

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	<input checked="" type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 20/03/2019	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 03/04/2023	Condition category Cancer	<input type="checkbox"/> Individual participant data <input type="checkbox"/> 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

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Contact details

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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, DR β 1 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 DR β 1, 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, DR β 1 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**

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United Kingdom

M13 9WL

Study participating centre

Freeman Hospital

Newcastle-Upon-Tyne

United Kingdom

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Study participating centre

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Oxford

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Study participating centre

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Study participating centre

Bristol Haematology and Oncology Centre

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BS2 8ED

Study participating centre

Addenbrookes Hospital

Cambridge

United Kingdom

CB2 0QQ

Study participating centre

University Hospital of Wales

Cardiff

United Kingdom

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Study participating centre
Hammersmith Hospital
London
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W12 0HS

Study participating centre
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Leicester
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LE1 5WW

Study participating centre
Nottingham City Hospital
Nottingham
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NG5 1PB

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PL6 8DH

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Study participating centre
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Sponsor information

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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