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# A comparison of response to treatment in patients with Myelodysplastic Syndrome /Myeloproliferative Neoplasm (MDS/MPN) Overlap Syndromes taking ASTX727 versus best supportive care

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|---|---|---|
| **Submission date** | **Recruitment status** | [X] Prospectively registered |
| 11/05/2022 | No longer recruiting | [_] Protocol |
| **Registration date** | **Overall study status** | [_] Statistical analysis plan |
| 13/05/2022 | Ongoing | [_] Results |
| **Last Edited** | **Condition category** | [_] Individual participant data |
| 30/12/2025 | Cancer | [X] Record updated in last year |

## Plain English summary of protocol

Background and study aims
MDS/MPN Overlap Syndromes are rare bone marrow cancers. For most patients there are no effective treatments available. Patients experience bone marrow failure, leading to fatigue, infections and bleeding, with a damaging overgrowth of white blood cells. Most patients don't live for more than two years from diagnosis. AMMO will test a new drug called ASTX727 to see how effective it is at treating and extending/improving the lives of people with these diseases. ASTX727 is a new tablet "hypomethylating drug". These work differently from typical chemotherapy, by altering how genes are switched on and off. They do this by blocking a protein whose job it is to "mark" which genes should be switched on in any particular cell. The hypomethylating drug azacitidine has been used for several years, including for some MDS/MPN patients. It can improve blood counts and symptoms, even putting the cancer into remission and helping patients live longer. However, it must be given as injections on repeated visits to hospital, and isn't available for most MDS/MPN patients. We want to know if ASTX727 can provide similar or possibly better results across all MDS/MPN Overlap syndromes, safely and more conveniently, and whether it overall improves the lives of patients.

Who can participate?
Adults over 18 years, with a diagnosis of MDS/MPN overlap syndromes

What does the study involve?
Patients will be allocated at random to receive either best supportive care or ASTX727. For patients on best supportive care they will go on to be treated as they would in normal routine care which would differ between patients and may include hydroxycarbamide, transfusional support and management of infections. Patients allocated to receive ASTX727 will take ASTX727 orally once daily on days 1-5 of 28 day cycles for up to 6 cycles. If the patient experiences a benefit from the drug they may continue to take it until disease progression,

unacceptable toxicity or patient chooses to discontinue. Patients will come into hospital on day 1 of each cycle (and day 15 of cycle 1) for standard tests including blood tests and a physical exam and patients will have a bone marrow aspirate at cycles 3 and 6 (and every 6 cycles for patients continuing ASTX727) to monitor their progress. Patients will be followed up annually until the end of the study.

What are the possible benefits and risks of participating?
There is no guaranteed benefit of taking part in this study because we do not yet know which of the two treatment approaches is better. ASTX727 has shown promise in early trials and so may be a useful treatment for these diseases; it may, however, not provide any overall benefit compared with best supportive care. The information gained from this study will help inform treatment for other people in the future. The main risk to taking part is side effects from ASTX727 or hydroxycarbamide. These will be outlined in the patient information sheet.

Where is the study run from?
University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
February 2020 to June 2026

Who is funding the study?
BLOODWISE (Blood Cancer UK)

Who is the main contact?
AMMO@trials.bham.ac.uk

# Contact information

### Type(s)
Scientific

### Contact name
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# Additional identifiers

### Clinical Trials Information System (CTIS)
2021-004585-35

### Integrated Research Application System (IRAS)
1004656

### ClinicalTrials.gov (NCT)
Nil known

### Protocol serial number
CPMS 52390, Grant Code 20001

# Study information

### Scientific Title
A randomised phase 2 study of ASTX727 versus best supportive care in(MDS/MPN) Overlap Syndromes

### Acronym
AMMO

### Study objectives
To compare the overall response rate of ASTX727 vs best supportive care +/- hydroxycarbamide, according to IWG 2015 MDS/MPN proposed response criteria. ORR includes patients who achieve best response of complete remission (CR), partial remission (PR), marrow response (MR) or clinical benefit (CB).

### Ethics approval required
Old ethics approval format

### Ethics approval(s)
Approved 22/02/2022, West of Scotland REC 1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 3140212; WoSREC1@ggc.scot.nhs.uk), ref: 22/WS/0011

### Study design
Interventional randomized controlled trial

### Primary study design
Interventional

### Study type(s)
Treatment

### Health condition(s) or problem(s) studied
Myelodysplastic Syndrome/Myeloproliferative Neoplasm (MDS/MPN) Overlap Syndromes

### Interventions
Patients will be randomised via a computer system, the site staff will log on to the study portal in order to randomise a patient between best supportive care and the experimental arm (ASTX727).
Patients on best supportive care will receive standard of care treatments which may include hydroxycarbamide, transfusional support and management of infections. We will collect this information for 6 months from trial entry (or 6 months+ 28 days for those on hydroxycarbamide). Best supportive care will differ between patients and will be at the Investigators discretion. Patients allocated to receive ASTX727 will take ASTX727 orally once

daily on days 1-5 of 28 day cycles for up to 6 cycles. If the patient experiences a benefit from the drug they may continue to take it until disease progression, unacceptable toxicity or patient chooses to discontinue.
All patients will come into hospital on day 1 of each cycle (and day 15 of cycle 1) for standard tests including blood tests and a physical exam and patients will have a bone marrow aspirate at cycles 3 and 6 (and every 6 cycles for patients continuing ASTX727) to monitor their progress. Patients will be followed up annually until the end of the study.

### Intervention Type
Drug

### Phase
Phase II

### Drug/device/biological/vaccine name(s)
ASTX727

### Primary outcome(s)
Best overall response at end of Cycle 6, defined as the patient experiencing Complete Remission (CR), Partial Remission (PR), Marrow Response (MR) or Clinical Benefit (CB) according to the IWG MDS/MPN response criteria. Any patient for whom neither response assessment (post Cycle 2; post Cycle 6) is recorded will be classed as a non-responder.

### Key secondary outcome(s))
1. Response will be assessed according to the IWG MDS/MPN response criteria at the end of cycles 2 and 6.. Patients will be classed as responding if they achieve complete remission (CR), partial remission (PR), marrow response (MR) or clinical benefit (CB). Patients with no response assessment available will be classed as a non-responder.
2. Transformation-free survival (TFS) defined as time from entry to the trial to time of transformation to AML or death. Patients who are alive and have not transformed to AML at the time of the analysis will be censored at date last seen. TFS will be assessed as time from study entry to time of transformation to AML or death.
3. Progression-free survival (PFS) defined as time from entry to the trial to first documentation of progressive disease (PD), as defined by the 2015 IWG MDS/MPN response criteria, or death from any cause. Patients who are alive and progression free at the time of analysis will be censored at their date last seen. PFS will be assessed from time of study entry to time of progressive disease.
4. Overall Survival (OS) defined as time between trial entry and date of death from any cause. Patients who are alive at the time of analysis will be censored at date last seen. OS will be assessed as time from study entry to date of death.
5. Treatment-related toxicity defined as the number of patients who experience one or more grade 3 or greater adverse event or serious adverse event of any grade. Toxicity will be assessed from start of trial treatment to 28 days post treatment discontinuation.
6. Quality of life assessed using EQ5D-5L and the MPN-SAF tools at baseline, cycle 3, cycle 6, 1 year post randomisation and thereafter every 6 months in patients continuing on treatment.

### Completion date
30/06/2026

## Eligibility

## Key inclusion criteria
1. ≥18 years of age at the time of trial entry
2. Morphologically confirmed diagnosis of MDS/MPN (excluding JMML), in accordance with WHO 2016 diagnostic criteria, with any of the following characteristics:
2.1. CMML-2 disease stage [CMML only]
2.2. CPSS [Such et al Blood 2013] or CPSS-Mol [Elena et al Blood 2016] score of intermediate-2 or high risk [CMML only]
2.3. Other patients with one or more of the following:
2.3.1. Bone Marrow blasts >10% (including promonocytes)
2.3.2. Adverse risk cytogenetics (as defined by CPSS or MDS R-IPSS)
2.3.3. WCC ≥50 (or ≥30 with symptoms attributable to myeloproliferation)
2.3.4. RBC transfusion dependence with pre-transfusion Hb <90 g/L
2.3.5. Symptomatic anaemia (with Hb ≤100 g/L)
2.3.6. Thrombocytopenia (Plt ≤50 x 10^9/L)
2.3.7. Symptomatic splenomegaly
2.3.8. Systemic symptoms with no alternative explanation (including weight loss ≥10% of baseline over previous 6 months)
2.3.9. Symptomatic extramedullary involvement (e.g. skin infiltration, serous effusions)
3. Treatment-naïve for prior hypomethylating agent, intensive chemotherapy or other disease-modifying anti-neoplastic therapy (e.g. lenalidomide); patients may have received prior hydroxycarbamide,recombinant erythropoietin, danazol, interferon or anagrelide.
4. ECOG performance status of 0,1 or 2 at trial entry (Appendix 3).
5. Life expectancy of ≥3 months at trial entry,as assessed by the treating physician.
6. Must have adequate hepatic, renal and endocrine function during screening as demonstrated by the following:
6.1. ALT and/or AST ≤3x upper limit of normal (ULN);
6.2. Total bilirubin ≤1.5x ULN or ≤2x ULN if upon judgement of the treating investigator the hyperbilirubinaemia is due to extramedullary haematopoiesis related to the underlying MDS /MPN or to Gilbert's disease;
6.3. Serum creatinine ≤1.5x ULN or estimated creatinine clearance >/=30ml/min/1.73m².
7. Patient willing and able to comply with scheduled visits,treatment plan and other study procedures.
8. Patient able to provide written informed consent for the trial

## Participant type(s)
Patient

## Healthy volunteers allowed
No

## Age group
Mixed

## Lower age limit
18 years

## Upper age limit
100 years

## Sex
All

### Total final enrolment
77

### Key exclusion criteria
1. Patients eligible for intensive chemotherapy and/or allogeneic haematopoietic stem cell transplantation (HSCT).
2. CMML with eosinophilia and 5q33 abnormality.
3. Previous cytotoxic chemotherapy for MDS/MPN, except hydroxycarbamide.
4. Prior hypomethylating agent exposure.
5. Transformation to AML (≥20% myeloid blasts in bone marrow or peripheral blood at screening).
6. Prior organ transplantation, including allogeneic haematopoietic stem cell transplant (HSCT).
7. Known or suspected central nervous system disease involvement.
8. Known history of clinically significant or uncontrolled cardiac disease, including recent history (within 6 months) of unstable angina, acute myocardial infarction, NYHA class III or IV congestive cardiac failure, or clinically significant arrhythmia.
9. Other active malignancy, not including localized non-melanoma skin cancer, cervical carcinoma in situ, breast ductal carcinoma in situ of the breast, or localized prostate cancer controlled with hormone therapy. Patients with history of other cancers should be free of disease without ongoing anti-neoplastic therapy for at least 2 years.
10. Receipt of wide-field radiotherapy (including therapeutic radioisotopes) ≤28 days or limited field radiation for palliation ≤14 days prior to starting any study medications (or has not recovered from side effects of such therapy).
11. Active,uncontrolled infection. Patients with infection under control with active treatment are eligible.
12. Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry).
13. Females of childbearing potential, and their partners, not willing to use adequate contraception during and for up to 6 months after treatment.
14. Any other concurrent serious or unstable medical, psychiatric, familial, geographic or sociological condition that in the investigator’s opinion would jeopardise the patient’s ability to comply with the protocol.

### Date of first enrolment
31/05/2022

### Date of final enrolment
22/05/2024

## Locations

### Countries of recruitment
United Kingdom

England

Northern Ireland

Scotland

Wales

**Study participating centre**
**The Christie NHS Foundation Trust**
550 Wilmslow Road
Withington
Manchester
England
M20 4BX

**Study participating centre**
**Oxford University Hospitals NHS Foundation Trust**
John Radcliffe Hospital
Headley Way
Headington
Oxford
England
OX3 9DU

**Study participating centre**
**University College London Hospitals NHS Foundation Trust**
250 Euston Road
London
England
NW1 2PG

**Study participating centre**
**University Hospitals Birmingham NHS Foundation Trust**
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2GW

**Study participating centre**
**NHS Greater Glasgow and Clyde**
J B Russell House
Gartnavel Royal Hospital
1055 Great Western Road Glasgow
Glasgow

Scotland
G12 0XH

**Study participating centre**
**Belfast Health and Social Care Trust**
Trust Headquarters
A Floor - Belfast City Hospital
Lisburn Road
Belfast
Northern Ireland
BT9 7AB

**Study participating centre**
**Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus**
Nottingham University Hospital
Derby Road
Nottingham
England
NG7 2UH

**Study participating centre**
**Sheffield Teaching Hospitals NHS Foundation Trust**
Northern General Hospital
Herries Road
Sheffield
England
S5 7AU

**Study participating centre**
**University Hospital Southampton NHS Foundation Trust**
Southampton General Hospital
Tremona Road
Southampton
England
SO16 6YD

**Study participating centre**
**Leeds Teaching Hospitals NHS Trust**
St. James's University Hospital
Beckett Street
Leeds

England
LS9 7TF

**Study participating centre**
**Cardiff & Vale University Lhb**
Woodland House
Maes-y-coed Road
Cardiff
Wales
CF14 4HH

**Study participating centre**
**NHS Grampian**
Summerfield House
2 Eday Road
Aberdeen
Scotland
AB15 6RE

**Study participating centre**
**Kings College Hospital**
King's College Hospital NHS Foundation Trust
Denmark Hill
London
England
SE5 9RS

# Sponsor information

**Organisation**
University of Birmingham

**ROR**
https://ror.org/03angcq70

# Funder(s)

**Funder type**
Charity

### Funder Name
Blood Cancer UK

### Alternative Name(s)
Blood Cancer UK Research

### Funding Body Type
Private sector organisation

### Funding Body Subtype
Trusts, charities, foundations (both public and private)

### Location
United Kingdom

## Results and Publications

### Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from the trial management group by contacting ammo@trials.bham.ac.uk following the end of the study. Each request will be considered on a case by case basis and any research must have the relevant approvals in place.

### IPD sharing plan summary
Available on request

### Study outputs

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
|---|---|---|---|---|---|
| HRA research summary | | | 28/06/2023 | No | No |