ISRCTN31682779 https://doi.org/10.1186/ISRCTN31682779

A trial for older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome

Submission date 04/09/2013	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 14/11/2013	**Overall study status** Completed	
Last Edited 17/02/2025	**Condition category** Cancer	

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/trials/a-trial-looking-at-treatment-for-older-people-with-acute-myeloid-leukaemia-and-high-risk-myelodysplastic-syndrome-aml18

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT02272478

Clinical Trials Information System (CTIS)
2013-002730-21

Protocol serial number
SPON1227-13

Study information

Scientific Title
AML18 - A trial for older patients with Acute Myeloid Leukaemia and high risk myelodysplastic syndrome

Acronym
AML18

Study objectives
Current study hypothesis as of 02/10/2019:
1. Does CPX-351 given for 3 courses improve survival compared to the current standard of care of DA plus two doses of Mylotarg (gemtuzumab ozogamicin; GO) 3 mg/m2 (maximum 5 mg per dose) for older patients with AML without known adverse risk cytogenetics?
2. Does the addition of either a short or long (maintenance) course of AC220 starting at course 2 after DA chemotherapy for patients with a FLT3 mutation in the diagnostic sample improve outcomes?
3. Is MRD status following course 1 of clinical value? In particular, can outcomes be improved by intensifying treatment in patients who show evidence of residual disease following course 1 of treatment?
4. To compare a further course of DA versus intermediate-dose cytarabine in patients who are in CR or CRi and MRD -ve after induction course 1 and have received a second course of DA induction
5. In patients with known adverse risk cytogenetics (using Grimwade 2010 classification favourable/intermediate/adverse, see table 1 appendix D) at diagnosis to evaluate the combination of vosaroxin and decitabine
6. To assess the value of reduced intensity allogeneic stem cell transplantation as consolidation for patients with a matched sibling or matched unrelated donor

Previous study hypothesis:
The trial hopes to address several therapeutic questions, including:
1. Does a fractionated schedule of two doses of gemtuzumab ozogamicin (GO) 3 mg/m2 [capped at a maximum of 5 mg per dose for patients with body surface area (BSA) above 1.67 m2] improve upon the current standard of care of 3 mg/m2 on day 1 of course 1?
2. Does the addition of the HSP90 inhibitor ganetespib starting at course 2 improve outcomes?
3. Does the addition of either a short or long (maintenance) course of AC220 starting at course 2 improve outcomes?
4. Is minimal residual disease (MRD) status following course 1 of clinical value? In particular, can outcomes be improved by intensifying treatment in patients who show evidence of residual disease following course 1 of treatment?
5. To compare a total of two versus three courses of treatment in patients who are in complete remission (CR) or complete remission with incomplete blood count recovery (CRi) and MRD -ve after induction course 1.
6. To assess the value of Reduced Intensity Allogeneic Stem Cell Transplantation as consolidation for patients with a matched sibling or matched unrelated donor.

Ethics approval required

Old ethics approval format

Ethics approval(s)
Approved 12/09/2013, Wales REC 3 (Health and Care Research Wales Support Centre, Castlebridge 4, 15-19 Cowbridge Road East, Cardiff, CF11 9AB, UK; +44 (0)2920 230457; Wales.REC3@wales.nhs.uk), ref: 13/WA/0205

Study design
Randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Acute myeloid leukaemia (AML) and high-risk myelodysplastic syndrome (MDS)

Interventions
Current interventions as of 02/10/2019:
The AML18 trial will evaluate several therapeutic questions in Acute Myeloid Leukaemia (AML). The trial will recruit 1600 patients primarily over the age of 60 who are considered fit for an intensive approach to treatment.
At diagnosis: For patients not known to have adverse risk cytogenetics
DA chemotherapy plus two doses of 3 mg/m2 (maximum 5mg per dose) of Mylotarg versus CPX-351. Patients ineligible for Mylotarg can enter the randomisation but receive DA alone or CPX-351. Patients ineligible for CPX-351 will receive DA alone
For patients who were allocated DA chemotherapy (with or without Mylotarg) in course 1 but are not in CR or who are MRD +ve, or for whom MRD is not assessable post-course 1. DA versus DAC versus FLAG-Ida
All patients at second course who have were allocated DA induction and who have a FLT3 mutation in the diagnostic sample. AC220 versus no AC220 for a maximum of 3 cycles; then with or without maintenance for 1 year for patients allocated AC220
For patients who are in CR or CRi and MRD -ve post course1 and have completed 2 courses of DA. DA versus intermediate-dose Cytarabine (IDAC)
For patients who were allocated CPX-351 chemotherapy in course 1 but are not in CR or who are MRD +ve, or for whom MRD is not assessable post-course 1. Course 2 : CPX-351 100 units/m2 x 3 doses (CPX-351 300) versus CPX-351 100 units/m2 x 2 doses (CPX-351 200). Course 3: CPX-351 65 units/m2 given on days 1 and 3 (CPX-351 130)

Previous interventions:
The AML18 trial will evaluate several therapeutic questions in Acute Myeloid Leukaemia (AML). The trial will recruit 1600 patients primarily over the age of 60 who are considered fit for an intensive approach to treatment.

A randomisation will compare standard chemotherapy schedule Daunorubicin/Ara-C(DA) combined with 1 or 2 doses of Mylotarg in course 1, patients who fail to achieve CR or are MRD positive after course 1 will be randomised to compare DA with DA plus Cladribine or Flag-Ida for up to 2 courses of therapy.

Patients who achieve CR after course 1 will be randomised to 1 or 2 further courses of DA. At course 2, patients will also be randomised to receive AC220 versus no AC220 with or without maintenance, or Ganetespib versus no Ganetespib for a maximum of 3 cycles.

Intervention Type
Drug

Phase
Phase II/III

Drug/device/biological/vaccine name(s)
Daunorubicin/Ara-C (cytarabine), Mylotarg (gemtuzumab ozogamicin), cladribine, FLAG-Ida (fludarabine, cytarabine, G-CSF and idarubicin), AC220 (quizartinib), ganetespib

Primary outcome(s)
Current primary outcome measures as of 27/02/2023:
1. Overall survival (at end of treatment)
2. Event-free survival. (Events: Death, relapse, resistant disease as measured by failure to achieve CR/CRi post course 2.)
3. Complete remission (CR + CRi) achievement and reasons for failure (for induction questions) (after course 1)
4. Duration of remission, relapse rates and deaths in first CR (after course 1)
5. Toxicity, both haematological and non-haematological (after each course)
6. Supportive care requirements (and other aspects of health economics) (after each course)

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Previous primary outcome measures:
1. Overall survival (at end of treatment)
2. Complete remission (CR + CRi) achievement and reasons for failure (for induction questions) (after course 1)
3. Duration of remission, relapse rates and deaths in first CR (after course 1)
4. Toxicity, both haematological and non-haematological (after each course)
5. Supportive care requirements (and other aspects of health economics) (after each course)

Key secondary outcome(s))
Blood and bone marrow will be collected at diagnosis, post course 1, during remission and at relapse to evaluate the therapeutic relevance of morphological, cytogenetic, molecular-genetic and immunophenotypic assessments, with particular respect to:
1. The relevance of the presence of a cytogenetic abnormality in the bone marrow of patients in morphological remission
2. The relevance of molecular characteristics and response to treatment
3. To store diagnostic tissue for future research in the AML Tissue Bank

4. To determine the predictive impact of the LSC17 gene signature on outcome of patients entering the two induction arms of the trial. (added 02/10/2019)

Completion date
31/07/2025

Eligibility

Key inclusion criteria

Current participant inclusion criteria as of 22/02/2023:
1. They have one of the forms of acute myeloid leukaemia, (except Acute Promyelocytic Leukaemia) as defined by the WHO Classification (Appendix A). This can be any type of de novo AML (including patients with AML with morphological MRC who do not have a history of MDS or known MDS-related cytogenetics) or high risk Myelodysplastic Syndrome, defined as greater than 10% marrow blasts (RAEB-2). Patients with a prior history of a myeloproliferative neoplasm may be included provided they meet none of the exclusion criteria.
2. Patients should normally be over the age of 60 years, but patients under this age are eligible if they are not considered eligible for the MRC AML19 trial. Please contact the trial team for further information.
3. They have given written informed consent
4. Serum creatinine ≤1.5 × ULN (upper limit of normal)
5. Sexually mature males must agree to use an adequate and medically accepted method of contraception throughout the study if them or their sexual partners are women of childbearing potential (WOCBP). These measures must be in place for 6 months for patients receiving CPX-351 and 7 months (females) or 4 months (males) for Mylotarg – more comprehensive guidance is included in the current Summary of Product Characteristics (SPC) for these agents. Men should be advised to not father a child while receiving trial treatment. Similarly women must agree to adequate contraceptive measures and avoid becoming pregnant while on protocol treatment. In the event of pregnancy at any point during the trial, the IMPs should be immediately stopped and the Trial Team should be contacted and pregnancy reporting procedures followed
6. ECOG Performance Status of 0-2

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Previous participant inclusion criteria as of 02/10/2019:
1. They have one of the forms of acute myeloid leukaemia, except Acute Promyelocytic Leukaemia as defined by the WHO Classification (Appendix A) this can be any type of de novo or secondary AML – or high risk Myelodysplastic Syndrome, defined as greater than 10% marrow blasts (RAEB-2). (NB patients with prior MDS (>10% blasts, RAEB2) who have received prior azacitidine are not eligible for the trial, but patients with <10% who have failed a hypomethylating agent and developed AML may enter the trial)
2. Patients should normally be over the age of 60, but patients under this age are eligible if they are not considered eligible for the MRC AML19 trial. Please contact the trial team for further information.
3. Patients entering the vosaroxin/decitabine arm must be over the age of 60 and have known adverse risk cytogenetics at entry
4. They have given written informed consent
5. Serum creatinine ≤ 1.5 × ULN (upper limit of normal)
6. Sexually mature males must agree to use an adequate and medically accepted method of contraception throughout the study if their sexual partners are women of child bearing potential (WOCBP). Men should be advised to not father a child while receiving trial treatment. Similarly women must agree to adequate contraceptive measures and avoid becoming pregnant while on protocol treatment. In both males and females these measures must be in place for at least 3 months following completion of Decitabine and at least 6 months after the last administration of Cladribine. The time period following treatment with Decitabine where it is safe to become pregnant is unknown. In the event of pregnancy at any point during the trial, the IMPs should be immediately stopped and the Trial Team should be contacted and pregnancy reporting procedures followed
7. ECOG Performance Status of 0-2

8. Only patients with a confirmed FLT3 mutation in the diagnostic sample are eligible for the AC220 randomisation.

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Previous participant inclusion criteria:
1. They have one of the forms of acute myeloid leukaemia, except Acute Promyelocytic Leukaemia as defined by the WHO Classification, this can be any type of de novo or secondary acute myeloid leukaemia (AML), or high risk myelodysplastic syndrome, defined as greater than 10% marrow blasts (RAEB-2).
2. They should normally be over the age of 60, but patients under this age are eligible if they are not considered eligible for the MRC AML17 trial.
3. They have given written informed consent.
4. Serum creatinine less than or equal to 1.5 x ULN (upper limit of normal)
5. Patients eligible for the Mylotarg randomisation must have Serum Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) less than or equal to 2.5 x ULN and bilirubin less than or equal to 2.x ULN
6. In order to be eligible to receive cladrabine, serum creatinine must be within the local ULN to enter that randomisation. Patients for whom this is not the case can be randomised between the remaining options.
7. Sexually mature males must agree to use an adequate and medically accepted method of contraception throughout the study if their sexual partners are women of child bearing potential (WOCBP). Similarly women must agree to adequate contraceptive measures. In both males and females these measures must be in place for at least 30 days after the last administration of ganetespib.
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-2

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
1935

Key exclusion criteria
Current participant exclusion criteria as of 22/02/2023:
Patients are not eligible for the AML18 trial if:
1. Patients that are known to either have adverse risk cytogenetics as defined by Grimwade or cytogenetic changes that meet the WHO definition of AML-MRC
2. They have therapy–related AML (t-AML) with documented history of prior cytotoxic therapy or radiotherapy
3. They have a documented history of CMMoL prior to transformation to AML
4. They have a documented history of MDS prior to transformation AML

5. They have previously received cytotoxic chemotherapy for AML. (Hydroxycarbamide, or similar low-dose therapy, to control the white cell count prior to initiation of intensive therapy, is not an exclusion.
6. They are in blast transformation of chronic myeloid leukaemia (CML)
7. They have a concurrent active malignancy excluding basal cell carcinoma
8. They are pregnant or lactating
9. They have Acute Promyelocytic Leukaemia
10. Known infection with human immunodeficiency virus (HIV)
11. Patients with prior cumulative anthracycline exposure (from prior treatment of a non-AML cancer) of greater than 300 mg/m2 daunorubicin (or equivalent)
12. History of myocardial infarction (MI), unstable angina, cerebrovascular accident, or transient ischemic attack (CVA/TIA) within 3 months before entry

Mylotarg-specific exclusion criteria:
1. Pre-existing liver impairment with known cirrhosis
2. Total bilirubin >2.0 x the upper limit of normal (ULN)
3. Aspartate aminotransferase (AST) >2.5 x ULN
4. Alanine aminotransferase (ALT) >2.5 x ULN

CPX-351-specific exclusion criteria:
1. Hypersensitivity to cytarabine, daunorubicin or liposomal products
2. History of Wilson's disease or other copper-metabolism disorder

In addition patients are not eligible for the AC220 randomisation if they have these cardiovascular system exclusion criteria:
1. Known serious cardiac illness or medical conditions, including but not limited to:
1.1. Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker
1.2. Ventricular tachycardia or a supraventricular tachycardia that requires treatment with a Class Ia antiarrhythmic drug (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic drug (e.g., sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted.
1.3. Use of medications that have been linked to the occurrence of torsades de pointes
1.4. Second- or third-degree atrioventricular (AV) block unless treated with a permanent pacemaker
1.5. Complete left bundle branch block (LBBB)
1.6. History of long QT Syndrome or a family member with this condition
1.7. Serum potassium, magnesium, and calcium levels outside the laboratory's reference range
1.8. QTc >450 ms (average of triplicate ECG recordings); a consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred. Please see the trial website for QTcF calculator.

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Previous participant exclusion criteria as of 02/10/2019:
Patients are not eligible for the AML18 trial if:
1. They have previously received cytotoxic chemotherapy for AML [Hydroxycarbamide, or similar low-dose therapy, to control the white count prior to initiation of intensive therapy, is not an exclusion]
2. They are in blast transformation of chronic myeloid leukaemia (CML)
3. They have a concurrent active malignancy excluding basal cell carcinoma

4. They are pregnant or lactating
5. They have Acute Promyelocytic Leukaemia
6. Known infection with human immunodeficiency virus (HIV)
7. Patients with prior cumulative anthracycline exposure (from prior treatment of a non AML cancer) of greater than 300 mg/m2 daunorubicin (or equivalent).
8. History of myocardial infarction (MI), unstable angina, cerebrovascular accident, or transient ischemic attack (CVA/TIA) within 3 months before entry
9. Patients with known adverse risk cytogenetics are excluded from entering the AML18 trial unless they are registered to receive vosaroxin and decitabine

Specific exclusion criteria for the Mylotarg Arm
1. Pre-existing liver impairment with known cirrhosis
2. Total bilirubin > 1.5 x the upper limit of normal (ULN)
3. Aspartate aminotransferase (AST) > 2.5 x ULN
4. Alanine aminotransferase (ALT) > 2.5 x ULN

Specific exclusion criteria for the Vosaroxin/Decitabine Arm
1. Total bilirubin > 1.5 x the upper limit of normal (ULN),
2. Aspartate aminotransferase (AST) > 2.5 x ULN
3. Alanine aminotransferase (ALT) > 2.5 x ULN
4. Left ventricular ejection fraction (LVEF) < 40% by multiple gated acquisition (MUGA) scan or echocardiogram (ECHO)]

Specific exclusion criteria for CPX-351 treatment
1. Hypersensitivity to cytarabine, daunorubicin or liposomal products
2. History of Wilson's disease or other copper-metabolism disorder
Specific exclusion criteria for Cladribine
1. Patient's serum creatinine must be within the local ULN to enter the randomisation. Patients for whom this is not the case can be randomised between the remaining options.

Specific exclusion for AC220:
Known serious cardiac illness or medical conditions, including but not limited to:
I. Clinically unstable cardiac disease, including unstable atrial fibrillation, symptomatic bradycardia, unstable congestive heart failure, active myocardial ischemia, or indwelling temporary pacemaker
II. Ventricular tachycardia or a supraventricular tachycardia that requires treatment with a Class Ia antiarrhythmic drug (e.g., quinidine, procainamide, disopyramide) or Class III antiarrhythmic drug (e.g., sotalol, amiodarone, dofetilide). Use of other antiarrhythmic drugs is permitted.
III. Use of medications that have been linked to the occurrence of torsades de pointes (see Appendix B for the list of such medications)
IV. Second- or third-degree atrioventricular (AV) block unless treated with a permanent pacemaker
V. Complete left bundle branch block (LBBB)
VI. History of long QT Syndrome or a family member with this condition
VII. Serum potassium, magnesium, and calcium levels outside the laboratory's reference range
VIII. QTc >450 ms (average of triplicate ECG recordings); a consistent method of QTc calculation must be used for each patient's QTc measurements. QTcF (Fridericia's formula) is preferred. Please see the trial website for QTcF calculator.

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Previous participant exclusion criteria:
Patients are not eligible for the AML18 trial if:
1. They have previously received cytotoxic chemotherapy for AML. [Hydroxycarbamide, or similar low-dose therapy, to control the white count prior to initiation of intensive therapy, is not an exclusion].
2. They are in blast transformation of chronic myeloid leukaemia (CML).
3. They have a concurrent active malignancy excluding basal cell carcinoma.
4. They are pregnant or lactating.
5. They have Acute Promyelocytic Leukaemia.
6. Patients with AST or ALT more than 2.5 times the local upper limit of normal, or bilirubin more than twice upper limit of normal, are not eligible for the Mylotarg randomisations.
7. In addition patients are not eligible for the AC220 or Ganetespib randomisation if they have uncontrolled or significant cardiovascular disease, including :
7.1. A myocardial infarction within 12 months
7.2. Uncontrolled angina within 6 months
7.3. Current or history of congestive heart failure New York Heart Association (NYHA) class 3 or 4, unless an echocardiogram (ECHO) or Multiple Gated Acquisition Scan (MUGA) performed either within 1 month prior to study screening or during screening results in a left ventricular ejection fraction (LVEF) that is greater than 45% (or institutional lower limit of normal value)
7.4. Diagnosed or suspected congenital long QT syndrome. Any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or torsades de pointes [TdP]); any history of arrhythmia will be discussed with the Sponsor's Medical Monitor prior to patient's entry into the study
7.5. Prolonged QTcF interval on pre-entry ECG (greater than 450 ms) - this will be the average of three readings within a 2 hour period
7.5. Any history of second or third degree heart block (may be eligible if the patient currently has a pacemaker)
7.6. Heart rate < 50/minute on pre-entry ECG
7.7. Uncontrolled hypertension
7.8. Obligate need for a cardiac pacemaker
7.9. Complete left bundle branch block
7.10. Atrial fibrillation

Date of first enrolment
31/10/2013

Date of final enrolment
31/12/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre

Nottingham City Hospital
Hucknall Road
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United Kingdom
NG5 1PB

Sponsor information

Organisation
Cardiff University (UK)

ROR
https://ror.org/03kk7td41

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

Results and Publications

Individual participant data (IPD) sharing plan
The Sponsor, Cardiff University, supports access to de-identified clinical trial data. Access to de-identified data generated during the trial may be requested by contacting the trial team (AML18@cardiff.ac.uk) . Data from earlier comparisons in the trial may become available while later comparisons are still in follow-up. Review of requests to access data, after relevant analyses and publications are finalised, is via a formalised Centre for Trials Research process. The

datasets generated and/or analysed during this study will also be included in the subsequent results publication.

IPD sharing plan summary

Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		18/11/2024	17/02/2025	Yes	No
HRA research summary			28/06/2023	No	No
Interim results article	Fractionated versus single-dose gemtuzumab ozogamicin	18/08/2023	21/08/2023	Yes	No
Protocol file	version 15.0	31/07/2022	27/02/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes