ISRCTN16308011 https://doi.org/10.1186/ISRCTN16308011

CATALYST: Carfilzomib-Thal-Dex in relapsed AL Amyloidosis

Submission date 08/08/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 08/08/2016	**Overall study status** Completed	
Last Edited 27/05/2021	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-carfilzomib-with-thalidomide-and-dexamethasone-for-relapsed-amyloidosis-catalyst

Contact information

Type(s)
Public

Contact name
Miss Erin Peat

Contact details
Clinical Trials Research Unit
University of Leeds
Leeds
United Kingdom
LS2 9JT
+44 113 3431658
medcatal@leeds.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2015-000594-40

Protocol serial number
30792

Study information

Scientific Title
A single arm open labeled multicentre phase 1b dose escalation study of carfilzomib taken in combination with thalidomide and dexamethasone in relapsed AL amyloidosis (CATALYST Trial)

Acronym
CATALYST

Study objectives
The aim of this study is to determine the maximum tolerated dose of carfilzomib within a combination chemotherapy regimen (KTD) and to access the safety and tolerability of this regimen in patients with relapsed or refractory AL amyloidosis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. London Brent Research Ethics Committee, 29/03/2016, ref: 16/LO/0087
2. Medicines & Healthcare Products Regulatory Agency, 08/02/2016, ref: 20363/0359/001-0001

Study design
Non-randomised; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Specialty: Cancer, Primary sub-specialty: Haematological oncology; UKCRC code/ Disease: Cancer/ Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissu

Interventions
The trial comprises a dose escalation phase and a dose expansion phase. The dose escalation phase will assess the safety and tolerability of various doses of carfilzomib (27 mg/m2, 36 mg /m2, 45 mg/m2, 56 mg/m2) to determine the maximum tolerated dose and recommended dose. Within the dose escalation phase, participants will be allocated a dose of carfilzomib based on their time of entry to the trial. The interventions used in the trial are the administration of carfilzomib, dexamethasone, and thalidomide.

Thalidomide (50 mg - 100 mg) will be given orally on Days 1-28 of the cycle.
Dexamethasone (20 mg) will be given orally on Days 1, 8, and 15 of the cycle.
Carfilzomib will be given intravenously on Days 1, 8, and 15 of the cycle.

The dose of carfilzomib patients will receive depends on the cohort allocation, but all patients will receive thalidomide and dexamethasone as outlined above. The cohort allocations are:

Cohort -1 - receive 27mg/m2 carfilzomib on Days 1, 8, and 15 of each cycle
Cohort 0 - receive 36mg/m2 carfilzomib on Days 1, 8, and 15 of each cycle
Cohort 1 – receive 45mg/m2 carfilzomib on Days 1, 8, and 15 of each cycle
Cohort 2 - receive 57mg/m2 carfilzomib on Days 1, 8, and 15 of each cycle

In the dose escalation phase, the trial will proceed as follows:
1. Recruit 3 patients onto dose level 0 (36 mg/m2 carfilzomib). If 0/3 patients experience a dose limiting toxicity, open dose level 1 (45 mg/m2 carfilzomib). If 1/3 experience a dose limiting toxicity, recruit 3 more patients onto dose level 0. If 2/3 patients experience a dose limiting toxicity, open dose level -1 (27 mg/m2 carfilzomib) and recruit three patients.
2. If dose level 1 opens, recruit 3 patients. If 0/3 patients experience a dose limiting toxicity, open dose level 2 (57 mg/m2 carfilzomib). If 1/3 experience a dose limiting toxicity, recruit 3 more patients onto dose level 1. If 2/3 patients experience a dose limiting toxicity, declare dose level 0 the maximum tolerated dose. Proceed to identifying recommended dose.
3. If dose level 2 opens, recruit 3 patients. If 0/3 patients experience a dose limiting toxicity, declare dose level 2 the maximum tolerated dose and recommended dose. If 1/3 experience a dose limiting toxicity, recruit 3 more patients onto dose level 2. If 2/3 patients experience a dose limiting toxicity, declare dose level 1 the maximum tolerated dose. Proceed to identifying recommended dose.
4. If dose level -1 opens, recruit 3 patients. If 0/3 or 1/3 patients experience a dose limiting toxicity, declare dose level 0 the maximum tolerated dose. If 2/3 patients experience a dose limiting toxicity, the trial will cease.
5. If in any case, >1/6 patients in any cohort experiences a dose limiting toxicity, the next lowest dose will be identified as the maximum tolerated dose and the trial team will proceed to identifying the recommended dose.

Patients on this part of the trial will receive up to 6 cycles of treatment. When the recommended dose has been identified using the dose escalation system outlined above, a further 20 patients will be recruited onto the dose expansion phase of the trial. These participants will receive thalidomide and dexamethasone as outlined above, plus the recommended dose of carfilzomib.

Patients will initially be seen at the National Amyloidosis Study and will be approached for the trial there. Patients who want to take will have screening assessments, including a physical examination, laboratory tests, a pregnancy test, an echocardiogram, a 24 hour Holter monitor test, a bone marrow examination (if the doctors think this is necessary), and an assessment of medical history. Patients will then be referred to their local participating hospital, where these assessment (with the exception of the echocardiogram, Holter monitor, and bone marrow examination) will be repeated.

If the patient can go on to the trial, they will need to visit their local participating hospital on Days 1, 8, and 15 of each 28-day cycle. This will be the case for up to 6 cycles of treatment. At every treatment visit, patients will have blood tests, and at the end of cycle 2, patients will have another echocardiogram. Before the fourth cycle, patients will attend to National Amyloidosis centre again and undergo a physical examination, laboratory tests, a pregnancy test, and an echocardiogram. Their response to the therapy will also be assessed and will be used to determine further treatment.

When all treatment has been completed, patients will visit the National Amyloidosis Centre a third time, where they will undergo a physical examination, laboratory tests, and a pregnancy test. There will be a single follow-up 6 months after starting treatment (or one month after the last cycle of treatment if 6 cycles are received) in which participants will undergo a physical examination, laboratory tests, a pregnancy test, and an echocardiogram.

Intervention Type
Drug

Phase
Phase I

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

Primary outcome(s)
1. Dose-Limiting Toxicities (Dose escalation phase), between the time of receiving the first registered dose of carfilzomib in cycle 1 and day 1 cycle 2, in order to establish the Maximum Tolerated Dose (MTD) and recommended dose (RD) of carfilzomib in combination with thalidomide and dexamethasone at the end of the dose escalation phase, as assessed by counting the total number of dose limiting toxicities reported on the case report forms. This will be carried out at the end of the dose escalation phase.
2. Proportion of patients treated who experience any grade 3 or 4 CTCAE toxicity throughout all treatment cycles, will be determined at the end of the dose escalation phase, as assessed by counting the number of patients experiencing any grade 3 or 4 CTCAE toxicity reported on the case report forms. This will be carried out at the end of the trial.

Key secondary outcome(s))
1. Clonal response rate within 3 months, at 3 months, within 6 months and at 6 months will be assessed by reporting of clonal response rates on case report forms for each patient. This assessment will be compiled and assessed as a whole at the end of the trial.
2. Amyloidotic organ response rate within 3 months and 6 months will be assessed by reporting of organ response rates on case report forms for each patient. This assessment will be compiled and assessed as a whole at the end of the trial.
3. Time to amyloidotic organ response will be assessed by reporting of organ response rates and determining how long it takes for this to happen as reported on case report forms for each patient. This assessment will be compiled and assessed as a whole at the end of the trial.
4. Number of deaths at 6 months will be assessed by counting the number of deaths reported on the case report forms at 6 months.
5. Number of patients progression free at 6 months will be assessed by counting the number of patients who have not progressed reported on the case report forms at 6 months.
6. Maximum response will be assessed by reporting of maximum response rates on case report forms for each patient. This assessment will be compiled and assessed as a whole at the end of the trial.
7. Time to maximum response will be assessed by reporting of maximum response rates and determining how long it takes for this to happen as reported on case report forms for each patient. This assessment will be compiled and assessed as a whole at the end of the trial.
8. Number of patients withdrawing from treatment will be assessed by counting the number of withdrawals reported on the case report forms at the end of the trial.
9. Number of patients experiencing dose delays, and compliance profile of KTD will be assessed by looking at how many patients experience dose delays and how patients are adhering to their chemotherapy regimen as reported on case report forms for each patient. This assessment will be compiled and assessed as a whole at the end of the trial.
10. Relative dose intensity will be assessed by comparing the reported prescribed dose and the reported received dose for each patient, as reported on the case report forms. This assessment will be compiled and assessed as a whole at the end of the trial.

Completion date
21/10/2019

Eligibility

Key inclusion criteria
1. Aged 18 years or greater
2. Diagnosis of systemic AL amyloidosis with
2.1. Exclusion of genetic mutations associated with hereditary amyloidosis and immunohistochemical exclusion of AA and TTR amyloidosis as appropraite
2.2. Amyloid related organ dysfunction or organ syndrome
3. Measurable clonal disease
4. Clonal relapse after previous chemotherapy or autograft stem cell transplant OR refractory clonal disease to previous chemotherapy or stem cell transplant
5. Capable of providing written, informed consent and willing to follow study protocol
6. Life expectancy ≥6 months
7. ECOG performance status of 0-2
8. Platelet count ≥50 x 10(9)/l
9. Neutrophil count ≥1 x 10(9)/l
10. Haemoglobin ≥8 g/dl
11. Bilirubin <2 times or alkaline phosphatase <4 times upper limit of normal
12. Female participants of child-bearing potential must have a negative pregnancy test prior to treatment and agree to use dual methods of contraception for the duration of the study and for 30 days following completion of study. Male participants must also agree to use a barrier method of contraception for the duration of the study and for 30 days following completion of study if sexually active with a female of child-bearing potential. Women who could become pregnant must have taken precautions not to become pregnant for 1 month before the start of the study
13. Participants must comply with the Celgene pregnancy prevention programme for thalidomide

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Overt symptomatic multiple myeloma
2. Amyloidosis of unknown or non AL type
3. Localised AL amyloidosis (in which amyloid deposits are limited to a typical single organ, for

example the bladder or larynx, in association with a clonal proliferative disorder within that organ)
4. Trivial or incidental AL amyloid deposits in the absence of a significant amyloid related organ syndrome (e.g., isolated carpal tunnel syndrome)
5. Refractory to or progressive disease with an IMid and proteasome inhibitor combination
6. Allogeneic stem cell transplantation
7. Solid organ transplantation
8. Severe peripheral or autonomic neuropathy causing significant functional impairment that, in the investigator's opinion, may interfere with protocol adherence
9. eGFR <20ml/min
10. Ejection fraction < 40% or NYHA class III or IV heart failure or uncontrolled hypertension that concerns the investigator
11. Severe pulmonary Hypertension that, in the investigator's opinion, may interfere with protocol adherence
12. Advanced Mayo stage III disease as defined by hs-Troponin T>0.07 and NT-proBNP >700 pMol /L OR NT-proBNP >1000 pMol/L OR supine SBP <100 mm of Hg
13. Myocardial infarction in the proceeding 6 months or unstable angina or conduction abnormalities uncontrolled by medication or devices
14. Concurrent active malignancies, except surgically removed basal cell carcinoma of the skin or other in situ carcinomas
15. Pregnant, lactating or unwilling to use adequate contraception
16. Systemic infection unless specific anti-infective therapy is employed.
17. Known or suspected HIV infection
18. Contraindication to any of the required concomitant drugs or supportive treatments
19. Any other clinically significant medical disease or condition or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a participant's ability to give informed consent
20. Previous experimental agents within 3 months before the date of registration
21. Known allergies to Carfilzomib, Thalidomide or Dexamethasone

Date of first enrolment
30/08/2016

Date of final enrolment
30/06/2018

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
Royal Free Hospital
Pond Street
London

United Kingdom
NW3 2QG

Study participating centre
Birmingham Heartlands Hospital
Bordersley Green East
Birmingham
United Kingdom
B9 5SS

Study participating centre
Derriford Hospital
Derriford Road
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Freeman Hospital
Freeman Road
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Guy's Hospital
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre
Leicester Royal Infirmary
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre

Manchester Royal Infirmary
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Norwich
United Kingdom
NR4 7UY

Study participating centre
Royal Bournemouth General Hospital
Castle Lane East
Bournemouth
United Kingdom
BH7 7DW

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
St James' University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Queen Elizabeth Hospital
Mindelsohn Way
Birmingham
United Kingdom
B15 2TH

Study participating centre
The Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
Christie Hospital
550 Wilmslow Road
Manchester
United Kingdom
M20 4BX

Study participating centre
Royal United Hospitals Bath
Combe Park
Bath
United Kingdom
NA1 3NG

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

Sponsor information

Organisation

University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Industry

Funder Name
Amgen Ltd

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results		10/11/2020	10/11/2020	No	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Plain English results			27/05/2021	No	Yes