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An international randomised clinical trial of therapeutic interventions with the potential to improve outcome in adults with acute myeloid leukaemia and high-risk myelodysplasia undergoing allogeneic stem cell transplantation

Submission date 18/03/2019	**Recruitment status** No longer recruiting	[X] Prospectively registered [ ] Protocol
Registration date 20/03/2019	**Overall study status** Completed	[ ] Statistical analysis plan [ ] Results
Last Edited 03/04/2023	**Condition category** Cancer	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-comparing-usual-treatment-new-treatments-acute-myeloid-leukaemia-myelodysplasia-cosi

Contact information

Type(s)
Scientific

Contact name
Dr Cosi trials

Contact details
Haematology Team – IMPACT
Room 15
Centre for Clinical Haematology
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH
+44 (0)121 371 7859
Cosi@trials.bham.ac.uk

Additional identifiers

EudraCT/CTIS number
2017-004801-42

IRAS number
252254

ClinicalTrials.gov number
NCT04217278

Secondary identifying numbers
CPMS 41409, IRAS 252254

Study information

Scientific Title
An international randomised clinical trial of therapeutic interventions with the potential to improve outcome in adults with acute myeloid leukaemia and high-risk myelodysplasia undergoing allogeneic stem cell transplantation

Acronym
COSI

Study objectives
The aim of the study is to evaluate new pre-transplant and transplant strategies to improve the outcome of patients allografted for AML or high-risk MDS.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 16/05/2019, North West - Liverpool Central Research Ethics Committee, 3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, Tel: +44 (0)207 104 8196, Email: liverpoolcentral.rec@hra.nhs.uk, ref: 19/NW/0135

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

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet

Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Acute myeloid leukaemia, myelodysplastic syndromes

Interventions
There are three separate randomisations in this trial.

Randomisation 1 (R1) - patients will be randomised 1:1 to either the experimental arm (Vyxeos pre-transplant consolidation therapy) or the control arm (Intermediate dose cytarabine pre-transplant consolidation therapy). In the control arm patients will receive up to 2 cycles of cytarabine administered as a 2-hour infusion at a dose of 1 g/m2 on days 1-5 of each cycle. In the experimental arm patients will receive up to 2 cycles of Vyxeos administered intravenously over 90 minutes at a dose of 29 mg/65mg/m² on days 1 and 3 of each cycle.

Randomisation 2 (R2) - patients aged under 55 years will be randomised 1:1 to either the experimental arm (novel myeloablative conditioning regimen TBF) or the control arm (standard myeloablative conditioning regimen FB4). Patients will receive the allocated myeloablative conditioning regimen in hospital immediately prior to allogeneic stem cell transplant.

Randomisation 3 (R3) - patients aged 55 years and over will be randomised 1:1:1 to either one of the two experimental arms (novel reduced intensity conditioning regimen mini TBF or mini FLAMSA-BU) or the control arm (standard reduced intensity conditioning regimen FB2). Patients will receive the allocated reduced-intensity conditioning regimen in hospital immediately prior to allogeneic stem cell transplant.

Patients can be randomised to just one of the above randomisations, or can be randomised twice (e.g. R1 and R2 or R1 and R3). All patients will be followed up for 2 years.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Liposomal cytarabine-daunorubicin (Vyxeos), cytarabine, fludarabine, busulphan, thiotepa

Primary outcome measure
Current primary outcome measure as of 09/12/2022:
Overall survival defined as the time from randomisation to the relevant question until death from any cause. Patients who are alive at the end of the trial or have been lost to follow-up will be censored at their date last seen. For randomisations 2 and 3 this outcome will also be calculated as time from
transplantation in order to run a sensitivity analysis.

Previous primary outcome measure:
Overall survival defined as the time from randomisation to death from any cause. Patients who

are alive at the end of the trial or have been lost to follow up will be censored at their date last seen. For randomisations 2 and 3 this outcome will also be calculated as time from transplantation in order to run a sensitivity analysis.

Secondary outcome measures

Current secondary outcome measure as of 09/12/2022:
1. Measurable residual disease (MRD) status, collected on randomisation and then again immediately prior to transplant. A patient will be categorised as either MRD status reduction (MRD positive to negative), MRD remain negative, MRD remain positive or MRD progression (MRD negative to positive) – Randomisation 1 only (closed to recruitment).
2. Disease-free survival defined as time from randomisation to the relevant question to the date of first relapse or death from any cause. Patients who are alive and disease free at the end of the trial will be censored at their date last known to be alive.
3. Cumulative incidence of disease relapse defined as time from randomisation to the relevant question to the date of relapse. Patients who die prior to relapse will be treated as a competing risk and patients who are alive and relapse free at the end of the trial will be censored at their date last seen
4. Non-relapse mortality defined as the time from randomisation to date of non-relapse death. Patients who die post-relapse will be treated as a competing risk and patients who are alive at the end of the trial will be censored at their date last seen
5. Quality of life measured by EORTC-QLQ-C30 and EQ-5D questionnaires pre transplant, at day 28 and months 3, 6, 9, 12, 18 and 24 – Randomisations 2 and 3 only
6. Incidence of acute and chronic GVHD of any grade – Randomisations 2 and 3 only
7. Incidence of primary graft failure – Randomisations 2 and 3 only
8. Incidence of toxicities reported as per CTCAE V4.0 defined as the number of patients who report one or more AE of grade 3 or higher or an SAE of any grade

Previous secondary outcome measure:
1. Measurable residual disease (MRD) status, collected on randomisation and then again immediately prior to transplant. A patient will be categorised as either MRD status reduction (MRD positive to negative), MRD remain negative, MRD remain positive or MRD progression (MRD negative to positive) – Randomisation 1 only
2. Disease-free survival defined as time from randomisation to the relevant question to the date of first relapse or death from any cause. Patients who are alive and disease free at the end of the trial will be censored at their date last known to be alive
3. Cumulative incidence of disease relapse defined as time from randomisation to the relevant question to the date of relapse. Patients who die prior to relapse will be treated as a competing risk and patients who are alive and relapse free at the end of the trial will be censored at their date last seen
4. Non-relapse mortality defined as the time from randomisation to date of non-relapse death. Patients who die post-relapse will be treated as a competing risk and patients who are alive at the end of the trial will be censored at their date last seen
5. Quality of life measured by EORTC-QLQ-C30 and EQ-5D questionnaires pre transplant, at day 28 and months 3, 6, 9, 12, 18 and 24 – Randomisations 2 and 3 only
6. Incidence of acute and chronic GVHD of any grade – Randomisations 2 and 3 only
7. Incidence of primary graft failure – Randomisations 2 and 3 only
8. Incidence of toxicities reported as per CTCAE V4.0 defined as the number of patients who report one or more AE of grade 3 or higher or an SAE of any grade

Overall study start date

07/07/2017

Completion date
15/03/2025

Eligibility

Key inclusion criteria
Inclusion Criteria for Randomisation 1:
1. Patients (≥ 18 years old) with a morphological documented diagnosis of AML or MDS who are deemed fit for allo-SCT with one of the following disease characteristics:
1.1. AML:
1.1.1. Patients in 1st complete remission (CR1) defined as < 5% blasts
1.1.2. Patients in 2nd complete remission (CR2) defined as < 5% blasts
1.1.3. Secondary AML (defined as previous history of MDS, antecedent haematological disease or chemotherapy
exposure) in CR1 or 2 defined as < 5% blasts
1.2. MDS:
1.2.1 Patients with high risk MDS with an IPSS-R of ≥3.5 (intermediate 3.5 or higher) including intermediate or high risk CMML (e.g. CPSS int-2 or high risk)
2. Patients with an identified HLA identical sibling or suitable matched unrelated donor (suitable match defined as no greater than a single allele mismatch at HLA-A, -B, -C, DRβ1 or DQB1 locus)
3. Patients must be considered suitable to undergo allo-SCT as clinically judged by the Local Investigator
4. Females of and male patients of reproductive potential (i.e., not post-menopausal or surgically sterilised) must use appropriate, highly effective, contraception from the point of commencing therapy until 6 months after treatment
5. Patients have given written informed consent
6. Patients willing and able to comply with scheduled study visits and laboratory tests

Inclusion Criteria for Randomisation 2:
1. Patients aged between 18 – 54 years with a morphological documented diagnosis of AML or MDS who are deemed fit for a MAC allo-SCT with one of the following disease characteristics:
1.1. AML:
1.1.1. Patients in 1st complete remission (CR1) defined as < 5% blasts
1.1.2. Patients in 2nd complete remission (CR2) defined as < 5% blasts
1.1.3. Secondary AML (defined as previous history of MDS, antecedent haematological disease or chemotherapy exposure) in CR1 or 2 defined as < 5% blasts
1.1.4. Must have received at least two courses of prior intensive chemotherapy prior to transplant unless there are exceptional circumstances. Patients with AML who have achieved CR with Venetoclax based induction regimen treatment as only prior treatment, will also be eligible.
1.2. MDS:
1.2.1 Patients with advanced or high risk MDS (with an IPSS-R of ≥3.5 (intermediate 3.5 or higher) including intermediate or high risk CMML (e.g. CPSS int-2 or high risk) who have
< 10% blasts at the time of randomisation following intensive chemotherapy (including R1 randomisation) or hypomethylating agents if necessary
2. Patients with an identified HLA identical sibling or suitable matched unrelated donor (suitable match defined as no greater than a single allele mismatch at HLA-A, -B, -C DRβ1, or DQB1 locus)
3. Patients with an ECOG performance status of 0,1 or 2
4. Patients considered suitable to undergo a MAC allo-SCT as clinically judged by the Local Investigator including:
4.1. Adequate hepatic and renal function as determined by full blood count and biochemistry assessment

4.2. Resolution of any toxic effects of prior therapy (including radiotherapy, chemotherapy or surgical procedures)
4.3. Performance of cardiac or pulmonary function tests (where there is a previous history of cardiac or pulmonary impairment)
5. Females of and male patients of reproductive potential (i.e., not post-menopausal or surgically sterilised) must use appropriate, highly effective, contraception from the point of commencing therapy until 12 months after treatment
6. Patients have given written informed consent
7. Patients willing and able to comply with scheduled study visits and laboratory tests

Inclusion Criteria for Randomisation 3:
1. Patients aged between 55 years or older with a morphological documented diagnosis of AML or MDS who are deemed fit for a RIC allo-SCT (or under the age of 55 with comorbidities which are deemed by the local investigator to preclude safe delivery of a MAC allo-SCT may be considered per investigators discretion) with one of the following disease characteristics:
1.1. AML
1.1.1. Patients in 1st complete remission (CR1) defined as < 5% blasts
1.1.2. Patients in 2nd complete remission (CR2) defined as < 5% blasts
1.1.3. Secondary AML (defined as previous history of MDS, antecedent haematological disease or chemotherapy exposure) in CR1 or 2 defined as < 5% blasts
1.1.4. Must have received at least two courses of prior intensive chemotherapy prior to transplant unless there are exceptional circumstances. Patients with AML who have achieved CR with Venetoclax based induction regimen treatment, as only prior treatment, will also be eligible
1.2. MDS
1.2.1. Patients with high-risk MDS (with an IPSS-R of ≥3.5 (intermediate 3.5 or higher) including intermediate or high risk CMML (e.g. CPSS int-2 or high risk) who have < 10% blasts at the time of randomisation following intensive chemotherapy (including R1 randomisation) or hypomethylating agents if necessary
2. Patients with an identified HLA identical sibling or suitable matched unrelated donor (suitable match defined as no greater than a single allele mismatch at HLA-A, -B, -C,DRβ1 or DQB1 locus)
3. Patients with an ECOG performance status of 0,1 or 2
4. Patients considered suitable to undergo a RIC allo-SCT as clinically judged by the Local Investigator including:
a. Adequate hepatic and renal function as determined by full blood count and biochemistry assessment
b. Resolution of any toxic effects of prior therapy (including radiotherapy, chemotherapy or surgical procedures)
c. Performance of cardiac or pulmonary function tests (where there is a previous history of cardiac or pulmonary impairment)
5. Females of and male patients of reproductive potential (i.e., not post-menopausal or surgically sterilised) must use appropriate, highly effective, contraception from the point of commencing therapy until 12 months after treatment
6. Patients have given written informed consent
7. Patients willing and able to comply with scheduled study visits and laboratory tests

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 394; UK Sample Size: 394

Total final enrolment
333

Key exclusion criteria
Exclusion criteria for Randomisation 1 (R1):
1. Patients with contraindications to receiving allo-SCT
2. Female patients who are pregnant or breastfeeding. All women of childbearing potential must have a negative pregnancy test before commencing treatment
3. Adults of reproductive potential not willing to use appropriate, highly effective, contraception during the specified period
4. Patients with renal or hepatic impairment as clinically judged by the Local Investigator
5. Patients with active infection, HIV-positive or chronic active HBV or HCV.
6. Patients with a prior malignancy, except lobular breast carcinoma in situ, fully resected basal cell or squamous cell carcinoma of skin or treated cervical carcinoma in situ, incidental histologic finding of prostate cancer (T1a or T1b using the tumor, node, metastasis (TNM) clinical staging system), previous MDS, CMML, MPN resulting in secondary AML. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed.
7. History of serious hypersensitivity reaction to cytarabine, daunorubicin, or any component of the Vyxeos formulation.
8. Known history of Wilson's disease or other copper-related metabolic disorder since copper gluconate is a component of the Vyxeos formulation

Exclusion criteria for Randomisation 2 (R2):
1. Patients with contraindications to receiving a MAC allo-SCT
2. Female patients who are pregnant or breastfeeding. All women of childbearing potential must have a negative pregnancy test before commencing treatment
3. Adults of reproductive potential not willing to use appropriate, effective, contraception during the specified period
4. Patients with renal or hepatic impairment as clinically judged by the Local Investigator
5. Patients with active infection, HIV-positive or chronic active HBV or HCV
6. Patients with a prior malignancy, except lobular breast carcinoma in situ, fully resected basal cell or squamous cell carcinoma of skin or treated cervical carcinoma in situ, incidental histologic finding of prostate cancer (T1a or T1b using the tumour, node, metastasis (TNM) clinical staging system), previous MDS, CMML, MPN resulting in secondary AML. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed.

Exclusion criteria for Randomisation 3 (R3):
1. Patients with contraindications to receiving a RIC allo-SCT
2. Female patients who are pregnant or breastfeeding. All women of childbearing potential must have a negative pregnancy test before commencing treatment

3. Adults of reproductive potential not willing to use appropriate, effective, contraception during the specified period
4. Patients with renal or hepatic impairment as clinically judged by the Local Investigator
5. Patients with active infection, HIV-positive or chronic active HBV or HCV
6. Patients with a prior malignancy, except lobular breast carcinoma in situ, fully resected basal cell or squamous cell carcinoma of skin or treated cervical carcinoma in situ, incidental histologic finding of prostate cancer (T1a or T1b using the tumour, node, metastasis (TNM) clinical staging system), previous MDS, CMML, MPN resulting in secondary AML. Cancer treated with curative intent ≥ 5 years previously will be allowed. Cancer treated with curative intent < 5 years previously will not be allowed.

Date of first enrolment
27/01/2020

Date of final enrolment
03/03/2023

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
King's College Hospital
London
United Kingdom
SE5 9RS

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

Study participating centre
Manchester Royal Infirmary
Manchester
United Kingdom
M13 9WL

Study participating centre
Freeman Hospital
Newcastle-Upon-Tyne
United Kingdom
NE7 7DN

Study participating centre
Churchill Hospital
Oxford
United Kingdom
OX3 7LE

Study participating centre
Queen Elizabeth Hospital
Birmingham
United Kingdom
B15 2GW

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

Study participating centre
Addenbrookes Hospital
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
University Hospital of Wales
Cardiff
United Kingdom
CF14 4XW

Study participating centre
Hammersmith Hospital
London
United Kingdom
W12 0HS

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

Study participating centre
Nottingham City Hospital
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Derriford Hospital
Plymouth
United Kingdom
PL6 8DH

Study participating centre
Royal Hallamshire Hospital
Sheffield
United Kingdom
S5 7AU

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

Study participating centre
Royal Stoke University Hospital
Stoke-on-Trent

United Kingdom
ST4 6QG

Study participating centre
ASST Papa Giovanni XXIII
BERGAMO
Italy
24127

Sponsor information

Organisation
University of Birmingham

Sponsor details
Research Support Group
Aston Webb Building
Edgbaston
Birmingham
England
United Kingdom
B15 2TT
+44 (0)121 371 7858
cosi@trials.bham.ac.uk

Sponsor type
University/education

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
IMPACT (funded by NHS Blood & Transplant, Anthony Nolan and Leukaemia UK)

Funder Name

Jazz Pharmaceuticals

Alternative Name(s)
Jazz Pharmaceuticals plc, Greenwich Biosciences, Jazz Pharmaceuticals, Inc.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Ireland

Funder Name
ADIENNE SA

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
01/06/2027

Individual participant data (IPD) sharing plan
The 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?
HRA research summary			28/06/2023	No	No