Trial Summary

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Title

A randomised phase 2 study of ASTX727 versus best supportive care in MDS/MPN Overlap Syndromes.

Trial Design

Prospective, phase II, 2 arm, multicentre, randomised, clinical trial. Patients will be randomised to receive either ASTX727 or Best Supportive Care (BSC) in a 2:1 fashion. ASTX727 (35mg decitabine/100mg cedazuridine) will be given days 1-5 of each of six 28-day cycles. Patients on the ASTX727 arm who at the end of 6 cycles are continuing to derive clinical benefit are permitted to continue until disease progression, unacceptable toxicity or patient choice. Management on the BSC arm will be given according to local practice. Patients will be recruited at 12-15 TAP centres over 2 years. Patients will be followed up for a minimum of 12 months.

Objectives

Primary Objectives

- To compare the overall response rate of ASTX727 vs best supportive care +/- hydroxycarbamide, according to IWG 2015 MDS/MPN proposed response criteria [1] (Appendix 2). ORR includes patients who achieve best response of complete remission (CR), partial remission (PR), marrow response (MR) or clinical benefit (CB).

Secondary Objectives

- To assess the morphological complete remission (CR) and marrow CR rates in MDS/MPN patients treated with ASTX727.
- To determine the effect of ASTX727 on Progression Free Survival (PFS) and Overall Survival (OS)
- To evaluate the response duration in responding patients.
- To compare the frequency of and times to AML transformation.
- To expand the safety analysis of ASTX727 in MDS/MPN Overlap patients.
- To evaluate the impact of ASTX727 on symptoms/patient-reported outcomes/quality of life, and pilot the feasibility/utility of the validated MPN-SAF tool in the MDS/MPN population.
- To collect prospective data for hydroxycarbamide response in MDS/MPN according to IWG MDS/MPN proposed response criteria
- To collect a centralised, prospective UK clinical dataset and sample biobank for MDS/MPN Overlap patients.

Exploratory Objectives

- To generate a UK mutation profile dataset for MDS/MPN Overlap syndromes, and evaluate impact of ASTX727 on variant allele frequency
- To seek genetic, transcriptional, epigenetic and proteomic signatures predictive of HMA response.
- To evaluate patient experience of taking part in the study to inform future trial modifications and support needs for this patient group.

Main Inclusion and Exclusion Criteria

Main Inclusion Criteria

- ≥18 years of age at the time of trial entry
- Morphologically confirmed diagnosis of MDS/MPN (excluding JMML), in accordance with WHO 2016 diagnostic criteria [2] (Appendix 4), with ***any*** of the following characteristics:
  - CMML-2 disease stage *[CMML only]*
  - CPSS [3] or CPSS-Mol [4] score of intermediate-2 or high risk *[CMML only]*
  - Other patients with ***one or more of*** the following:
    - Bone Marrow blasts >10% (including promonocytes)
    - Adverse risk cytogenetics (as defined by CPSS or MDS R-IPSS)
    - WCC ≥50 (or ≥30 with symptoms attributable to myeloproliferation)
    - RBC transfusion dependence with pre-transfusion Hb <90 g/L
    - Symptomatic anaemia (with Hb ≤100 g/L)
    - Thrombocytopenia (Plt ≤50 x 10^9/L)
    - Symptomatic splenomegaly
    - Systemic symptoms with no alternative explanation (including weight loss ≥10% of baseline over previous 6 months)
    - Symptomatic extramedullary involvement (e.g. skin infiltration, serous effusions)
- 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.
- ECOG performance status of 0, 1 or 2 at trial entry (Appendix 3).
- Life expectancy of ≥3 months at trial entry, as assessed by the treating physician.
- Must have adequate hepatic, renal and endocrine function during screening

Main Exclusion Criteria

- Patients eligible for intensive chemotherapy and/or allogeneic haematopoietic stem cell transplantation (HSCT).
- CMML with eosinophilia and 5q33 abnormality.
- Previous cytotoxic chemotherapy for MDS/MPN, except hydroxycarbamide.
- Prior hypomethylating agent exposure.
- Transformation to AML (≥20% myeloid blasts in bone marrow or peripheral blood at screening).
- Prior organ transplantation, including allogeneic haematopoietic stem cell transplant (HSCT).
- Known or suspected central nervous system disease involvement.
- 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.
- 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.
- 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).

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