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MUKtwelve protocol: a phase II randomised, controlled, open, parallel group, multicentre trial of selinexor, cyclophosphamide and prednisolone (SCP) versus cyclophosphamide and prednisolone (CP) in patients with relapsed or refractory multiple myeloma

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ABSTRACT

Introduction Multiple myeloma is a malignancy of plasma cells with around 6000 new cases per year in the UK. Cyclophosphamide plus prednisolone is considered a standard of care for disease and symptom control in the advanced relapsed or refractory myeloma setting within the UK NHS. The selective nuclear export inhibitor, selinexor, has been relatively well tolerated in previous clinical trials and offers promise when used in combination with a wide range of other anti-cancer treatments. Here, we investigate if the addition of selinexor can improve responses to cyclophosphamide plus prednisolone without adding prohibitive toxicity.

Methods and analysis MUKtwelve is a UK-based, randomised, controlled, open, parallel group, multicentre phase II trial designed to evaluate clinical efficacy of selinexor in combination with cyclophosphamide and prednisolone (SCP) in patients with relapsed or refractory multiple myeloma. A calibration arm will receive cyclophosphamide and prednisolone alone (CP). Participants who experience disease progression on the CP arm may, if eligible, receive SCP.

The MUK*twelve* trial results will be the first to assess clinical efficacy of selinexor with low-dose CP in relapsed/refractory multiple myeloma. It is widely accepted that the relapsing-remitting nature of the disease is accompanied by cellular changes that often result in the requirement for novel agents and drug combinations to regain disease control. Patients also often experience cumulative toxicities throughout their treatments, limiting the treatment intensity that can be given at relapse. Thus, there is a need for novel effective combination therapies with acceptable toxicity profiles.

Ethics and dissemination Ethics approval is obtained. Results will be submitted for publication in a peer-reviewed journal.

Trial registration number ISRCTN15028850.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The MUK*twelve* trial results will be the first to assess the clinical efficacy of selinexor with low-dose cyclophosphamide and prednisolone in relapsed/refractory multiple myeloma.
⇒ Low continuous doses of cyclophosphamide and intermittent doses of prednisolone have been chosen to limit toxicity in the elderly patient population sought for the trial.
⇒ A calibration group will receive cyclophosphamide and prednisolone alone and will be used to evaluate the validity of the outcome.

BACKGROUND

Multiple myeloma is a clonal late B-cell disorder in which malignant plasma cells expand and accumulate in the bone marrow. The more effective myeloma treatment combinations are based on both disease-related and patient-related factors including duration of response to previous treatments, age, quality of life and pre-existing toxicities.[1] Since the early 1990s, myeloma incidence rates have increased by around a third (32%), representing 2% of all malignant disease in the UK. This accounts for 5951 new cases and 3098 deaths, each year in the UK.[2]

Despite advancements in therapeutic options for patients, myeloma remains incurable and patients develop resistance to both proteasome inhibitors and immunomodulatory drugs. With subsequent relapses, the disease changes and requires novel therapies to regain control. In addition to this, patients experience cumulative toxicities throughout

their treatments, limiting treatment intensity at relapse. Thus, there is a need for novel effective combination therapies with acceptable toxicity profiles for these patients.

Selinexor is a selective inhibitor of nuclear export compound that binds and inactivates Exportin-1 (XPO1). XPO1 is overexpressed in several cancers studied to date and has been shown to correlate with poor prognosis and survival. XPO1 inhibition triggers cell death in a range of malignant cell types, including multiple myeloma. Selinexor is an oral, first in class drug.

Selinexor has been investigated in phase I studies in advanced haematological malignancies including non-Hodgkin's lymphoma, chronic lymphocytic leukaemia and multiple myeloma. Even as a single agent it has shown durable, anti-cancer activity in participants with multiple relapsed or refractory haematological malignancies, including heavily pre-treated patients. As of 31 March 2018, 2601 patients with haematologic or solid-tumour malignancies had received selinexor or blinded study treatment. It has been suggested that selinexor may be administered long-term with acceptable tolerability. Specifically, the phase I and II trials involving patients with multiple myeloma have suggested the efficacy of selinexor within the *MUKtwelve* population [Selinexor Investigator's Brochure, 2017]. Based on the results of the STORM trial (Selinexor Treatment of Refractory Myeloma), the US FDA has granted accelerated approval for Selinexor in combination with dexamethasone for adult patients with relapsed or refractory multiple myeloma (RRMM) who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.[3 4] More recently, on December 2020, the FDA has granted the second approval in multiple myeloma for selinexor in combination with bortezomib and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy.[5] Selinexor has also received European Medicines Agency (EMA) approval.

Selinexor side effects can include gastrointestinal symptoms such as nausea and cachexia. However, their occurrence and severity vary widely between patients and enhanced preventative and supportive care protocols have been developed. In contrast to other therapies currently in development for RRMM, selinexor offers the applicability of an oral regimen, without need for inpatient supervision for the start of therapy, making it accessible also in environments with temporary (eg, during the COVID-19 pandemic) or permanent resource restrictions. This offers promise, in particular when used in other oral anti-cancer therapy combinations.

The combination of cyclophosphamide (chemotherapy) with prednisolone (steroid) is known to be an effective, tolerable and low-toxicity treatment for advanced multiple myeloma within the UK NHS. Prednisolone can be the preferred choice over dexamethasone owing to better tolerability.[6] Cyclophosphamide has long been used as alkylating chemotherapy with potent anti-myeloma activity and manageable toxicity in low doses.[7] To maximise response to Selinexor, the novel agent will be combined with cyclophosphamide and prednisolone (CP). Low continuous doses of cyclophosphamide and intermittent doses of prednisolone have been chosen to limit toxicity in the elderly patient population sought for the trial.[8]

METHODS

Study aims

The study will evaluate the clinical efficacy of selinexor in combination with CP, in patients with relapsed or refractory multiple myeloma.

Trial objectives

Primary objective

To determine whether the addition of selinexor to CP may lead to an increased progression-free survival (PFS) compared with historic CP data. In addition, the trial also incorporates a CP calibration arm to assess whether the efficacy estimates observed in this study are representative of the patient population from the historic control data.

Secondary objectives

- To assess the safety and toxicity profile.
- To estimate PFS.
- To estimate the proportion of participants with each maximum response category.
- To estimate time to maximum response.
- To estimate duration of maximum response.
- To assess compliance to therapy.

Exploratory objectives

- To process (including CD138 selection) and biobank bone marrow and peripheral blood tissue for future analysis.

For the treatment switch phase of the trial (from CP to selinexor, cyclophosphamide and prednisolone (SCP) after progression on CP):

- To estimate second PFS (PFS2).
- To evaluate the clinical activity of SCP with regard to additional secondary endpoints.
- To determine the safety and toxicity profile of SCP.

Study design

The MUKtwelve trial is a randomised, controlled, open, parallel group, multicentre phase II trial to evaluate clinical efficacy of selinexor in combination with cyclophosphamide and prednisolone in relapsed or refractory multiple myeloma patients who have received at least two prior lines of treatment including a proteasome inhibitor and lenalidomide. A calibration group will receive cyclophosphamide and prednisolone alone and will be used to evaluate the validity of the outcome. The participants on the calibration arm may go on to receive SCP once they progress on CP, if eligible to do so.

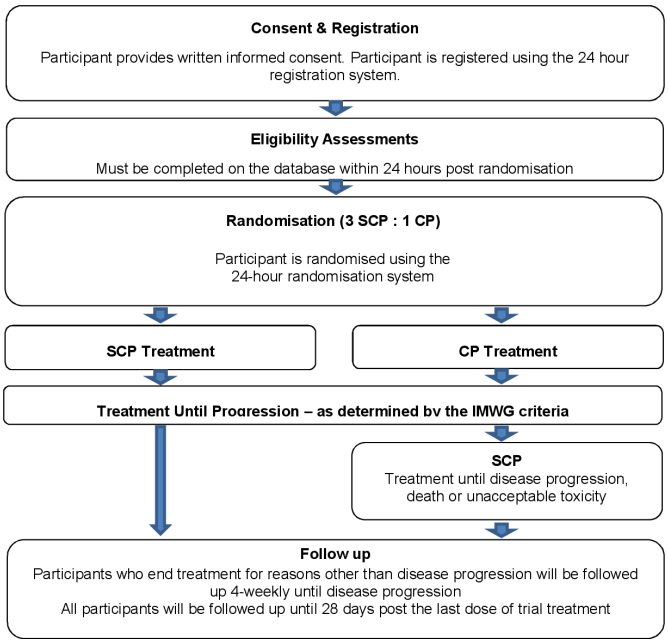

Figure 1 Trial flow diagram. CP, cyclophosphamide and prednisolone; IMWG, International Myeloma Working Group; SCP, selinexor, cyclophosphamide and prednisolone.

A maximum of 60 participants will be recruited and randomised on a 3:1 basis in favour of SCP (45 patients in the SCP arm and 15 in the CP calibration arm).

A three outcome design is used to determine whether the triplet combination (SCP) warrants further investigation in later phase clinical trials.[9] This will be based on the experimental arm only and has the following three possible conclusions:

- The combination is not sufficiently active and warrants no further study in a later phase clinical trial.
- The combination is sufficiently active and warrants further study in later phase clinical trials.
- There is insufficient evidence to determine whether or not the combination warrants further study on the basis of the primary endpoint. Therefore, additional secondary endpoint data must be taken into consideration.

Primary analysis will be based on the SCP arm only. The CP calibration arm is used to determine whether the population of patients recruited to the trial are representative of the patient population on which the historical control data are based. This arm also aims to reduce selection bias within the trial. Participants who are randomised to the CP arm and experience disease progression may receive SCP (figure 1) if they are deemed eligible.

The trial is expected to last 2.5–3 years, due to an estimated rate of recruitment of approximately three participants per month for up to 2 years. The duration of the treatment for individual participants will vary, as participants receive treatment until disease progression, unacceptable toxicity or withdrawal of consent, whichever is sooner. The participants who experience disease progression while on the CP arm that are eligible and switch to SCP are expected to have less than 6 months of additional follow-up, as the median PFS2 is expected to be shorter.

Sample size

Based on the historic data from the FOCUS study (a study of carfilzomib vs best supportive care in subjects with RRMM),[7] median PFS with CP is expected to be around 3.3 months, equivalent to approximately 28% patients alive and progression-free at 6 months postrandomisation, assuming an exponential survival model. A clinically relevant improvement in median PFS with the addition of selinexor is defined as at least 1.8 months (ie, improvement to at least 5.1 months, equivalent to 44% patients alive and progressions-free at 6 months).

The trial is designed to test the null hypothesis that the proportion of participants alive and progression-free at 6 months is≤0.28 against an alternative of≥0.44. With 90% power and testing at the one-sided 10% significance level, a total of 45 participants are required in the SCP arm. Based on the three-outcome design, the cut-off values and conclusions for the statistical test are defined as follows:

- ≤14/45 participants alive and progression-free at 6 months, do not reject the null hypothesis. The combination does not warrant further study, equivalent to 31.1% participants progression-free at 6 months or less (3.6-month median PFS or less).
- ≥17/45 participants alive and progression-free at 6 months, reject the null hypothesis. The combination has demonstrated sufficient evidence to warrant further study, equivalent to at least 37.8% participants progression-free at 6 months (4.2-month median PFS or more).
- 15 or 16/45 participants alive and progression-free at 6 months, reject neither hypothesis. The decision to continue is uncertain and can be based on other secondary endpoints.

The specified cut points give at least 90% power to observe a 6-month PFS rate of 0.44 and rule out a rate of 0.28 at the one-sided 10% significance level. The chance of declaring uncertainty and basing the decision to take the SCP combination forward on secondary endpoints, when there is not a treatment effect is 16%. Similarly, when there is a treatment effect the chance of declaring uncertainty is 11%. The cut points were determined using exact binomial probabilities in a program written in the statistical program R.

To enable a 3:1 randomisation in favour of the SCP arm, 15 participants included in the CP arm and are selected to safeguard the trial from selection bias and give context to the historic control rate of 0.28.

Recruitment process

Participants are recruited from approximately 10 National Health Service (NHS) hospitals in the UK. Potential participants will be approached by members of the hospital trial team during standard clinic visits for the management of their disease. They will be provided with verbal information about the trial and an information sheet, and at least

24 hours to consider the trial. Assenting participants will then be invited to provide written consent before assessments for eligibility take place.

All consented participants are registered to the trial using the 24 hour registration system at Clinical Trials Research Unit (CTRU) and provided with a trial number at this stage.

To be eligible for the trial participants must satisfy all eligibility criteria in table 1.

Sites opened to recruitment in June 2018 and the first patient was randomised on 16 July 2018. Recruitment is expected to close May 2021. The current protocol is V.3.0, 16 July 2018.

Randomisation

Once confirmed as eligible, participants will be randomised on a 3:1 basis to receive either SCP or CP using the 24-hour system provided by the CTRU. A computer-generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well-balanced for pre-specified factors:

- Age (<60 vs. 60–69 years vs.≥70 years).
- Number of prior lines of therapy (≤3 vs. >3).

Intervention

Treatment should start within 14 days after randomisation.

Treatments for both arms will be administered on a 28-day cycle. All participants will receive 50 mg oral cyclophosphamide one time per day (days 1–28) and 30 mg oral prednisolone every other day, starting on day 1 of the cycle. For participants receiving SCP, they will also receive 100 mg oral selinexor once a week (days 1, 8, 15 and 22), as defined in table 2.

To maintain treatment, there are a number of dose modifications that can be made if toxicity is seen. The goal of the dose modifications recommended in the protocol is to maintain the intensity of selinexor as much as is safely possible, and to dose reduce cyclophosphamide preferentially. If participants experience toxicity then sites should:

- If the toxicity is related to selinexor, reduce the weekly dose of selinexor in 20 mg increments (down to 40 mg) until discontinued.
- If the toxicity is related to cyclophosphamide, reduce the total weekly dose of cyclophosphamide from 350 mg to 250 mg, 150 mg, 100 mg or discontinue.
- If the toxicity is related to prednisolone, reduce the total weekly dose of prednisolone from 100 mg (when calculated across 2 weeks) to 90 mg, 60 mg, 30 mg or discontinue.

If mixed causality is expected, the investigator may determine dose modifications as they see appropriate to the toxicity.

Participants will receive SCP treatment or CP treatment, until disease progression, death, unacceptable toxicity or withdrawal of consent. Those participants who progress on CP may go on to receive SCP until further progression. The disease progression after CP will be confirmed by the chief investigator and in accordance with the International Myeloma Working Group criteria.[10] They should start treatment with SCP within 14 days of stopping CP treatment.

Trial assessments

Participants will be followed up until disease progression post-SCP or post-CP if the participant does not go on to receive SCP.

Data will be collected at baseline, during treatment, the end of treatment and at progression time points. Data will be entered into a secure database stored on a private network protected by a firewall by staff at the hospital site. Data will be managed at CTRU alongside existing standard operating procedures. All data will be linked anonymised identifiable only by trial ID, date of birth and initials. Site monitoring of source data will be performed by CTRU following the trial monitoring plan.

Trial assessments will be performed in line with the schedule in table 3.

Statistical analysis

There are three analysis sets defined for analysis of all endpoints:

- The full analysis set for the experimental and calibration arms will include all participants who received at least one dose of selinexor or one dose of cyclophosphamide, respectively.
- The safety set for the calibration and experimental arms will include all participants who received at least one dose of cyclophosphamide or one dose of selinexor and one dose of cyclophosphamide, respectively, and is equivalent to the full analysis set.
- The per protocol set will include all participants in the full analysis set, who are assessable for the primary endpoint (PFS at 6 months). Only those who withdraw from the trial for reasons other than progression and have an undeterminable progression status at 6 months will be excluded from the per protocol analysis set.

All safety analyses will be based on the safety analysis set; safety data from participants not included in this analysis set will be listed separately. PFS at 6 months and other efficacy endpoints will be assessed using the per protocol set. All other secondary endpoints will use the full analysis set.

Primary endpoint analysis

The number and proportion of participants alive and progression-free at 6 months postrandomisation will be presented, with corresponding 80% CIs.

Participants will be censored at the last date they were known to be alive and progression-free, if they have not progressed at the time of final analysis.

Table 1 Eligibility criteria

Inclusion criteria	1. Able to give informed consent and willing to follow all trial protocol assessments 2. Aged 18 years or over 3. Participants with confirmed myeloma based on International Myeloma Working Group (IMWG) criteria Rajkumar *et al*[11] 4. Measurable disease with at least one of the following: – Paraprotein ≥5 g/L – Serum free light chains ≥100 mg/L with abnormal ratio for light chain only myeloma – Bence Jones protein ≥200 mg/24 hours 5. Participants with relapsed or relapsed refractory myeloma who have received ≥2 prior anti-myeloma treatments including a proteasome inhibitor and lenalidomide, and now require further treatment. 6. Patients for which cyclophosphamide and prednisolone alone would be a suitable treatment 7. Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 8. Female participants of childbearing potential must agree to use two methods of contraception and have a negative urine pregnancy test at screening. Male participants must use an effective barrier method of contraception if sexually active with a female of childbearing potential. For both male and female participants, effective methods of contraception must be used throughout the trial and for at least 12 months following the last dose of trial treatment. 9. Required laboratory values are required at registration and within 14 days prior to randomisation: – Platelet count ≥50×10^9/L. Platelet count of 30–50 is acceptable if bone marrow aspirate or trephine shows tumour replacement of >50%. Platelet support is permitted within 14 days prior to randomisation, although platelet transfusions to help participants meet eligibility criteria are not allowed within 72 hours prior to the blood sample to confirm protocol eligibility – Absolute neutrophil count ≥1.0 x 10^9/L. Growth factor support is not permitted within 14 days prior to randomisation – Haemoglobin ≥80 g/L. Blood support is permitted – Alanine transaminase (ALT) and/or aspartate transaminase (AST) ≤3 x upper limit of normal – Creatinine clearance ≥20 mL/min (using Cockcroft Gault formula) – Bilirubin ≤1.5 x upper limit of normal. Suspected Gilberts syndrome patients must have a total bilirubin ≤3 x upper limit of normal

Continued

Table 1 Continued

Exclusion criteria	1. The following participants will be excluded: – those with non-measurable disease – those with a solitary bone or solitary extramedullary plasmacytoma – plasma cell leukaemia 2. Participants with a history of malignancy (other than myeloma) within 5 years before registration (exceptions are squamous and basal cell carcinomas of the skin, carcinoma in situ of the cervix or breast or other non-invasive lesion that, in the opinion of the investigator, with concurrence with the chief investigator, is considered cured with minimal risk of recurrence within 5 years) 3. Participants with a known or underlying uncontrolled concurrent illness that, in the investigator's opinion, would make the administration of the trial drug hazardous or circumstances that could limit compliance with the trial, including, but not limited to the following: – acute or chronic graft vs host disease – uncontrolled hypertension – symptomatic congestive heart failure – unstable angina pectoris – myocardial infarction within past 6 months – uncontrolled cardiac arrhythmia (CTCAE grade≥2) – active symptomatic fungal, bacterial, and/or viral infection including known active HIV or known viral (A, B or C) hepatitis – psychiatric or social conditions that may interfere with participant compliance – uncontrolled (ie, clinically unstable) infection requiring parenteral antibiotics, antivirals, or antifungals within 1 week prior to first dose; however, prophylactic use of these agents is acceptable even if parenteral – ocular herpes simplex – or any other condition (including laboratory abnormalities) that in the opinion of the Investigator places the participant at unacceptable risk for adverse outcome if he/she were to participate in the trial 4. Participants who have previously received Selinexor or any other Selective Inhibitor of Nuclear Export (SINE) compound 5. Previous anti-tumour therapies including investigational medicinal products at any dose within 28 days before the start of protocol treatment. (N.B. Prednisolone up to a dose of 175 mg per week may be given between screening and the beginning of treatment if medically required but should be stopped before trial treatment starts. Other steroids are not permitted. Bisphosphonates for bone disease are also permitted) 6. Participants with a history of a refractory nausea, diarrhoea, vomiting, malabsorption, gastrointestinal surgery or other procedures or conditions that might, in the opinion of the Investigator, interfere with the absorption or swallowing of the trial drug(s) 7. Female participants who are lactating or have a positive pregnancy test at screening 8. Known allergy or previous intolerance to any of the trial medications, their analogues, or excipients in the various formulations of any agent that would prevent the participant receiving these as directed in the protocol 9. Major surgery within 14 days prior to randomisation 10. Radiotherapy within 7 days prior to randomisation for palliative pain control or therapeutic radiotherapy within 14 days prior to randomisation 11. Myeloma involving the central nervous system

Continued

Table 1 Continued

SCP following disease progression on CP treatment eligibility criteria	1. Randomised to CP on the MUKtwelve trial, has tolerated treatment and can continue on CP during the SCP treatment 2. Received at least one full cycle of CP treatment 3. Centrally confirmed disease progression by IMWG criteria. 4. ECOG performance status ≤2 5. Required laboratory values within 14 days prior to starting treatment on SCP: – Platelet count ≥50×10^9/L. Platelet count of 30–50 is acceptable if bone marrow aspirate or trephine shows tumour replacement of >50%. Platelet support is permitted within 14 days prior to starting SCP, although platelet transfusions to help participants meet eligibility criteria are not allowed within 72 hours prior to the blood sample to confirm protocol eligibility – Absolute neutrophil count ≥1.0 x 10^9/L. – Haemoglobin ≥80 g/L. Blood support is permitted – ALT and/or AST ≤3 x upper limit of normal – Creatinine clearance ≥20 mL/min (using Cockcroft Gault formula) – Bilirubin ≤1.5 x upper limit of normal. Suspected Gilberts syndrome patients must have a total bilirubin ≤3 x upper limit of normal – B2M performed 6. Female participants of childbearing potential must agree to use two methods of contraception. Male participants must use an effective barrier method of contraception if sexually active with a female of childbearing potential.
Formal eligibility assessments will be performed. Central laboratory samples will be taken.	

B2M, beta-2 microglobulin; CP, cyclophosphamide and prednisolone; IMWG, International Myeloma Working Group; SCP, selinexor, cyclophosphamide and prednisolone.

Secondary endpoint analysis

Secondary endpoint analyses are outlined in table 4.

Exploratory endpoint analysis includes PFS2 and PFS from treatment switch. For both of these, survival curves will be calculated using the Kaplan-Meier method. Also, PFS estimates at 3, 6 and 12 months, and median PFS2 estimated, with corresponding 95% CIs will be presented. In addition, exploratory analyses of the ratio of PFS from treatment switch against PFS on CP prior to the treatment switch phase will be performed.

All other exploratory endpoints from the treatment switch phase will be analysed as for the equivalent secondary endpoint, as defined in table 4.

Frequency of analyses

The Data Monitoring and Ethics Committee (DMEC) will independently review data on safety, recruitment and adherence to the protocol, to identify any safety concerns or trends. At least once a year, interim reports will be presented to the DMEC. To ensure safety, a full interim safety report of the first 10 patients treated with SCP will be reviewed by the DMEC. The Trial Steering Committee will review safety data periodically throughout the trial and discuss recommendations made by the DMEC. No formal interim analyses are planned.

Final analyses will take place after all participants have been followed up for at least 6 months or have progressed on the first phase of treatment (whichever is sooner). Further analyses related to the treatment switch phase of the trial will take place after all participants have been followed up for at least 6 months or have progressed for a second time (whichever is sooner).

DISCUSSION

There are limited treatment options for patients with multiple myeloma and although improvements have been made, more options for treatment are required, in particular within the UK NHS and other public health-care systems.

Selinexor is demonstrating efficacy in relapsed/refractory multiple myeloma and has, in combination with dexamethasone, been very recently granted accelerated approval by the US FDA for this indication. Selinexor has also received EMA approval. Our trial aims to explore whether Selinexor anti-myeloma efficacy can be further enhanced by combining it with a well-tolerated standard of care (UK NHS) backbone of low-dose continuous cyclophosphamide and prednisolone. Safety of the combination is a key read-out of MUKtwelve and will be monitored closely. The trial is designed to provide direct evidence related to the UK population and to fit within prescribing criteria in the UK NHS and elsewhere.

MUKtwelve is primarily designed for patients with RRMM that have exhausted most or all standard treatment options on the UK NHS. However, due to strict limitations on the use of drug regimens in the NHS, some patients can be left without accessible options very

Table 2 Summary of treatment

Cyclophosphamide	Oral	50 mg	Once daily, starting on day 1
Prednisolone	Oral	30 mg	Every other day, starting on day 1
Selinexor	Oral	100 mg	Once a week—days 1, 8, 15 and 22

early in their disease, sometimes after two prior lines of therapy. MUKtwelve screening criteria are designed to be inclusive for these patients as well. There is a possibility that patients could be enrolled that have not exhausted standard care options. However, there is very limited incentive to do so in the specific setting of the NHS, and the anticipation is that most people will indeed only be enrolled when standard treatment options have been exhausted.

ETHICS AND DISSEMINATION

The trial has received national research ethics approval from the NHS National Research Ethics Service, London-Hampstead Research Ethics Committee (Ref: 17/LO/1847). Results will be submitted for publication in a peer-reviewed journal.

Patient and public involvement statement

The trial was designed to generate evidence for an unmet patient need. Patient feedback from a previous study conducted by the group resulted in adding the crossover component, so all patients had access to Selinexor at some point during the trial. Patients were involved in the review and development of study protocol and patient information sheets (model consent form provided in online supplemental file). Patient advocacy is an important part of our oversight committees, and we have specific patients and/or representation from Myeloma UK to ensure the patient perspective is presented throughout the duration

Table 3 Trial assessments

	Baseline	Treatment		End of treatment		Follow-up		
Investigations	**Baseline**	**Day 1 of each cycle of treatment**	**Cycle 1 day 15 only**	**End of SCP treatment**	**End of CP treatment**	**Follow-up at 28 days post last dose of treatment**	**Follow-up for patients who come off trial for reasons other than disease progression—4 weekly follow-up**	**Disease progression**
Consent	X							
Registration	X							
Central laboratory samples*	X		X†					X
Randomisation	X							
Physical exam	X	X		X	X			
ECOG performance status	X	X		X	X			
Haematology‡	X	X	X	X	X			
Biochemistry§	X	X		X	X			
Disease assessment¶	X	X		X	X		X	X
Pregnancy testing	X	X		X	X			
Adverse events		X		X	X	X	X	
Dispense drug		X						

*Bone marrow aspirate (10 mL; 5 mL first draw) and peripheral blood sample (5 mL) to be sent to the Institute of Cancer Research.
†Peripheral blood only on cycle 1 day.
‡Haematology—full blood count.
§Biochemistry—U&E, LFT, serum creatinine, corrected calcium, AST or ALT. Plus the following at baseline; LDH, B2M. Plus prior to the start of SCP treatment following CP treatment; B2M.
¶Response Assessment—paraprotein, serum free light chains, urinary light chains. 24 hour urinalysis if done by site.
ALT, alanine transaminase; AST, aspartate transaminase; B2M, beta-2 microglobulin; CP, cyclophosphamide and prednisolone; LDH, lactate dehydrogenase; LFT, liver function test; SCP, selinexor, cyclophosphamide and prednisolone; U&E, urea and electrolytes.

Table 4 Secondary endpoints

Secondary endpoint	Details of analysis methods
Safety and toxicity	► Rates of SAEs, SARs, SUSARs for each treatment arm ► Number and proportion of participants with at least one safety event ► SAEs presented by relationship to treatment, seriousness criteria, duration and MedDRA body system coding ► Number of SAEs per participant, with details on the causality, expectedness and outcome of each SAE experienced ► Causes of death in all patients will be tabulated ► Proportion of patients experiencing each grade of toxicity overall and during each treatment cycle, for each treatment arm
Progression-free survival	► PFS curves will be calculated for the treatment groups using the Kaplan-Meier method ► For each treatment group: PFS estimates at 3, 6, 12 months and median PFS estimates will be presented, with corresponding 95% CIs
Maximum response	► Number and proportion of patients who achieve each of the IMWG response categories[12] (sCR, CR, VGPR, PR, MR or SD) as their maximum response to treatment, with corresponding 95% CIs
Time to maximum response	► Time to maximum response curves will be calculated using the Kaplan-Meier method ► Median time to maximum response with corresponding 95% CIs
Duration of response	► Duration of maximum response curves will be created using the Kaplan-Meier method ► For both treatment arms, median duration of response estimates will be presented, with corresponding 95% CIs
Compliance to therapy	► Mean dose, number of doses missed, dose reductions and delays (including reasons)

CR, complete response; MR, minimal response; PFS, progression-free survival; PR, partial response; SAEs, serious adverse events; SARs, serious adverse reactions; sCR, stringent complete response; SUSARs, suspected unexpected serious adverse reactions; VGPR, very good partial response.

of the trial lifecycle. Publications from the study are made available to patients through the treating clinician, on request.

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Contributors JK, AH, SR, SB, KB, HWA, MG and MK designed the trial. JK, AH and SB developed the statistical analysis plan and are responsible for the ongoing statistical monitoring, analysis and interpretation of data. JK, AH and MK wrote the manuscript. KB, HWA, MG and MK perform the research and collect data. SR performs trial and data management. All authors reviewed and approved the final manuscript.

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Competing interests JK, AH, SR and SB declare they have no competing interests; MG has served as a consultant and received honoraria from Novartis; KB: honoraria and travel support from Celgene and Janssen; 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.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by NHS National Research Ethics Service, London-Hampstead Research Ethics Committee (Ref: 17/LO/1847). Participants gave informed consent to participate in the study before taking part.

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