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Comparing a new combination of medicines to the normal standard of care chemotherapy treatment given to patients who have been recently diagnosed with acute myeloid leukaemia

Submission date 18/02/2023	**Recruitment status** Stopped	[X] Prospectively registered [ ] Protocol [ ] Statistical analysis plan [ ] Results [ ] Individual participant data [ ] Record updated in last year
Registration date 14/09/2023	**Overall study status** Stopped	
Last Edited 01/05/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Acute myeloid leukaemia (AML) is a type of blood cancer that affects myeloid stem cells in the bone marrow. Blood cells grow from a stem cell (a cell at the earliest stage of development) in the bone marrow. The purpose of this study is to test the safety and effectiveness of a new combination of three medicines (magrolimab, venetoclax and azacitidine; Arm B) compared with the normal standard-of-care intensive chemotherapy treatment (Arm A), in fit adults with newly diagnosed AML. The aim is to increase the number of patients who can proceed to a potentially curative stem cell transplant.
Magrolimab is a new medicine which is currently under investigation in other studies for patients with AML but has not yet been tested in patients who need intensive treatment. Venetoclax and azacitidine are already given together to patients with AML who cannot have intensive chemotherapy.

Who can participate?
Patients aged 18 to 70 years with AML

What does the study involve?
Patients will be assigned randomly to one of two groups (A and B). Patients in both groups will receive a minimum of two cycles of induction treatment.
Standard of care induction chemotherapy will be either daunorubicin and cytarabine (DA), DA and gemtuzumab ozogamicin (DA+GO), a combination of daunorubicin and cytarabine called CPX-351 (Vyxeos), or fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF) and idarubicin (FLAG-Ida).
Patients will be recruited over about 18 months and followed up for up to 5 years. This study will consist of screening, study treatment, study treatment discontinuation, long-term follow-up and survival follow-up periods.

What are the possible benefits and risks of participating?
The study design is based as closely as possible on the standard of care (SOC) pathway in this patient population; therefore the additional burden to patients as a result of being on the study is minimal. Only the following assessments are additional to SOC in both arms: bone marrow (BM) and peripheral blood (PB) sample repeated at screening for translational studies; pregnancy test for females of childbearing potential at treatment discontinuation; blood typing at screening due to haemolytic magrolimab risks; quality of life (QoL) questionnaires at 4-6 timepoints during the study; optional saliva sample for translational studies. To help minimise the impact of the baseline molecular genetic testing and measurable residual disease (MRD) disease assessment (using the BM and PB), a separate Informed Consent Form (ICF) can be used, either prior to or following the patient's formal acute myeloid leukaemia (AML) diagnosis, to allow for these to be collected from the patient's diagnostic samples and to avoid having to repeat them at screening. This was implemented following widespread discussions with the proposed investigational sites.
Possible side effects to participants if they need an extra BM and PB sample at screening (above SOC) include bleeding, bruising, infection, pain and tingling of the leg.
The SOC Arm A treatment options were agreed following discussions with various UK consultant haematologists, to ensure this is a true reflection of the current UK patient population /treatment. Therefore, patients randomised to Arm A will receive the same treatment they would receive if they chose not to join the study.
Dose levels of magrolimab, venetoclax and azacitidine (MAG/VEN/AZA) have been carefully selected. MAG dosing is based on previous studies with acceptable safety profiles and encouraging efficacy signals. VEN/AZA doses are based on the Summary of Products Characteristics (SmPC) and current UK practice.
MAG is currently not approved and is being studied in people with haematologic and solid tumour cancers.
In previous studies, the most common drug-related adverse events (AEs) were: anaemia, chills, decreased appetite, diarrhoea, fatigue, fever, headache, infusion-related reaction (IRRs), nausea and vomiting. Safety considerations have been provided by the IMP manufacturer, Gilead Sciences, and included in the protocol. These include eligibility exclusions, dose modifications, safety monitoring assessments and additional screening assessments. Baseline haemoglobin limits and ongoing monitoring, anti-infectious prophylaxis and pre-medication to avoid IRRs are mandated.
MAG may also interfere with blood typing. The primary concern is that patients could receive the wrong blood type during a transfusion. Blood typing is required at screening, and a Study Patient Information Card will be provided to indicate the patient's pre-treatment blood type in case the patient receives emergency transfusion at another hospital. Further guidance for Investigators is included in the protocol.
Other AEs reported include: abdominal pain, increase of liver enzymes, arthralgia, back pain, blood bilirubin increased, constipation, cough, dizziness, falls, febrile neutropenia, insomnia, hypokalaemia, hypomagnesemia, hypophosphatemia, hypotension, neutrophil count decreased and neutropenia, peripheral oedema, platelet count decreased and thrombocytopenia, pneumonia, pruritus, shortness of breath and white blood cell count decreased.
Common AEs in people treated with VEN include: increased risk of infection, lung problems, anaemia, changes in levels of minerals in the blood, such as high potassium and phosphate and low calcium, diarrhoea or constipation, feeling or being sick, and fatigue. Occasional AEs are detailed in the PIS.
Common AEs in people treated with AZA include: increased risk of infection, lung problems, inflammation of the nose and throat, anaemia, bruising and bleeding, loss of appetite and weight loss, difficulty sleeping, dizziness and headaches, diarrhoea or constipation, feeling or being sick, abdominal pain, rash, itchy skin, joint and muscle pain, high temperature, tiredness,

chest pain, and redness/pain/swelling at the injection site. Occasional and rare side AEs are detailed in the PIS.
Potential risks and burdens are described in the PIS so that potential patients can clearly understand what is involved if they consent to take part. Supportive medications will be given as per local practice.

Where is the study run from?
DIDACT Foundation (UK)

When is the study starting and how long is it expected to run for?
February 2023 to January 2029

Who is funding the study?
1. DIDACT Foundation (UK)
2. Gilead Sciences (USA)

Who is the main contact?
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Type(s)
Principal investigator

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Integrated Research Application System (IRAS)
1006624

Central Portfolio Management System (CPMS)
54561

Protocol serial number
ACT-AML-101

Study information

Scientific Title

A Phase II, randomised, open-label study evaluating the safety and efficacy of magrolimab in combination with venetoclax and azacitidine versus intensive chemotherapy in fit adults with high risk newly diagnosed acute myeloid leukaemia

Acronym
ACT-AML-101

Study objectives
The current standard of care in fit adults with newly diagnosed acute myeloid leukaemia (AML) consists of induction chemotherapy with either DA, DA+GO, CPX351 (Vyxeos) or FLAG-Ida, depending on patient fitness and disease biology. Patients who achieve a blast clearance will then proceed to either consolidation chemotherapy or an allogeneic stem cell transplant (allo-SCT) dependent on both their predicted risk of relapse if treated with chemotherapy alone and their ability to proceed to transplant. In patients with a predicted risk of disease relapse greater than 40%, allo-SCT is widely recognised as a key component of the treatment algorithm for patients in CR1, providing a suitable donor is available and the patient is deemed fit enough for allo-SCT. Patients deemed ineligible for allo-SCT either because of a predicted low risk of relapse or on the grounds of patient fitness, receive further consolidation chemotherapy followed in selected patients by CC-486 (an orally administrated formulation of azacitidine) maintenance.

Increased donor availability coupled with the advent of better tolerated reduced intensity conditioning (RIC) regimens has led to a substantial rise in the number of patients with AML in CR1 who proceed to allo-SCT. Two major factors currently limit allo-SCT access and represent major barriers to the delivery of a potentially curative allograft. Firstly, a significant number of adults with either adverse risk AML or older patients with intermediate-risk AML do not achieve blast clearance with current induction chemotherapy regimens. Secondly, induction chemotherapy is associated with increased treatment-related mortality in both these groups, which can preclude the safe delivery of a subsequent allo-SCT. Taken together with the fact that the presence of high levels of pre-allo-SCT measurable residual disease (MRD) is associated with an increased risk of relapse post-allo-SCT, and the fact that the toxicity of induction chemotherapy can increase allo-SCT related mortality, there is therefore an urgent requirement for the development of improved induction regimens in fit adults with allo-mandatory AML. Such innovative induction strategies should have the ability to increase the CR rate and at the same time reduce treatment-related mortality.

Recent Phase I/II data have demonstrated that a magrolimab, venetoclax and azacitidine triplet is well tolerated and has the capacity to result in an overall response rate (CR/CRi/MLFS) of 80% in patients with newly diagnosed AML, deemed unfit for IC. Of interest 86% of TP53wt (n = 14) patients achieved a CR/CRi and 63% of TP53mut patients (n = 27) achieved a CR/CRi. Notably, there was no treatment-related mortality at 8 weeks in this high-risk population. These encouraging results may reflect the novel mechanism of action of the magrolimab, venetoclax and azacitidine triplet compared with intensive chemotherapy.

It is therefore hypothesised that a magrolimab, venetoclax and azacitidine triplet induction regimen is clinically superior to the standard induction chemotherapy options in fit adults with adverse risk newly diagnosed AML, or older adults with intermediate risk newly diagnosed AML. We therefore wish to test this hypothesis in this Phase II, randomized, superiority study which will examine clinical outcomes in fit adults with newly diagnosed adverse risk AML (18 to 70 years of age), or older adults with newly diagnosed intermediate-risk AML (50 to 70 years of age) who are treated with the magrolimab, venetoclax and azacitidine combination compared with standard of care induction chemotherapy regimens.

Primary objective:
To compare the efficacy of magrolimab, venetoclax and azacitidine combination therapy (experimental arm) with standard-of-care intensive chemotherapy (IC) (control arm) as measured by event-free survival (EFS).

Secondary objectives:
To compare and evaluate the safety, efficacy and tolerability of magrolimab, venetoclax and azacitidine combination
therapy (experimental arm) versus standard of care IC (control arm) as measured by:
1. Overall survival (OS) time
2. Complete response (CR) rate)
3. Composite CR and CR with incomplete haematologic recovery (CRi) rate
4. Overall response rate (CR, CRi and morphologic leukaemia-free state (MLFS)
5. Day 60 treatment-related mortality
6. Rate of measurable residual disease (MRD) negative CR (CRMRD-)
7. Disease free survival (DFS)
8. Cumulative incidence of relapse (CIR)
9. Survival post allogeneic stem cell transplant (allo-SCT)
10. Incidence of grade 3 and 4 non-haematological adverse events (AEs)
11. Proportion of patients proceeding to allo-SCT
12. Duration of hospitalisation in patients prior to allo-SCT

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 11/09/2023, North East - Newcastle & North Tyneside 2 Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8086; newcastlenorthtyneside2.rec@hra.nhs.uk), ref: 23/NE/0047

Primary study design
Interventional

Study design
Open controlled randomized parallel-group trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Newly diagnosed acute myeloid leukaemia (AML)

Interventions
The ACT-AML-101 study is a prospective, multi-centre, open-label, Phase II, 1:1 randomized study comparing magrolimab, venetoclax and azacitidine combination therapy with the current standard of care induction chemotherapy schedules and consolidation chemotherapy schedules in fit adults, with either newly diagnosed European LeukaemiaNet (ELN) 2022 adverse risk AML (18 to 70 years of age) or ELN 2022 intermediate-risk AML (50 to 70 years of age).

Patients will be randomly allocated to one of two treatment groups (1:1), Arm A (Control) or Arm B (Experimental)

Arm A (control arm):
Two cycles, up to 42 days each, of standard-of-care intensive induction chemotherapy, with either daunorubicin and cytarabine (DA), DA with gemtuzumab ozogamicin (DA+GO), CPX-351 (Vyxeos) or FLAG-Ida (fludarabine, cytarabine, granulocyte-colony stimulating factor (G-CSF) and idarubicin.
Patients who achieve < 5% bone marrow blasts after 2 cycles of induction chemotherapy should be considered candidates for allogeneic stem cell transplantation (allo-SCT) as definitive therapy.
Patients may receive an additional 1-2 cycles of standard-of-care consolidation chemotherapy (high dose cytarabine or Vyxeos) prior to allo-SCT as clinically indicated.
The above medications are defined as Non-Investigational Medicinal Products (NIMPs) in the context of this study as these are only being given as per standard of care to newly diagnosed AML patients.

Arm B (experimental arm):
Two cycles, up to 42 days each, of magrolimab, venetoclax and azacitidine combination induction therapy.
Patients who achieve <5% bone marrow blasts after 2 cycles of magrolimab, venetoclax and azacitidine induction chemotherapy should be considered candidates for allo-SCT.
Patients may receive additional cycles of magrolimab, venetoclax and azacitidine therapy prior to allo-SCT as clinically indicated.

The above medications are defined as Investigational Medicinal Products (IMPs) in the context of this study

A total of 164 adults with newly diagnosed AML who fulfil the eligibility criteria will be recruited.

Patients will be recruited over approximately 18 months and followed for 5 years from the date of randomisation of the first patient. The entire study is expected to last approximately 5 years.

All patients will be followed for survival until death, withdrawal of consent, loss to follow-up, completion of survival follow-up, or study termination by the sponsor, whichever occurs first.

Follow-up of patients on both Arms A and B, who progress to allo-SCT, will be performed as follows: monthly during year 1 post allo-SCT, every 2 months during year 2 post allo-SCT and 6-monthly during year 3 onwards post allo-SCT.

Patients who do not progress to allo-SCT will be followed up as follows: every 2 months during year 1 from the last dose of induction and/or consolidation chemotherapy and 6-monthly during year 2 onwards from the last dose of induction and/or consolidation chemotherapy and onwards.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Magrolimab, venetoclax, azacitidine

Primary outcome(s)

Superiority of the magrolimab, venetoclax and azacitidine combination therapy versus standard-of-care intensive chemotherapy as measured by event-free survival (EFS).
EFS is defined as the time from randomisation to:
1. Treatment failure (failure to achieve complete remission (CR) or CR with incomplete haematologic recovery (CRi) after two cycles of therapy)
2. Confirmed relapse; or
3. Death from any cause whichever occurred earlier.
The study will be analysed when 115 EFS events have occurred, or all patients have been followed for a minimum of 1 year, whichever is later. If 164 patients are recruited over 18 months, 5% of patients are lost to follow-up and the EFS hazard rate reduces by 90% after 12 months, it is estimated that the 115 events will occur approximately 1 year after the last patient is recruited.

Key secondary outcome(s)

1. Overall survival (OS) time. OS will be measured from date of randomisation to the date of death from any cause.
2. Complete response (CR). Defined by the proportion of patients with CR.
3. The composite CR and CR with incomplete haematologic recovery (CRi) rate. The proportion of patients with either CR or CRi will be assessed in patients on both arms based on peripheral blood count and bone marrow assessment.
4. The overall response rate. Defined as the proportion of patients with either CR, CRi or morphologic leukaemia-free state (MLFS).
5. Day 60 treatment-related mortality. Treatment-related mortality will be captured by the date of the first dose to survival data captured at day 60 and estimated from the OS Kaplan-Meier (KM) curve at Day 60.
6. The rate of measurable residual disease (MRD) negative CR (CRMRD-) defined by flow cytometry and or next-generation sequencing (NGS) pre-allo-SCT
7. Disease-free survival (DFS). DFS is defined for all patients achieving CR or CRi; measured from the date of achievement of remission until the earliest date of relapse or death. DFS assessment will be based on the results of bone marrow assessment obtained according to defined endpoints in the protocol.
8. Cumulative incidence of relapse (CIR). Defined for all patients achieving CR or CRi; measured from the date of achievement of a remission until the date of relapse.
9. Survival post allogeneic stem cell transplant (allo-SCT). Survival post-allo-SCT will be calculated from date of allo-SCT to the date of death and estimated from the corresponding KM curve.
10. Tolerability of magrolimab, venetoclax and azacitidine versus standard-of-care intensive chemotherapy. ≥CTCAE Grade 3 non-haematological adverse events (AEs) will be captured from the date of informed consent until 70 days from administration of the last dose of magrolimab /30 days from administration of any other study treatment (whichever is latest), or until the start of new anti-cancer therapy (including allo-SCT).
11. The proportion of patients proceeding to allo-SCT
12. The duration of hospitalisation in patients prior to allo-SCT. The number of days as an inpatient will be captured during both induction courses and any consolidation chemotherapy.

A primary analysis will be performed when 115 event-free survivals (EFS) have occurred, or all patients have been followed for a minimum of 1 year, whichever is later. This primary analysis will include the final analysis of all secondary endpoints, with the exception of overall survival (OS).

Following this, patients will be followed up for survival only, up to 5 years from first patient in (FPI). The follow-up survival analysis will take place 5 years after the date of randomisation of the first patient into the study.

Whilst the study is not powered to demonstrate a statistically significant increase in OS, OS will be analysed at the time of the primary analysis and 5 years after the first patient is randomised to characterise the long-term effect on OS.

Completion date
31/01/2029

Reason abandoned (if study stopped)
Objectives no longer viable

Eligibility

Key inclusion criteria
1. 18 to 70 years of age at the time of signing the Informed Consent Form (ICF)
2. Able to provide written informed consent for the study
3. Willing and able to adhere to the study visit schedule, treatment plan and other protocol requirements
4. Newly diagnosed acute myeloid leukaemia (AML) (previously untreated for AML) and morphological confirmation of AML fulfilling European LeukaemiaNet (ELN) 2022 criteria
5. Patients must be considered fit for intensive chemotherapy (IC) by the treating Investigator, using DA, DA+GO, CPX-351 (Vyxeos) or FLAG-Ida, and have either:
5.1. Adverse risk AML as defined by the ELN 2022 criteria and be 18 to 70 years of age; OR
5.2. Intermediate risk AML according to the ELN 2022 criteria and be 50 to 70 years of age
6. Genotype FLT3-ITD mutation-negative
7. ECOG performance status 0-2
8. Adequate renal function, as demonstrated by serum creatinine ≤1.5 x upper limit of normal (ULN)
9. Adequate liver function, as demonstrated by:
9.1. Aspartate aminotransferase (AST) ≤3 ULN
9.2. Alanine aminotransferase (ALT) ≤3 ULN
9.3. Total bilirubin ≤3 x ULN
10. Adequate cardiac function as demonstrated by left ventricular ejection fraction (LVEF) ≥ 50% by echocardiogram (ECHO)
11. Patients must agree to use an adequate and medically accepted method of contraception throughout the study if they or their sexual partners are female-born of childbearing potential
11.1. Arm A patients: These measures must be in place during the study and for 3 months after the last dose of study treatment
11.2 Arm B female-born patients of childbearing potential: These measures must be in place during the study and for 6 months after the last dose of study treatment
11.3 Arm B non-sterilised male-born patients with female partners of childbearing potential: These measures must be in place during the study and for 3 months after the last dose of study treatment
11.4. Male-born patients should be advised to not father a child while receiving study treatment
11.5 Female-born patients of childbearing potential must agree to avoid becoming pregnant while on protocol treatment

12. Negative pregnancy test within 2 weeks prior to randomisation in female-born patients of childbearing potential
13. Pre-treatment blood cross-match completed

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Key exclusion criteria
1. Have received previous cytotoxic chemotherapy (intensive or non-intensive), targeted therapies, hypomethylating agents or venetoclax for AML or any other antecedent haematological condition, with the exception of hydroxycarbamide to control white blood cell (WBC) count or lenalidomide for treatment of myelodysplasia (MDS) 5q syndrome
2. Have received prior treatment with CD47 or signal regulatory protein alpha-targeting agents
3. Are in blastic transformation of chronic myeloid leukaemia (CML)
4. Clinical suspicion of active central nervous system (CNS) involvement with AML
5. Are not deemed fit for intensive chemotherapy (IC) on the basis of age or comorbidities
6. Have secondary malignancy, except MDS, treated basal cell carcinoma or localised squamous skin carcinomas, localised prostate cancer, or other malignancies for which patients are not on active anti-cancer therapies and have had no evidence of active malignancy for at least 1 year. Note: patients on maintenance therapy alone, who have no evidence of active malignancy for at least 1 year are eligible
7. Have acute promyelocytic leukaemia (APL)
8. Known newly diagnosed or uncontrolled human immunodeficiency virus (HIV), hepatitis B or hepatitis C infection. Patients with known chronic infections may enrol if the last two tests for viral load have been negative and their current therapy does not include a protease inhibitor or a non-nucleoside reverse-transcriptase inhibitor
9. Significant disease or medical conditions, as assessed by the Investigator, that would substantially increase the risk-benefit ratio of participating in the study. This includes, but is not limited to:
9.1. Acute myocardial infarction within 6 months of randomisation,
9.2. Unstable angina, cerebrovascular accident (CVA), transient ischemic attack (TIA), uncontrolled diabetes mellitus, significant active infections, and congestive heart failure New York Heart Association Class III to IV, within 3 months of randomisation.
10. History of Wilson's disease or other copper-metabolism disorder
11. Pre-existing liver impairment with known cirrhosis
12. Judgement by the local Investigator that the patient should not participate in the study, if the patient is unlikely to comply with study procedures, restrictions and requirements
13. Concomitant use of:
13.1. Any strong or moderate CYP3A inhibitors, except posaconazole or voriconazole
13.2. Any strong or moderate CYP3A inducers
13.3. Preparations containing St John's Wort
14. Known history, diagnosis or suspicion of haemophagocytic lymphohistiocytosis syndrome

(HLH)
15. Pregnant and lactating patients
16. Female-born patients of childbearing potential, or male-born patients with female partners of childbearing potential, not willing to use adequate contraception during study and for the required contraceptive periods
17. Patients who are unable to swallow tablets whole
18. Unable to understand and therefore to give voluntary consent
19. Known hypersensitivity to any of the IMPs, the metabolites or formulation excipients
20. Current participation is another interventional clinical study. Patients in follow-up who have not received the interventional treatment within 4 weeks of randomisation may enrol.
21. Patients receiving any live vaccine within 4 weeks prior to initiation of study treatments
22. Patients known to require vaccination with a live vaccine during the treatment period or for 3 months after the end of study treatment
23. Known inherited or acquired bleeding disorders

Date of first enrolment
31/01/2024

Date of final enrolment
31/07/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
DIDACT Foundation

Funder(s)

Funder type
Charity

Funder Name

DIDACT Foundation

Funder Name
Gilead Sciences

Alternative Name(s)
Gilead, Gilead Sciences, Inc., Oligogen

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study will be published as a supplement to the results publication.

IPD sharing plan summary
Published as a supplement to the results publication