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A randomised comparison of thalidomide and lenalidomide combinations in myeloma patients of all ages

Submission date
24/04/2009

Recruitment status
No longer recruiting

Registration date
29/06/2009

Overall study status
Completed

Last Edited
21/08/2025

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol
Cancer Research UK plain English summary for the intensive pathway:
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-lenalidomide-bortezomib-intensive-treatment-group-myeloma-XI

Cancer Research UK plain English summary for the non-intensive pathway:
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-lenalidomide-bortezomib-myeloma-non-intensive-treatment-group-myeloma-XI

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Additional identifiers

Clinical Trials Information System (CTIS)
2009-010956-93

ClinicalTrials.gov (NCT)
NCT01554852

Protocol serial number
HM09/8885

Study information

Scientific Title
Randomised comparisons, in myeloma patients of all ages, of thalidomide, lenalidomide, carfilzomib and bortezomib induction combinations, and of lenalidomide and combination lenalidomide plus vorinostat as maintenance

Acronym
Myeloma XI

Study objectives
Current hypothesis as of 03/06/2016:
Myeloma XI has two treatment pathways; an intensive pathway for younger/fitter patients where intensive high-dose therapy (HDT) with stem cell support is considered appropriate, and a non-intensive pathway for older/less fit patients. The trial aims to answer three main questions at induction, consolidation and maintenance:
1. Is cyclophosphamide-lenalidomide-dexamethasone (RCD) or a 4-drug regimen including both lenalidomide and carfilzomib (CCRD) given to maximum response, a better induction regimen than the current UK gold standard of cyclophosphamide-thalidomide-dexamethasone (CTD)?
2. For patients achieving a sub-optimal response to induction across both treatment pathways (less than very good partial response [VGPR]), can the use of bortezomib, cyclophosphamide and dexamethasone (VCD) improve responses and does this translate into improved progression-free survival (PFS) and overall survival (OS)?
3. Can lenalidomide at maintenance improve PFS and OS when compared to the use of no maintenance?

Previous hypothesis:
Myeloma XI has two treatment pathways; an intensive pathway for younger/fitter patients where intensive high-dose therapy (HDT) with stem cell support is considered appropriate, and a non-intensive pathway for older/less fit patients. The trial aims to answer three main questions

at induction, consolidation and maintenance:
1. Is cyclophosphamide-lenalidomide-dexamethasone (RCD) given to maximum response, a better induction regimen than the current UK gold standard of cyclophosphamide-thalidomide-dexamethasone (CTD)?
2. For patients achieving a sub-optimal response to induction across both treatment pathways (less than very good partial response [VGPR]), can the use of bortezomib, cyclophosphamide and dexamethasone (VCD) improve responses and does this translate into improved progression-free survival (PFS) and overall survival (OS)?
3. Can lenalidomide at maintenance improve PFS and OS when compared to the use of no maintenance?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxfordshire REC A, 17/09/2009, ref:09/H0604/79

Study design
Randomized Phase III multicentre open-label trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Myeloma

Interventions
Intensive pathway: current interventions as of 02/06/2016:
Patients will be initially randomised to receive either CTD (cyclophosphamide, thalidomide, and dexamethasone), RCD (cyclophsphamide, lenalidomide, and dexamethasone), or CCRD (carfilzomib, cyclophosphamide, lenalidomide, and dexamethasone), and will receive a minimum of 4 cycles of induction chemotherapy to maximum response or patient intolerance.
All patients showing a complete response (CR) or very good partial response (VGPR) to CTD/RCD /CCRD will proceed to peripheral blood stem cell harvest and standard high-dose melphalan (HDM) with supporting autologous peripheral blood stem cell transplant (ASCT).
Patients showing a partial response (PR) or minimal response (MR) to CTD/ RCD/CCRD will be randomised to receive consolidation bortezomib plus cyclophosphamide and dexamethasone (VCD) to maximum response or intolerance (up to 8 cycles), or proceed straight to peripheral blood stem cell harvest and standard HDM with supporting ASCT. Once randomised patients have received VCD, they will proceed with harvest, HDM and ASCT.
Patients showing progressive disease (PD) or no change (NC) during induction chemotherapy (CTD, RCD, or CCRD) will all receive consolidation VCD (i.e. will not undergo the VCD vs nothing randomisation) to maximum response or intolerance (up to 8 cycles), then proceed to peripheral blood stem cell harvest and standard HDM with supporting ASCT.
Following HDM/ASCT, all patients who are disease progression-free (except those who demonstrated PD or NC during RCD) will undergo maintenance randomisation to either lenalidomide maintenance or no maintenance treatment. Patients randomised to lenalidomide maintenance will commence lenalidomide approximately 100 days post HDM/ASCT. In the

absence of toxicity, lenalidomide maintenance will continue (21 days out of every 28) until disease progression.

Intensive pathway: previous interventions
Patients will be initially randomised to receive either CTD (cyclophosphamide, thalidomide and dexamethasone) or RCD (cyclophsphamide, lenalidomide and dexamethasone) and will receive a minimum of 4 cycles of induction chemotherapy to maximum response or patient intolerance.
All patients showing a complete response (CR) or very good partial response (VGPR) to RCD/CTD will proceed to peripheral blood stem cell harvest and standard high-dose melphalan (HDM) with supporting autologous peripheral blood stem cell transplant (ASCT).
Patients showing a partial response (PR) or minimal response (MR) to RCD/CTD will be randomised to receive consolidation bortezomib plus cyclophosphamide and dexamethasone (VCD) to maximum response or intolerance (up to 8 cycles), or proceed straight to peripheral blood stem cell harvest and standard HDM with supporting ASCT. Once randomised patients have received VCD, they will proceed with harvest, HDM and ASCT.
Patients showing progressive disease (PD) or no change (NC) during induction chemotherapy (RCD or CTD) will all receive consolidation VCD (ie will not undergo the VCD vs nothing randomisation) to maximum response or intolerance (up to 8 cycles), then proceed to peripheral blood stem cell harvest and standard HDM with supporting ASCT.
Following HDM/ASCT, all patients who are disease progression-free (except those who demonstrated PD or NC during RCD) will undergo maintenance randomisation to either lenalidomide maintenance or no maintenance treatment. Patients randomised to lenalidomide maintenance will commence lenalidomide approximately 100 days post HDM/ASCT. In the absence of toxicity, lenalidomide maintenance will continue (21 days out of every 28) until disease progression.

Non-intensive pathway
Patients will be randomised to RCDa (RCD with a reduced dose of dexamethasone) or CTDa (CTD with a reduced dose of dexamethasone and lower starting dose of thalidomide) and will receive a minimum 6 cycles of their randomised induction treatment regimen to maximum response.
All patients showing CR or VGPR will proceed to maintenance randomisation (lenalidomide or no maintenance). Patients showing PR or MR to RCDa/CTDa will be randomised to receive consolidation VCD to maximum response or intolerance (up to 8 cycles), or proceed to maintenance randomisation. Once randomised patients have received VCD, they will proceed with maintenance randomisation.
Patients showing progressive disease (PD) or NC during induction chemotherapy (RCDa or CTDa) will all receive consolidation VCD (i.e., will not undergo the VCD versus nothing randomisation) to maximum response or intolerance (up to 8 cycles).
Following RCD/CTD/VCD, all patients who are disease progression-free (except those who demonstrated PD or NC during RCDa) will undergo maintenance randomisation to either lenalidomide maintenance or no maintenance treatment. In the absence of toxicity, lenalidomide maintenance will continue (21 days out of every 28) until disease progression.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)

Cyclophosphamide, thalidomide, dexamethasone, lenalidomide, melphalan, bortezomib, carfilzomib

Primary outcome(s)
1. Overall survival
2. Progression-free survival

Interim analyses will be presented to the DMEC at approximately yearly intervals and the trial will have a formal interim analysis when half the total number of deaths has been observed. No other formal analyses are planned until after the trial is closed to accrual.

Key secondary outcome(s))
Current secondary outcome measures as of 21/10/2024:

1. Response including CR rate at the end of induction
2. Conversion rate to CR/VGPR for patients who undergo VCD randomisation
3. Toxicity
4. PFS2
5. Relevant biological endpoints

Interim analyses will be presented to the DMEC at approximately yearly intervals and the trial will have a formal interim analysis when half the total number of deaths has been observed. No other formal analyses are planned until after the trial is closed to accrual.

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Previous secondary outcome measures:

1. Response
2. Conversion rate to CR/VGPR for patients who undergo VCD randomisation
3. Toxicity

Interim analyses will be presented to the DMEC at approximately yearly intervals and the trial will have a formal interim analysis when half the total number of deaths has been observed. No other formal analyses are planned until after the trial is closed to accrual.

Completion date
31/12/2023

Eligibility

Key inclusion criteria
1. Aged 18 years or greater, either sex
2. Newly diagnosed as having symptomatic multiple myeloma or non-secretory multiple myeloma based on:
2.1. Paraprotein (M-protein) in serum and/or urine
2.2. Bone marrow clonal plasma cells or plasmacytoma
2.3. Related organ or tissue impairment and/or symptoms considered by the clinician to be myeloma related
3. Provide written informed consent
4. Women of childbearing potential and male patients whose partner is a woman of child bearing

potential must be prepared to use contraception in accordance with (and consent to) the Celgene approved process for thalidomide and lenalidomide Risk Management and Pregnancy Prevention, or commit to absolute and continuous abstinence
5. Women of child bearing potential must have a negative pregnancy test in accordance with the Celgene approved process for thalidomide and lenalidomide Risk Management and Pregnancy Prevention

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
4420

Key exclusion criteria
1. Asymptomatic myeloma
2. Solitary plasmacytoma of bone (patients with previous solitary plasmacytoma that have now progressed to symptomatic or non-secretory myeloma are eligible)
3. Extramedullary plasmacytoma (without evidence of myeloma)
4. Previous or concurrent active malignancies, except surgically-removed basal cell carcinoma of the skin or other in situ carcinomas. Patients with remote histories (greater than 5 years) of other cured malignancies may be entered.
5. Previous treatment for myeloma, except the following:
5.1. Local radiotherapy to relieve bone pain or spinal cord compression
5.2. Prior bisphosphonate treatment
5.3. Corticosteroids within the last 3 months
6. Known history of allergy contributable to compounds containing boron or mannitol
7. Grade 2 or greater (National Cancer Institute [NCI] criteria) peripheral neuropathy
8. Caution is advised in patients with a past history of ischaemic heart disease, pericardial disease, acute diffuse infiltrative pulmonary disease or psychiatric disorders, evidence of impaired marrow function or elevated liver function tests, but exclusion is essentially to be at the discretion of the treating clinician
9. Acute renal failure (unresponsive to up to 72 hours of rehydration, characterised by creatinine greater than 500 µmol/l or urine output less than 400 ml/day or requirement for dialysis)

Added 02/06/2016:
1. Documented diagnosis of Myelodysplastic Syndrome (MDS) that meets International Prognostic Scoring System (IPSS) criteria for high-risk disease
2. Patient has active or prior hepatitis C

Added 21/10/2024:
3. Lactating or breastfeeding

Date of first enrolment
25/05/2010

Date of final enrolment
24/02/2016

Locations

Countries of recruitment
United Kingdom

Study participating centre
112 trial sites
United Kingdom
-

Sponsor information

Organisation
University of Leeds (UK)

ROR
https://ror.org/024mrxd33

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (CRUK) (UK) (ref: CRUK/09/014)

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 Ltd (UK)

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 believes 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 on suitable requirements for release

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results for maintenance therapy with lenalidomide versus placebo	01/01/2019		Yes	No
Results	response-adapted intensification treatment results	01/12	21/10		

article		/2019	/2019	Yes	No
Results article	renal outcome results	24/11 /2020	25/11 /2020	Yes	No
Results article		01/12 /2020	03/12 /2020	Yes	No
Results article		11/01 /2021	12/01 /2021	Yes	No
Results article	maintenance randomisation comparing combination lenalidomide-vorinostat and lenalidomide	21/12 /2022	14/01 /2025	Yes	No
Results article		20/08 /2025	21/08 /2025	Yes	No
Abstract results	Final Analysis of the Randomised UK MRA Myeloma XI+ Trial Examining Krdc (carfilzomib, lenalidomide, dexamethasone and cyclophosphamide) As Induction Therapy for Newly Diagnosed Multiple Myeloma Patients	05/11 /2024	05/02 /2025	No	No
Abstract results	MRD and Molecular Risk Status Help to De.ne Optimal Maintenance Delivery Strategies after ASCT: Long Term Outcomes of the UK MRA Myeloma XI Trial Comparing Lenalidomide to Observation	05/11 /2024	05/02 /2025	No	No
Abstract results	Optimising the Duration of Therapy for Newly Diagnosed Transplant Ineligible Patients - Analysis of Long Term Follow up Data from the UK MRA Myeloma XI Trial	05/11 /2024	05/02 /2025	No	No
HRA research summary			28/06 /2023	No	No
Other publications	genetic profiling study	06/04 /2023	14/01 /2025	Yes	No
Protocol file	version 9.0	02/11 /2017	21/04 /2023	No	No
Study website	Study website	11/11 /2025	11/11 /2025	No	Yes