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A phase II and phase III trial comparing treatment escalation and de-escalation strategies in newly diagnosed patients with multiple myeloma suitable for stem cell transplant

Submission date 14/04/2020	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 10/06/2020	**Overall study status** Ongoing	
Last Edited 25/02/2026	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Myeloma is a cancer of the bone marrow cells. Combining stem cell transplantation (SCT) with new drug treatments has shown to improve outcomes in myeloma patients. Some patients have been found to have genetic abnormalities in the myeloma cells and these 'high-risk' patients do not respond well to standard treatment. Some patients without these genetic abnormalities are also known to not respond as well to initial treatment. This study will investigate different treatment combinations for these two groups of patients. It will also investigate whether a third group of patients, who do respond well to initial treatment, can receive treatment for a shorter period of time without coming to harm. This study gives access to new treatments (the unlicensed drug isatuximab) and treatment combinations.

Who can participate?
Newly diagnosed myeloma patients, above the age of 18, who are suitable for stem cell transplant

What does the study involve?
All participants will receive the same initial induction treatment and during this time will have genetic tests to determine whether they have 'standard-risk' or 'high-risk' disease. The initial induction therapy is called RCyBorD and is a combination of lenalidomide (also called Revlimid®), cyclophosphamide, bortezomib and dexamethasone. Most patients will then have a stem cell transplant (also called ASCT - A stands for autologous, which means the patient's own stem cells are used), providing the myeloma responds and they remain fit enough. Patients will enter the second treatment stage of the study after they have recovered from the ASCT. Patients will be allocated to different treatment groups (called R1, R2 and R3) depending on their genetic risk, high-risk or standard-risk, and on how well the myeloma has responded to the initial treatment. Each treatment group will then receive different combinations of medication

to investigate if they offer benefit to patients. Treatment will comprise combinations of isatuximab, bortezomib, cyclophosphamide, lenalidomide and dexamethasone. Patients will be required to attend hospital in order to undergo routine investigations, to receive some of the study treatments and in order to undergo bone marrow, blood and urine tests throughout the trial. There is an option for participants to complete questionnaires about their quality of life.

What are the possible benefits and risks of participating?
Currently, none of the treatment combinations used in this study are available on the NHS for the treatment of newly diagnosed myeloma, and so this study gives access to new treatment combinations. The individual drugs have been used a lot in patients with myeloma in other studies and in the USA, however, the best combinations remain unclear. The goal of this study is to gain a greater understanding of these new treatment options and how they compare to each other. In addition, the study will look at making treatment decisions based on the participants' myeloma genetics and on how good their response is to the treatment. This may or may not be a better approach to treating myeloma compared to what doctors do currently. By taking part participants will be helping to answer important questions and it is hoped that this will improve treatment for them now and for future patients. There are potential risks associated with the study as well as potential side effects from the trial treatments and drugs. A small number of patients may develop additional types of cancer, and it is possible that this risk may be increased with lenalidomide treatment. When lenalidomide is given with dexamethasone, a higher number of skin cancers and solid tumours have been reported. Some medications, and complementary health supplements such as St. John’s Wort and green tea, should not be used during this study as they may interact with the study medications. Patients who take part in this study are potentially at risk of becoming sterile or infertile. This is also the case with other chemotherapy treatments participants would likely receive if they were not on the study. If appropriate, counselling and a referral for fertility assessment and preservation will be available. Some patients with myeloma find that they can continue to work during treatment.

Where is the study run from?
The study will be run by the Clinical Trials Research Unit (CTRU) at the University of Leeds. The study will be conducted in multiple hospitals throughout the UK.

When is the study starting and how long is it expected to run for?
September 2018 to December 2029

Who is funding the study?
The study is largely funded by Cancer Research UK. Funding for some of the costs of the drugs being used in the study, as well as some additional funding for the running of the study, is being provided by the companies who make two of the drugs being investigated: Sanofi (isatuximab) and Celgene (lenalidomide).

Who is the main contact?
RADAR Study Team
RADAR@leeds.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-different-combinations-of-treatment-for-newly-diagnosed-myeloma-radar-myeloma-xv

Contact information

Type(s)

Scientific

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Clinical Trials Information System (CTIS)
2019-001258-25

Integrated Research Application System (IRAS)
265114

Central Portfolio Management System (CPMS)
44923

Study information

Scientific Title
Risk-Adapted therapy Directed According to Response comparing treatment escalation and de-escalation strategies in newly diagnosed patients with multiple myeloma (NDMM) suitable for stem cell transplant (TE)

Acronym
RADAR (UK-MRA Myeloma XV)

Study objectives
Current study objectives as of 05/09/2025:

At R1 pathway:
The alternative hypothesis that treatment cessation is inferior to continuing treatment with isatuximab in terms of PFS at two years post-R1 by no more than 10% (thereby proving non-inferiority). The null hypothesis is that treatment cessation is inferior to continuing treatment with isatuximab in terms of 2 year PFS by more than 10% (i.e. it is inferior).

At R2 pathway:
The three separate alternative hypotheses, one for each experimental arm, which state that the proportion of participants attaining MRD negativity at 6 months after R2 in participants treated within an experimental arm (RBorD + R, R + Isa and RBorISaD + RIsa) is superior compared to those treated with R alone. The null hypothesis in each case is that there is no difference.

At R3 pathway:
Separately within each arm, the alternative hypothesis is that the percentage of participants alive and progression-free at 28 months post-R3 is 50%. The null hypothesis is that the percentage of participants alive and progression-free at 28 months post-R3 is 36%.

The high-risk pathway (in V4 and subsequent versions of the protocol) primarily aims to assess the activity of a treatment pathway (induction, ASCT, consolidation and maintenance) in terms of the progression-free survival (PFS) rate in participants who are stratified as high-risk at diagnosis.

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Previous study objectives:

At R1 pathway:
The alternative hypothesis that treatment cessation is inferior to continuing treatment with isatuximab in terms of PFS at two years post-R1 by no more than 10% (thereby proving non-inferiority). The null hypothesis is that treatment cessation is inferior to continuing treatment with isatuximab in terms of 2 year PFS by more than 10% (i.e. it is inferior).

At R2 pathway:
The three separate alternative hypotheses, one for each experimental arm, which state that the proportion of participants attaining MRD negativity at 6 months after R2 in participants treated within an experimental arm (RBorD + R, R + Isa and RBorISaD + RIsa) is superior compared to those treated with R alone. The null hypothesis in each case is that there is no difference.

At R3 pathway:
Separately within each arm, the alternative hypothesis is that the percentage of participants alive and progression-free at 28 months post-R3 is 50%. The null hypothesis is that the percentage of participants alive and progression-free at 28 months post-R3 is 36%.

Ethics approval required
Ethics approval required

Ethics approval(s)
1. approved 15/05/2020, London - Central Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 (0)207 104 8221; londoncentral.rec@hra.nhs.uk), ref: 20/LO/0238

2. approved 07/01/2025, London Central Research Ethics Committee (3rd Floor 3 Piccadilly Place, London Road, Manchester, M1 3BN, United Kingdom; +44 (0)20 7104 8077; londoncentral.rec@hra.nhs.uk), ref: 20/LO/0238

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Multiple myeloma

Interventions
Current interventions, as of 05/09/2025:

Induction treatment consists of Revlimid (R), cyclophosphamide (Cy), bortezomib (Bor) and dexamethasone (D) (RCyBorD) followed by ASCT. In v4.0 of the protocol isatuximab (Isa) was added to the induction treatment for high-risk patients only.
Following induction treatment and ASCT participants will be allocated to further treatment based on the participant's genetic risk according to FISH testing (or a diagnosis of plasma cell leukaemia, V6.0 of the protocol onwards) and response to the initial treatment, measured using an MRD test. Randomisation will be completed using a computer-generated minimisation programme that incorporates a random element to ensure treatment groups are well balanced for certain patient characteristics dependent on the randomisation. Participants will receive treatment until disease progression.

R1
Participants who are standard-risk and MRD-negative following induction treatment and ASCT will be allocated to R1. Initially, participants will receive 12 cycles of isatuximab, each cycle lasting 28 days. Isatuximab will be administered via IV at a dose of 10mg/kg on days 1, 8, 15 and 22 of cycle 1, then days 1 and 15 from cycle 2 onwards.

After receiving 12 cycles of isatuximab, R1 participants will be randomised to one of two treatment arms on a 1:1 basis to either:
1. Receive isatuximab maintenance until intolerance (Isa)
2. To discontinue isatuximab

Isa maintenance
Those randomised to receive isatuximab will receive 10 mg/kg by infusion into a vein on day 1 of each 28-day cycle.

R2
Participants who are standard-risk and MRD-positive following induction treatment and ASCT will be allocated to R2. R2 participants will be randomised to one of four treatment arms on a 1:1:1:1 basis, receiving either:
1. Revlimid (R) maintenance
2. Revlimid, bortezomib (Bor) and dexamethasone (D) consolidation and revlimid maintenance (RBorD+R)
3. Lenalidomide and isatuximab (RIsa) maintenance
4. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance (RBorIsaD+RIsa)

1. Revlimid maintenance
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will receive 10 mg capsules to be taken on days 1-21 of each 28-day cycle.

2. Revlimid, bortezomib and dexamethasone consolidation and revlimid maintenance
Consolidation:
Bortezomib is given by injection. Participants will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.

Revlimid is a hard capsule that is taken orally. Participants will receive 15mg capsules to be taken on days 1-14 of each 21-day cycle.
Dexamethasone is a hard capsule that is taken orally. Participants will receive 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants will receive 10mg capsules to be taken on days 1-21 of each 28-day cycle.

3. Lenalidomide and isatuximab maintenance
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1, 8, 15 and 22 of cycle 1, then days 1 and 15 from cycle 2 onwards.

4. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will receive 15mg capsules to be taken on days 1-14 of each 21-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1, 8 and 15 of cycle 1, then days 1 and 8 for cycle 2, then days 1 and 15 from cycle 3 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will receive 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1 and 15 of each 28-day cycle.

R3
Participants who are identified as high-risk (recruited prior to v4.0 of the protocol) will be allocated to R3. R3 participants will be randomised to one of two treatment arms on a 1:1 basis.

1. Revlimid, bortezomib and dexamethasone consolidation and revlimid maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15mg capsules to be taken on days 1-14 of each 21-day cycle.
Dexamethasone is hard casual that is taken orally. Participants randomised to this arm will 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.

2. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.

Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15 mg capsules to be taken on days 1-14 of each 21-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1, 8 and 15 of cycle 1, then days 1 and 8 for cycle 2, then days 1 and 15 from cycle 3 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will receive 20 mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10 mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1 and 15 of each 28-day cycle.

HRv4 and HRv6
Participants who are identified as high-risk (recruited to v4.0, v5.0 or v6.0 of the protocol). These participants will not be randomised and will receive the following treatment:
Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation (4 cycles):
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15 mg capsules to be taken on days 1-14 of each 21-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1, 8 and 15 of cycle 1, then days 1 and 8 for cycle 2, then days 1 and 15 from cycle 3 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will receive 20 mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10 mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1 and 15 of each 28-day cycle.
HRv7
Participants who are identified as high-risk (recruited to v7.0 of the protocol). These participants will not be randomised and will receive the following treatment:
Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation (24 cycles):
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8, 15 and 22 of each 28-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15 mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1, 8, 15 and 22 of cycle 1, then days 1 and 15 for cycle 2 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will receive 20 mg capsules to be taken on days 1, 8, 15 and 22 of each 28-day cycle.
After 6 cycles of consolidation bortezomib is reduced to days 1 and 15 of the 28-day cycle and dexamethasone is stopped.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10 mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1 and 15 of each 28-day cycle.

Previous interventions as of 29/01/2025:

Induction treatment consists of Revlimid (R), cyclophosphamide (Cy), bortezomib (Bor) and dexamethasone (D) (RCyBorD) followed by ASCT. In v4.0 of the protocol isatuximab (Isa) was added to the induction treatment for high-risk patients only.
Following induction treatment and ASCT participants will be allocated to further treatment based on the participant's genetic risk according to FISH testing (or a diagnosis of plasma cell leukaemia, V6.0 of the protocol onwards) and response to the initial treatment, measured using an MRD test. Randomisation will be completed using a computer-generated minimisation programme that incorporates a random element to ensure treatment groups are well balanced for certain patient characteristics dependent on the randomisation. Participants will receive treatment until disease progression.

R1
Participants who are standard-risk and MRD-negative following induction treatment and ASCT will be allocated to R1. Initially, participants will receive 12 cycles of isatuximab, each cycle lasting 28 days. Isatuximab will be administered via IV at a dose of 10mg/kg on days 1, 8, 15 and 22 of cycle 1, then days 1 and 15 from cycle 2 onwards.

After receiving 12 cycles of isatuximab, R1 participants will be randomised to one of two treatment arms on a 1:1 basis to either:
1. Receive isatuximab maintenance until intolerance (Isa)
2. To discontinue isatuximab

Isa maintenance
Those randomised to receive isatuximab will receive 10 mg/kg by infusion into a vein on day 1 of each 28-day cycle.

R2
Participants who are standard-risk and MRD-positive following induction treatment and ASCT will be allocated to R2. R2 participants will be randomised to one of four treatment arms on a 1: 1:1:1 basis, receiving either:
1. Revlimid (R) maintenance
2. Revlimid, bortezomib (Bor) and dexamethasone (D) consolidation and revlimid maintenance (RBorD+R)
3. Lenalidomide and isatuximab (RIsa) maintenance
4. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance (RBorIsaD+RIsa)

1. Revlimid maintenance
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will receive 10 mg capsules to be taken on days 1-21 of each 28-day cycle.

2. Revlimid, bortezomib and dexamethasone consolidation and revlimid maintenance
Consolidation:
Bortezomib is given by injection. Participants will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants will receive 15mg capsules to be taken on days 1-14 of each 21-day cycle.

Dexamethasone is a hard capsule that is taken orally. Participants will receive 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants will receive 10mg capsules to be taken on days 1-21 of each 28-day cycle.

3. Lenalidomide and isatuximab maintenance
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1, 8, 15 and 22 of cycle 1, then days 1 and 15 from cycle 2 onwards.

4. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will receive 15mg capsules to be taken on days 1-14 of each 21-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1, 8 and 15 of cycle 1, then days 1 and 8 for cycle 2, then days 1 and 15 from cycle 3 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will receive 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1 and 15 of each 28-day cycle.

R3
Participants who are identified as high-risk (recruited prior to v4.0 of the protocol) will be allocated to R3. R3 participants will be randomised to one of two treatment arms on a 1:1 basis.

1. Revlimid, bortezomib and dexamethasone consolidation and revlimid maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15mg capsules to be taken on days 1-14 of each 21-day cycle.
Dexamethasone is hard casual that is taken orally. Participants randomised to this arm will 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.

2. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15 mg capsules to be taken on days 1-14 of each 21-day cycle.

Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1, 8 and 15 of cycle 1, then days 1 and 8 for cycle 2, then days 1 and 15 from cycle 3 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will receive 20 mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10 mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1 and 15 of each 28-day cycle.

HRv4 and HRv6
Participants who are identified as high-risk (recruited to v4.0, v5.0 or v6.0 of the protocol). These participants will not be randomised and will receive the following treatment:

Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15 mg capsules to be taken on days 1-14 of each 21-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1, 8 and 15 of cycle 1, then days 1 and 8 for cycle 2, then days 1 and 15 from cycle 3 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will receive 20 mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10 mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1 and 15 of each 28-day cycle.

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Previous interventions:

Following induction treatment participants who have not experienced disease progression will be randomised to R1, R2 or R3. This allocation is based on the participant's genetic risk according to FISH testing and response to the initial treatment, measured using an MRD test.
Randomisation will be completed using a computer-generated minimisation programme that incorporates a random element to ensure treatment groups are well balanced for certain patient characteristics dependent on the randomisation. Participants will receive treatment until disease progression.

R1
Participants who are standard-risk and MRD-negative following induction treatment and ASCT will be allocated to R1. Initially, participants will receive 12 cycles of isatuximab, each cycle lasting 28 days. Isatuximab will be administered via IV at a dose of 10mg/kg on days 1, 8, 15 and 22 of cycle 1, then days 1 and 15 from cycle 2 onwards.

After receiving 12 cycles of isatuximab, R1 participants will be randomised to one of two treatment arms on a 1:1 basis to either:
1. Receive isatuximab maintenance until intolerance (Isa)
2. To discontinue isatuximab

Isa maintenance
Those randomised to receive isatuximab will receive 10 mg/kg by infusion into a vein on day 1 of each 28-day cycle.

R2
Participants who are standard-risk and MRD-positive following induction treatment and ASCT will be allocated to R2. R2 participants will be randomised to one of four treatment arms on a 1:1:1:1 basis, receiving either:
1. Revlimid (R) maintenance
2. Revlimid, bortezomib (Bor) and dexamethasone (D) consolidation and revlimid maintenance (RBorD+R)
3. Lenalidomide and isatuximab (RIsa) maintenance
4. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance (RBorIsaD+RIsa)

1. Revlimid maintenance
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will receive 10 mg capsules to be taken on days 1-21 of each 28-day cycle.

2. Revlimid, bortezomib and dexamethasone consolidation and revlimid maintenance
Consolidation:
Bortezomib is given by injection. Participants will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants will receive 15mg capsules to be taken on days 1-14 of each 21-day cycle.
Dexamethasone is a hard capsule that is taken orally. Participants will receive 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants will receive 10mg capsules to be taken on days 1-21 of each 28-day cycle.

3. Lenalidomide and isatuximab maintenance
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1, 8, 15 and 22 of cycle 1, then days 1 and 15 from cycle 2 onwards.

4. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will receive 15mg capsules to be taken on days 1-14 of each 21-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1, 8 and 15 of cycle 1, then days 1 and 8 for cycle 2, then days 1 and 15 from cycle 3 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will

receive 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10mg/kg on days 1 and 15 of each 28-day cycle.

R3
Participants who are identified as high-risk will be allocated to R3. R3 participants will be randomised to one of two treatment arms on a 1:1 basis.

1. Revlimid, bortezomib and dexamethasone consolidation and revlimid maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15mg capsules to be taken on days 1-14 of each 21-day cycle.
Dexamethasone is hard casual that is taken orally. Participants randomised to this arm will 20mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10mg capsules to be taken on days 1-21 of each 28-day cycle.

2. Bortezomib, lenalidomide, isatuximab and dexamethasone consolidation and lenalidomide and isatuximab maintenance
Consolidation:
Bortezomib is given by injection. Participants randomised to this arm will receive 1.3 mg/m2 on days 1, 8 and 15 of each 21-day cycle.
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 15 mg capsules to be taken on days 1-14 of each 21-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1, 8 and 15 of cycle 1, then days 1 and 8 for cycle 2, then days 1 and 15 from cycle 3 onwards.
Dexamethasone is a hard capsule that is taken orally. Participants randomised to this arm will receive 20 mg capsules to be taken on days 1, 8 and 15 of each 21-day cycle.
Maintenance:
Revlimid is a hard capsule that is taken orally. Participants randomised to this arm will 10 mg capsules to be taken on days 1-21 of each 28-day cycle.
Isatuximab is a solution that is given by infusion into a vein. Participants will receive 10 mg/kg on days 1 and 15 of each 28-day cycle.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Isatuximab, lenalidomide, cyclophosphamide, bortezomib, dexamethasone

Primary outcome(s)
Current primary outcome measure as of 05/09/2025:

Randomisation 1: Progression-free survival (PFS-1). PFS-R1 is defined as the time from R1 to the time of first documented evidence of disease progression or death from any cause. Individuals who are lost to follow-up or progression-free at the time of analysis will be censored at their last known date to be alive and progression-free. Disease progression is defined according to the IMWG Uniform Response Criteria for Multiple Myeloma

Randomisation 2: Attainment of MRD Negativity. Attainment of Minimal Residual Disease (MRD) negativity is defined as a binary endpoint. MRD negativity will be determined at 6 months post-R2 (end of cycle 6 post-ASCT treatment for participants allocated to maintenance only strategies and end of cycle 7 post-ASCT treatment for participants allocated to maintenance and consolidation strategies) according to the IMWG MRD criteria

Randomisation 3: Progression-Free Survival Rate. The progression-free survival rate is defined as the proportion of participants who are alive and progression-free 28 months post-R3. Disease progression is defined according to the IMWG Uniform Response Criteria for Multiple Myeloma

High-risk pathways (HRv4, HRv6, HRv7): Progression-Free Survival Rate. The progression-free survival rate is defined as the proportion of participants who are alive and progression-free 18 months post-main trial registration. Disease progression is defined according to the IMWG Uniform Response Criteria for Multiple Myeloma.

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Previous primary outcome measure:

Randomisation 1: Progression-free survival (PFS-1). PFS-R1 is defined as the time from R1 to the time of first documented evidence of disease progression or death from any cause. Individuals who are lost to follow-up or progression-free at the time of analysis will be censored at their last known date to be alive and progression-free. Disease progression is defined according to the IMWG Uniform Response Criteria for Multiple Myeloma

Randomisation 2: Attainment of MRD Negativity. Attainment of Minimal Residual Disease (MRD) negativity is defined as a binary endpoint. MRD negativity will be determined at 6 months post-R2 (end of cycle 6 post-ASCT treatment for participants allocated to maintenance only strategies and end of cycle 7 post-ASCT treatment for participants allocated to maintenance and consolidation strategies) according to the IMWG MRD criteria

Randomisation 3: Progression-Free Survival Rate. The progression-free survival rate is defined as the proportion of participants who are alive and progression-free 28 months post-R3. Disease progression is defined according to the IMWG Uniform Response Criteria for Multiple Myeloma

Key secondary outcome(s))

Current secondary outcome measures as of 05/09/2025:

1. Progression-Free Survival (PFS-R2) measured from the time of R2 randomisation to the time of first documented evidence of disease progression or death from any cause. Disease progression will be measured according to the IMWG Uniform Response Criteria for Multiple Myeloma.
2. Progression-Free Survival (PFS-HRv4/PFS-HRv6/PFS-HRv7) is defined for each of the high-risk pathways (HRv4, HRv6 and HRv7) separately as the time from main trial registration to the time of first documented evidence of disease progression or death from any cause. Disease progression is defined according to the IMWG Uniform Response Criteria for Multiple Myeloma

(Appendix 2).
3. Progression-Free Survival (PFS-R3) measured from the time from R3 randomisation to the time of first documented evidence of disease progression or death from any cause. Disease progression will be measured according to the IMWG Uniform Response Criteria for Multiple Myeloma.
4. Time to progression (TTP) measured for all randomisations as the time from randomisation to the date of first documented evidence of disease progression. Disease progression will be measured according to the IMWG Uniform Response Criteria for Multiple Myeloma.
5. Progression-Free Survival two (PFS2); for all randomisations progression-free survival two is measured at the time of randomisation to the time of the second documented disease progression. Disease progression will be measured according to the IMWG Uniform Response Criteria for Multiple Myeloma.
6. Overall Survival (OS) defined separately for each randomisation, for each randomisation it will be measured from the time of randomisation to the time of death from any cause.
7. Survival after progression measured from the date of first documented evidence of disease progression to the date of death from any cause.
8. Objective response rate (ORR) defined as a categorical outcome consisting of whether a participant had sCR, CR, VGPR, PR, MR, SD or PD according to the IMWG Uniform Response Criteria for Multiple Myeloma at the end of RCyBorD induction, 100 days post-ASCT in both the standard and high-risk pathways, at the end of consolidation (3 months post R2 and R3), after 6 months of post-ASCT treatment (equivalent to 6 or 7 cycles of post-ASCT treatment*), after 12 months of post-ASCT treatment (equivalent to 12 or 13 cycles of post-ASCT treatment**) and after 24 cycles of post-ASCT treatment in R1 only (equivalent to 12 cycles of post-R1 treatment).
9. Successful stem cell harvest is defined as a binary endpoint. A participant will be defined as having a successful stem cell harvest if an adequate number of stem cells is harvested for autologous stem cell transplant (ASCT). An adequate stem cell harvest for ASCT is defined as 2.0 x106 CD34+ cells/kg. OR A CFU GM count of 40x10^4 per kg if used as part of standard of care. This endpoint is defined for all participants who receive a stem cell harvest as part of their trial treatment.
10. Attainment of ≥VGPR measured as a whether a participant had ≥VGPR (VGPR, CR, sCR) or <VGPR (PR, MR, SD, PD) according to the IMWG Uniform Response Criteria for Multiple Myeloma at the end of RCyBorD induction, 100 days post-ASCT in both the standard and high-risk pathways, at the end of consolidation (3 months post R2 and R3), after 6 months of post-ASCT treatment (equivalent to 6 or 7 cycles of post-ASCT treatment*), after 12 months of post-ASCT treatment (equivalent to 12 or 13 cycles of post-ASCT treatment**) and after 24 months of post-ASCT treatment in R1 only (equivalent to 12 cycles of post-R1 treatment).
11. Attainment of Minimal Residual Disease (MRD) negativity measured according to the IMWG MRD criteria at the end of RCyBorD induction, 100 days post-ASCT in both the standard and high-risk pathways, at the end of consolidation (3 months post R2 and R3), after 6 months of post-ASCT treatment (equivalent to 6 or 7 cycles of post-ASCT treatment*), after 12 months of post-ASCT treatment (equivalent to 12 or 13 cycles of post-ASCT treatment**), after 18 months of post-ASCT treatment in R2 and R3 only (equivalent to 18 or 19 cycles of post-ASCT treatment***) and after 24 months of post-ASCT treatment in R1 only (equivalent to 12 cycles of post-R1 treatment).
12. Duration of MRD negativity is first defined as whether the participant changes their MRD status between MRD sample timepoints.
For R1 these are:
12.1. 100 days post-ASCT to 6 months of post-ASCT treatment (end of cycle 6 post-ASCT treatment),
12.2. 100 days post-ASCT to 12 months of post-ASCT treatment (end of cycle 12 post-ASCT treatment, R1)
12.3. R1 to 12 months post R1 (end of cycle 24 post-ASCT treatment)

For R2 and R3 these are:
12.1. 100 days post-ASCT to end of consolidation (end of cycle 4 post-ASCT)
12.2. 100 days post-ASCT to 6 months post-randomisation (end of cycle 6 or 7 post-ASCT treatment*)
12.3. 100 days post-ASCT to 12 months post-randomisation (end of cycle 12 or 13 post-ASCT treatment**) 6 months post-randomisation to 18 months post randomisation (end of cycle 6 or 7 to end of cycle 18 or 19 post-ASCT treatment***)
For HRv7
12.4. 12 months post-ASCT treatment (end of cycle 12 treatment) to 24 months post-ASCT treatment (end cycle 24 post-ASCT treatment)
*equivalent to 6 cycles of post-ASCT treatment for R2 participant's reciving R or RIsa; equivalent to 7 cycles of post-ASCT treatment for R2 and R3 participants receiving RBorD+R or RBorDIsa+RIsa
** equivalent to 12 cycles of post-ASCT treatment for R2 participant's reciving R or RIsa; equivalent to 13 cycles of post-ASCT treatment for R2 and R3 participants receiving RBorD+R or RBorDIsa+RIsa
*** equivalent to 18 cycles of post-ASCT treatment for R2 participant's reciving R or RIsa; equivalent to 19 cycles of post-ASCT treatment for R2 and R3 participants receiving RBorD+R or RBorDIsa+RIsa
13. Time to improved response measured as the time from randomisation to the date the response category is first improved based on the Modified International Uniform Response Criteria for Multiple Myeloma.
14. Time to next treatment measured as the time from registration to the start date of the next line of treatment or death from any cause.
15. Treatment compliance and total amount of therapy delivered. In the first instance treatment compliance is measured as a binary outcome in each pathway (standard or high-risk) as if the participant receive four cycles of induction treatment or not. The total amount of therapy delivered will be first defined as the number of induction and maintenance (and/or consolidation) cycles which the participant received overall, by pathway and by randomisation.
16. Toxicity and safety, including incidence of second malignancies, reported based on the adverse events, as graded by CTCAE V5.0 and determined by routine clinical assessments at each centre. The number of SAEs will be reported according to MedDRA System Organ Class. All second primary malignancies will be reported based on information collected on the eCRF.
17. Quality of life defined using the patient-reported outcome measures: EORTC-QLQ-C30, EORTC-QLQ-MY20 and EQ-5D-3L at:
17.1. All participants: baseline, end of induction, 100 days post-ASCT
17.2. R1 pathway participants: after cycles 6, 12, 24 and 36 (for participants randomised to 'stop isatuximab' at R1, the cycle 24 and 36 questionnaires should still be completed at equivalent timepoints)
17.3. Timepoints for R2 and R3 pathway participants receiving R or RIsa: after cycles 6, 12 and 24 of maintenance
17.4. Timepoints for R2 and R3 pathway participants receiving RBorD+R or RBorIsaD+RIsa: after cycles 3, 9 and 21 of maintenance
18. Cost-effectiveness defined as a cost per incremental QALY below £20,000 and/or a positive incremental net monetary benefit. The cost-effectiveness of treatment options at each randomisation will be evaluated with respect to this criteria.
19. RADIUS Sub-study. Understand participants' feelings and attitudes about receiving treatment tailored to their specific results.

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Previous secondary outcome measures:

1. Progression-Free Survival (PFS-R2) measured from the time of R2 randomisation to the time of first documented evidence of disease progression or death from any cause. Disease progression will be measured according to the IMWG Uniform Response Criteria for Multiple Myeloma.
2. Progression-Free Survival (PFS-R3) measured from the time from R3 randomisation to the time of first documented evidence of disease progression or death from any cause. Disease progression will be measured according to the IMWG Uniform Response Criteria for Multiple Myeloma.
3. Time to progression (TTP) measured for all randomisations as the time from randomisation to the date of first documented evidence of disease progression. Disease progression will be measured according to the IMWG Uniform Response Criteria for Multiple Myeloma.
4. Progression-Free Survival two (PFS2); for all randomisations progression-free survival two is measured at the time of randomisation to the time of the second documented disease progression. Disease progression will be measured according to the IMWG Uniform Response Criteria for Multiple Myeloma.
5. Overall Survival (OS) defined separately for each randomisation, for each randomisation it will be measured from the time of randomisation to the time of death from any cause.
6. Survival after progression measured from the date of first documented evidence of disease progression to the date of death from any cause.
7. Objective response rate (ORR) defined as a categorical outcome consisting of whether a participant had sCR, CR, VGPR, PR, MR, SD or PD according to the IMWG Uniform Response Criteria for Multiple Myeloma at the end of RCyBorD induction, 100 days post-ASCT in both the standard and high-risk pathways, at the end of consolidation (3 months post R2 and R3), after 6 months of post-ASCT treatment (equivalent to 6 or 7 cycles of post-ASCT treatment*), after 12 months of post-ASCT treatment (equivalent to 12 or 13 cycles of post-ASCT treatment**) and after 24 cycles of post-ASCT treatment in R1 only (equivalent to 12 cycles of post-R1 treatment) .
8. Attainment of ≥VGPR measured as a whether a participant had ≥VGPR (VGPR, CR, sCR) or <VGPR (PR, MR, SD, PD) according to the IMWG Uniform Response Criteria for Multiple Myeloma at the end of RCyBorD induction, 100 days post-ASCT in both the standard and high-risk pathways, at the end of consolidation (3 months post R2 and R3), after 6 months of post-ASCT treatment (equivalent to 6 or 7 cycles of post-ASCT treatment*), after 12 months of post-ASCT treatment (equivalent to 12 or 13 cycles of post-ASCT treatment**) and after 24 months of post-ASCT treatment in R1 only (equivalent to 12 cycles of post-R1 treatment).
9. Attainment of Minimal Residual Disease (MRD) negativity measured according to the IMWG MRD criteria at the end of RCyBorD induction, 100 days post-ASCT in both the standard and high-risk pathways, at the end of consolidation (3 months post R2 and R3), after 6 months of post-ASCT treatment (equivalent to 6 or 7 cycles of post-ASCT treatment*), after 12 months of post-ASCT treatment (equivalent to 12 or 13 cycles of post-ASCT treatment**), after 18 months of post-ASCT treatment in R2 and R3 only (equivalent to 18 or 19 cycles of post-ASCT treatment***) and after 24 months of post-ASCT treatment in R1 only (equivalent to 12 cycles of post-R1 treatment).
10. Duration of MRD negativity is first defined as whether the participant changes their MRD status between MRD sample timepoints.
For R1 these are:
10.1. 100 days post-ASCT to 6 months of post-ASCT treatment (end of cycle 6 post-ASCT treatment),
10.2. 100 days post-ASCT to 12 months of post-ASCT treatment (end of cycle 12 post-ASCT treatment, R1)
10.3. R1 to 12 months post R1 (end of cycle 24 post-ASCT treatment)
For R2 and R3 these are:
10.1. 100 days post-ASCT to end of consolidation (end of cycle 4 post-ASCT)

10.2. 100 days post-ASCT to 6 months post-randomisation (end of cycle 6 or 7 post-ASCT treatment*)
10.3. 100 days post-ASCT to 12 months post-randomisation (end of cycle 12 or 13 post-ASCT treatment**) 6 months post-randomisation to 18 months post randomisation (end of cycle 6 or 7 to end of cycle 18 or 19 post-ASCT treatment***)
*equivalent to 6 cycles of post-ASCT treatment for R2 participant's reciving R or RIsa; equivalent to 7 cycles of post-ASCT treatment for R2 and R3 participants receiving RBorD+R or RBorDIsa+RIsa
** equivalent to 12 cycles of post-ASCT treatment for R2 participant's reciving R or RIsa; equivalent to 13 cycles of post-ASCT treatment for R2 and R3 participants receiving RBorD+R or RBorDIsa+RIsa
*** equivalent to 18 cycles of post-ASCT treatment for R2 participant's reciving R or RIsa; equivalent to 19 cycles of post-ASCT treatment for R2 and R3 participants receiving RBorD+R or RBorDIsa+RIsa
11. Time to improved response measured as the time from randomisation to the date the response category is first improved based on the Modified International Uniform Response Criteria for Multiple Myeloma.
12. Time to next treatment measured as the time from registration to the start date of the next line of treatment or death from any cause.
13. Treatment compliance and total amount of therapy delivered. In the first instance treatment compliance is measured as a binary outcome in each pathway (standard or high-risk) as if the participant receive four cycles of induction treatment or not. The total amount of therapy delivered will be first defined as the number of induction and maintenance (and/or consolidation) cycles which the participant received overall, by pathway and by randomisation.
14. Toxicity and safety, including incidence of second malignancies, reported based on the adverse events, as graded by CTCAE V5.0 and determined by routine clinical assessments at each centre. The number of SAEs will be reported according to MedDRA System Organ Class. All second primary malignancies will be reported based on information collected on the eCRF.
15. Quality of life defined using the patient-reported outcome measures: EORTC-QLQ-C30, EORTC-QLQ-MY20 and EQ-5D-3L at:
15.1. All participants: baseline, end of induction, 100 days post-ASCT
15.2. R1 pathway participants: after cycles 6, 12, 24 and 36 (for participants randomised to 'stop isatuximab' at R1, the cycle 24 and 36 questionnaires should still be completed at equivalent timepoints)
15.3. Timepoints for R2 and R3 pathway participants receiving R or RIsa: after cycles 6, 12 and 24 of maintenance
15.4. Timepoints for R2 and R3 pathway participants receiving RBorD+R or RBorIsaD+RIsa: after cycles 3, 9 and 21 of maintenance
16. Cost-effectiveness defined as a cost per incremental QALY below £20,000 and/or a positive incremental net monetary benefit. The cost-effectiveness of treatment options at each randomisation will be evaluated with respect to this criteria

Completion date
31/12/2029

Eligibility

Key inclusion criteria
Inclusion criteria for registration:
1. Previously untreated patients with multiple myeloma requiring therapy, defined as having myeloma defining events or with biomarkers of malignancy according to IMWG diagnostic

criteria
2. Eligible for stem cell transplant
3. Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG > 2 is due to effects of myeloma eg spinal cord compression);
4. Total bilirubin ≤ 1.5 x upper limit of normal (ULN)
5. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 3 x ULN (if ALT and AST are tested, both must meet this criteria)
6. Adequate marrow function:
6.1. Neutrophils > = 1.0 × 10^9/L (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC > = 0.75 x 109/L is allowed)
6.2. Haemoglobin (Hb) > = 80g/L. Blood transfusions within 3 days prior to eligibility assessments are not permitted
6.3. Platelets > = 75 × 10^9/L (in the case of heavy bone marrow infiltration (> 50%) which is, in the opinion of the investigator, the cause of the thrombocytopaenia and provided appropriate supportive measures and patient monitoring are in place, a platelet count of > = 50 × 10^9/L is permitted. Platelet transfusions within 3 days prior to eligibility assessments are not permitted.
7. Creatinine clearance (CrCl) > = 30 mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
8. Able to swallow oral medication
9. Aged at least 18 years
10. Agree to follow the pregnancy prevention guidelines
11. Able to provide written informed consent

Inclusion criteria for starting isatuximab maintenance, R1, R2 and R3:
1. 4 cycles of RCyBorD received
2. Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG > 2 is due to effects of myeloma eg spinal cord compression);
3. Total bilirubin < 3 x upper limit of normal (ULN)
4. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) < = 3 x ULN
5. Adequate marrow function:
5.1. Neutrophils > = 1.0 × 10^9/L (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC > = 0.75 x 10^9/L is allowed),
5.2. Haemoglobin (Hb) > = 80g/L. Blood transfusions within 3 days prior to eligibility assessments are not permitted,
5.3. Platelets > = 75 × 10^9/L (in the case of heavy bone marrow infiltration (> 50%) which is, in the opinion of the investigator, the cause of the thrombocytopaenia and provided appropriate supportive measures and patient monitoring are in place, a platelet count of > = 50 × 10^9/L is permitted. Platelet transfusions within 3 days prior to eligibility assessments are not permitted
6. Creatinine clearance (CrCl) > = 30 mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
7. Agree to follow the pregnancy prevention guidelines

Additional inclusion criteria for starting isatuximab maintenance:
1. Standard-risk (participant is not confirmed to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q), as confirmed by the CTRU
2. 4 cycles of RCyBorD received
3. MRD-negative (proportion of malignant cells in the bone marrow is < 1 in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT
4. Received > = 100mg/m^2 high-dose melphalan and ASCT
5. Signed the Informed Consent Document for the R1 treatment pathway

Additional inclusion criteria for R1:
1. 12 cycles of isatuximab maintenance received
2. MRD-negative (proportion of malignant cells in the bone marrow is < 1 in 100,000, confirmed by HMDS central lab) after 12 cycles of isatuximab

Additional inclusion criteria for R2:
1. Standard-risk (participant is not confirmed to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q) as confirmed by CTRU.
2. 4 cycles of RCyBorD received
3. At least minimal response (MR; according to IMWG criteria) at 100 days post-ASCT
4. MRD-positive (proportion of malignant cells in the bone marrow is > = 1 in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT
5. Received > = 100mg/m^2 high-dose melphalan and ASCT
6. Signed the Informed Consent Document for the R2 treatment pathway

Additional inclusion criteria for R3:
1. High-risk (participant is confirmed to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q)) as confirmed by CTRU
2. 4 cycles of RCyBord received
3. At least minimal response (MR; according to IMWG criteria) at 100 days post-ASCT
4. Received > = 100mg/m^2 high-dose melphalan and ASCT
5. Signed the Informed Consent Document for the R3 treatment pathway

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
100 years

Sex
All

Total final enrolment
0

Key exclusion criteria
Exclusion criteria for registration (and for starting isatuximab maintenance, R1, R2 and R3):
1. Smouldering MM, monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma of bone, or extramedullary plasmacytoma (without evidence of MM)
2. Received previous treatment for MM, with the exception of local radiotherapy to relieve bone pain or spinal cord compression, prior bisphosphonate treatment, or corticosteroids as long as the total dose does not exceed the equivalent of 160mg dexamethasone. This criteria is not

applicable at R1, R2 and R3 when participants will have received previous treatment for MM as part of this trial.
3. Unstable angina or myocardial infarction within 4 months prior to registration (or at any time since registration for participants starting isatuximab maintenance, R1, R2 and R3), NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
4. Cardiac disorder identified according to local practice (eg left ventricular ejection fraction, LVEF; results from formal measurements acceptable within 28 days prior to registration)
5. Significant neuropathy (Grade > = 3, or Grade 2 with pain)
6. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to registration. Cancer treated with curative intent for > 5 years previously and without evidence of recurrence will be allowed
7. Pregnant, lactating or breastfeeding female participants (within 28 days prior to starting isatuximab maintenance, R1, R2 and R3
8. Known resistance, intolerance or hypersensitivity to any component of the planned therapies, except in the case of hypersensitivity which is amenable to premedication with steroids or H2 blocker. Intolerance includes hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
9. Major surgery within 14 days before registration (or starting isatuximab maintenance, R1, R2 and R3). This would include surgical intervention for relief of cord compression but does not include vertebroplasty or kyphoplasty.
10. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of trial treatment, including difficulty swallowing.
11. Active systemic infection
12. Participant is hepatitis B surface antigen positive, hepatitis C antibody positive or HIV positive. Participants must have hepatitis and HIV screening conducted within 28 days prior to registration.
13. Any other medical or psychiatric condition which, in the opinion of the investigator, contraindicates the participant’s participation in this study.
14. Receipt of live vaccination within 30 days prior to registration, for the duration of the study and for 3 months after the last dose of study drug.
15. Participant has risk factors for thromboembolism including the use of agents which may increase their risk of thrombosis, such as hormone replacement therapy (this exclusion criteria is applicable only at registration and when starting R2 or R3 pathway)
16. Participant has risk factors for seizures (this exclusion criteria is applicable only at registration and when starting R2 or R3 pathway)

Exclusion criteria for starting isatuximab:
1. Disease progression
2. MRD-positive at 100 days post-ASCT
3. Registration exclusion criteria

Exclusion criteria for R1:
1. Disease progression
2. MRD-positive at 100 days post-ASCT or after 12 cycles of isatuximab
3. Registration exclusion criteria

Exclusion criteria for R2 and R3:
1. Disease progression
2. Registration exclusion criteria in Section

Date of first enrolment
11/05/2021

Date of final enrolment
09/03/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University College Hospitals
250 Euston Road
1st Floor Central
London
England
NW1 2PG

Study participating centre
St James's Hospital
Beckett Street
Leeds
England
LS9 7TF

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK; Grant Codes: C9203/A24078

Alternative Name(s)
CR_UK, Cancer Research UK - London, Cancer Research UK (CRUK), CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Celgene

Alternative Name(s)
Celgene Corporation

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
Sanofi

Alternative Name(s)
sanofi-aventis, Sanofi US, Sanofi-Aventis U.S. LLC, Sanofi U.S.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.
CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.
The CTRU encourages a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.
The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		17/11/2022	25/02/2026	Yes	No
HRA research summary			28/06/2023	No	No