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Myeloma XII (ACCoRd trial)

Submission date 28/11/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol
Registration date 15/12/2016	**Overall study status** Ongoing	[_] Statistical analysis plan [X] Results
Last Edited 10/09/2024	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-ixazomib-for-people-with-myeloma-that-has-come-back-myeloma-xii-accord

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2016-000905-35

Protocol serial number
32907

Study information

Scientific Title

Myeloma XII (ACCoRd): A phase III study to determine the role of ixazomib as an augmented conditioning therapy in salvage autologous stem cell transplant (ASCT) and as a post-ASCT consolidation and maintenance strategy in patients with relapsed multiple myeloma

Acronym
ACCoRd

Study objectives
This trial aims to determine and compare:
1. The depth of response between standard melphalan conditioning and augmented (adding ixazomib) melphalan conditioning at second ASCT
2. The impact of adding consolidation and maintenance treatment versus no further treatment, on progression free survival

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Greater Manchester South Research Ethics Committee, 11/10/2016, ref: 16/NW /0517

Study design
Randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

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

Interventions
Participants are randomised in a 1:1 ratio to receive 2 cycles ITD.

ITD re-induction therapy
All participants will be registered at trial entry and will receive re-induction therapy with 4-6 cycles of ixazomib, thalidomide, and dexamethasone (ITD), as per the dosing regimen below:

Cycles 1-6 of ITD re-induction (28-day cycles)
Ixazomib: 4mg/day on days 1, 8, 15, taken orally
Thalidomide: 100mg/day on days 1-28, taken orally
Dexamethasone: 40mg/day on days 1, 8, 15, 22, taken orally

Response assessment after ITD re-induction to determine eligibility for Randomisation 1, according to International Myeloma Working Group criteria.

Randomisation 1
Eligible participants who reach at least stable disease after ITD re-induction will be randomised

on a 1:1 basis to receive either (a) conventional autologous stem cell transplant (ASCT-con) using melphalan, or (b) augmented autologous stem cell transplant (ASCT-aug) using melphalan with ixazomib. Dosing regimens below:

ASCT-con:
Melphalan 200mg/m2/day on D-1, intravenously
ASCT on D0

ASCT-aug:
Ixazomib 4mg/day on D-4 and D-1, taken orally
Melphalan 100mg/m2/day on D-3 and D-2, intravenously
ASCT on D0

Response assessment 100 days after ASCT-con or ASCT-aug to determine eligibility for Randomisation 2, according to International Myeloma Working Group criteria.

Randomisation 2 (R2)
Eligible participants who reach at least minimum response 100 days after ASCT-con or ASCT-aug will be randomised on a 1:1 basis to receive either (a) ITD consolidation and ixazomib maintenance, or (b) no further therapy. If participants are randomised to receive further therapy, the dosing regimens are below:

2 cycles of ITD consolidation (28-day cycles):
Ixazomib: 4mg/day on days 1, 8, 15, taken orally
Thalidomide: 100mg/day on days 1-28, taken orally
Dexamethasone: 40mg/day on days 1, 8, 15, 22, taken orally

Ixazomib maintenance, taken until disease progression (28-day cycles):
Ixazomib: 4mg/day on days 1, 8, 15, taken orally

For participants randomised to further therapy at R2, follow-up will be done at the end of consolidation and subsequently at 3-monthly intervals (starting from 3 months post-R2). For participants randomised to no further therapy at R2, follow-up will be done at 8 weeks post-R2 and subsequently 3-monthly visits (starting from 3 months post R2) thereafter until disease progression. Following disease progression, follow-up will be done annually post-progression until death.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Ixazomib, thalidomide, dexamethasone, melphalan

Primary outcome(s)
All outcome measures are measured at baseline, the end of each re-induction cycle, the end of re-induction, 100 days post-ASCT, the end of consolidation, 8 weeks post-randomisation 2, 3 monthly post randomisation-2 until disease progression and at the time of disease progression:
1. Overall response rate following ASCT, defined as the impact on Depth of Response (DoR:

<VGPR vs. ≥VGPR) when salvage ASCT conditioning is augmented by the addition of a proteasome inhibitor, will be determined according to the IMWG Uniform Response Criteria for Multiple Myeloma
2. Progression-free survival, is defined as the time from randomisation to the consolidation part of the trial to first documented evidence of disease progression or death from any cause. Participants who do not progress will be censored at the last date they were known to be alive and progression free

Key secondary outcome(s))

All outcome measures are measured at baseline, the end of each re-induction cycle, the end of re-induction, 100 days post-ASCT, the end of consolidation, 8 weeks post-randomisation 2, 3 monthly post randomisation-2 until disease progression and at the time of disease progression:
1. Overall survival is defined as the time from randomisation to the consolidation/ maintenance part of the trial post-ASCT to death from any cause or last follow-up
2. Time to disease progression is defined as time from randomisation to the consolidation/ maintenance part of the trial post-ASCT to first documented evidence of disease progression. Participants who die without disease progression will be censored in the analysis.
3. Overall response rate following re-induction will be determined according to the IMWG Uniform Response Criteria for Multiple Myeloma
4. Progression-free survival 2 is defined as the time from second randomisation to the consolidation/maintenance part of the trial post-ASCT to second documented disease progression (or the start of next line anti-myeloma treatment), or death from any cause, whichever occurs first. Participants alive and for whom a second progression after second randomisation has not been observed will be censored at the last day they were known to be alive and second progression-free.
5. Time to next line treatment is defined as the time from the date of randomisation to the date of commencement of next line treatment. Participants who do not receive next line treatment will be censored at the date of the last assessment or follow-up visit where they are known to have received no new therapy.
6. Duration of response to protocol treatment is defined from the time of achieving at least a partial response to the date of first documented evidence of disease progression. Participants who die prior to documentation of disease progression will be censored at the date of death. Participants dying from causes not primarily due to progression will also be censored at the date of death. Participants not reaching disease progression at the time of analysis will be censored at the last date known to be progression-free.
7. Engraftment kinetics will be summarised based on summaries of stem cell remobilisation protocol and success of remobilisation and stem cell harvest after the completion of ASCT for all participants
8. Rate of Minimal Residual Disease negativity is defined as the proportion of participants with minimal residual disease (MRD) as assessed by flow cytometry will be assessed at various points in trial protocol treatment
9. Toxicity and safety will be reported based on adverse events, as graded by CTCAE V4.03 and determined by routine clinical assessments at each centre
10. Quality of Life (QoL) i.e. EORTC QLQ-C30, EORTC QLQ-MY20, and the EQ-5D will be used to measure participant-assessed QoL at registration, post re-induction, 100 days post-ASCT and annually post second randomisation until 24 months post second randomisation, or until disease progression whichever is earlier

Completion date

30/04/2027

Eligibility

Key inclusion criteria

1. Diagnosed with relapsed MM (with measurable disease, according to IMWG criteria) previously treated with ASCT
2. First Progressive Disease (PD) at least 12 months following first ASCT, requiring therapy
3. Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2
4. Aged at least 18 years
5. Participants must have the following blood results within 14 days before registration: a. Absolute neutrophil count (ANC) ≥1x109/L b.Platelet count ≥75x109/L. If the participant has ≥50% bone marrow infiltration a platelet count of ≥50x109/L is allowed. Platelet transfusions are not allowed within 3 days before registration in order to meet these values.
6. Adequate renal function within 14 days before registration: a.Creatinine clearance ≥30ml/min (calculated according to Cockcroft-Gault equation or other locally approved formula)
7. Adequate hepatobiliary function within 14 days before registration: a. Total bilirubin <2 x upper limit of normal (ULN) b. ALT <2 x ULN
8. Adequate pulmonary function within 14 days before registration: a. Adequate respiratory functional reserve (delineated by KCO/DLCO (carbon monoxide diffusion in the lung) of ≥50%). No evidence of a history of pulmonary disease. If a significant history, then a review by a respiratory medicine physician is required
9. Adequate cardiac function within 12 weeks before registration: a. Left ventricular ejection fraction (LVEF) ≥40%. Note: repeat confirmation of cardiac function is needed if treatment is given between this assessment and registration
10. Female participants who:
10.1. Are not of childbearing potential (Appendix 8), OR
10.2. If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 90 days after the last dose of study drug, OR
10.3. Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception)
Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following: a. Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR b. Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.) Contraception for female and male participants must be in accordance with (and consent to) the Celgene-approved Thalidomide Pregnancy Prevention Programme
11. If female and of childbearing potential (see Appendix 8), must have a negative pregnancy test performed by a healthcare professional in accordance with the Celgene Thalidomide Pregnancy Prevention Programme
12. Patients agree not to receive other clinical trials treatment, including investigational medicinal products (IMPs) not included in this trial, within 30 days of trial registration and throughout the duration of the trial, until disease progression
13. Able to provide written informed consent

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Received prior second line therapy for their relapsed disease other than local radiotherapy, therapeutic plasma exchange, or dexamethasone (up to a maximum of 200mg is allowed but not within 30 days prior to registration). Radiotherapy sufficient to alleviate or control pain of local invasion is permitted, but must not be within 14 days before registration. Patients who have received hemi-body radiation or similar since relapse will not be eligible
2. ≥Grade 2 peripheral neuropathy within 14 days before registration
3. Known HIV or Hepatitis B/C seropositivity
4. Known resistance, intolerance or sensitivity to any component of the planned therapies
5. Any medical or psychiatric condition which, in the opinion of the investigator, contraindicates the participant's participation in this study
6.Previous or concurrent malignancies at other sites (excluding completely resected non-melanoma skin cancer or carcinoma in situ of any type, such as cervical cancer)
7. Pregnant, lactating or breast feeding female participants
8. Failure to have fully recovered (i.e. less than or equal to Grade 1 toxicity) from the reversible effects of prior chemotherapy.
9. Major surgery within 14 days before registration
10. Central nervous system involvement with myeloma
11. Ongoing or active infection requiring systemic antibiotic therapy or other serious infection within 14 days before registration
12. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months
13. Systemic treatment, within 14 days before the first dose of ixazomib with strong CYP3A inducers (e.g. rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort
14. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib, including difficulty swallowing
15. Patients that have previously been treated with ixazomib or participated in a study with ixazomib whether treated with ixazomib or not

Date of first enrolment
20/03/2017

Date of final enrolment
31/05/2022

Locations

Countries of recruitment

United Kingdom

England

Northern Ireland

Scotland

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

Study participating centre
Addenbrookes Hospital
Hills Road
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CB2 0QQ

Study participating centre
Arrowe Park Hospital
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CH49 5PE

Study participating centre
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Gawber Road
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S75 2EP

Study participating centre
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RG24 9NA

Study participating centre
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Great Western Road
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Study participating centre
Belfast City Hospital
Lisburn Road
Belfast
United Kingdom
BT9 7AB

Study participating centre
Birmingham Heartlands Hospital
Bordesley Green E
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B9 5SS

Study participating centre
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Blackpool
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FY3 8NR

Study participating centre
Bradford Royal Infirmary
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BD9 6RJ

Study participating centre
Bristol Haematology and Oncology Centre
Horfield Road
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BS2 8ED

Study participating centre
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Salterhebble
Halifax
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HX3 0PW

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Chesterfield Road
Calow
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S44 5BL

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Liverpool Road
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CH2 1UL

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DA2 8DA

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NE7 7DN

Study participating centre
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101 Manthorpe Road
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NG31 8DG

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OX3 9DU

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NG17 4JL

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Study participating centre
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ML6 0JS

Study participating centre
Ninewells Hospital
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Newcastle Road
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Combe Park
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BA1 3NG

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Pensnett Road
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DY1 2HQ

Study participating centre
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SP2 8BJ

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Stepping Hill Hospital
Poplar Grove
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Study participating centre
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TQ2 7AA

Study participating centre
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TN2 4QJ

Study participating centre
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Study participating centre
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WR5 1DD

Sponsor information

Organisation
University of Leeds

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

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
Takeda Development Center Americas, Inc.

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		06/09/2024	10/09/2024	Yes	No
Protocol article	protocol	07/03/2018		Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes