influences on predicting response to treatments and predisposition to multiple myeloma, ...

but the results of these investigations are unlikely to have any implications for me personally.

9. I agree to take part in the trial. .....

The following points are OPTIONAL. Even if you agree to take part in this trial, you do not have to agree to this part

Participant initial Yes or No

Yes No

1. If I am diagnosed with any disease other than symptomatic multiple myeloma or plasma cell leukaemia, I give permission to be contacted through my hospital about other research that may be available to me in the future ☐ ☐

Consent for storage and use in possible future research projects

1. I agree that the samples I have given and anonymised information stored about me can be stored for possible use in future projects. I understand that some projects may be carried out by researchers at different institutions other than the trial team who ran the first trial. I understand that any future research using these samples would require further ethical approval. ☐ ☐

2. I agree that information obtained through this research about the molecular features of my multiple myeloma or plasma cell leukaemia, e.g. findings about tumour mutations, may be fed back to my treating doctor if they are of potential relevance for my future treatment. ☐ ☐

3. If I am diagnosed with any disease other than symptomatic multiple myeloma or plasma cell leukaemia, I give permission for the samples sent to the central laboratories to be stored and used in future research that receives ethical approval. I understand that the samples and data collected from them may be shared with researchers, possibly outside the European Economic Area (EEA). ☐ ☐

Consent for the imaging study

My hospital is not taking part in the imaging study ☐

1. I agree to take part in the whole body MRI study. ☐ ☐

2. I agree that the whole body MRI images I have given and anonymised information stored about me can be stored for possible use in future projects. I understand that some projects may be carried out by researchers at different institutions other than the trial team who ran the first trial. I understand that any future research using these scans would require further ethical approval. ☐ ☐

Participant:

Signature……

Name (block capitals)……

Date……

Investigator:

I have explained the trial to the above named participant and he/she has indicated his/her willingness to participate.

Signature……

Name (block capitals)……

Date……

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1, 2, 4-9, 11-15, Tables 1 and 2
Protocol version	3	Date and version identifier	6
Funding	4	Sources and types of financial, material, and other support	14, 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,14
	5b	Name and contact information for the trial sponsor	15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14, 15
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12, 13, 14

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-7
	6b	Explanation for choice of comparators	3, 8, 12
Objectives	7	Specific objectives or hypotheses	7, 8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	2, 8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8, 9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Table 2
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Table 1
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9, 10 and Table 3
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	9
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Table 2, Table 3
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	11, 12, supplementary file 1
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-11, Figure 1, Table 4

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	8, 9
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA, not randomised
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA, not randomised
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA, not randomised
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA, not randomised or blinded
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA, not randomised or blinded
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	9-13, Table 4

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13, 14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11, 12, Supplementary file 1
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Supplementary file 1
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Supplementary file 1
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12, 13
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	9, 12, supplementary file 1
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Table 4, 10, 11, 12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	13
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2, 13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8-10, 13.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9, 10.
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	12, 13, 14.
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	12
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2, 13
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	13
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary file 2

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	9, 10, Table 4.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.