RAVVA

Phase II Randomised Trial of 5-Azacitidine versus 5-Azacitidine in combination with Vorinostat in patients with Acute Myeloid Leukaemia or High Risk Myelodysplastic Syndrome Ineligible for Intensive Chemotherapy

Chief Investigator: Professor Charles Craddock

Trial Coordinator: Louise Dudley

Although the outcome for children and young adults with Acute Myeloid Leukaemia (AML) and Myelodysplastic Syndrome (MDS) has improved considerably, new treatments for older adults with AML and MDS are lacking, this particularly applies to older patients who are deemed ineligible for intensive chemotherapy therapy for whom limited treatment options are currently available.

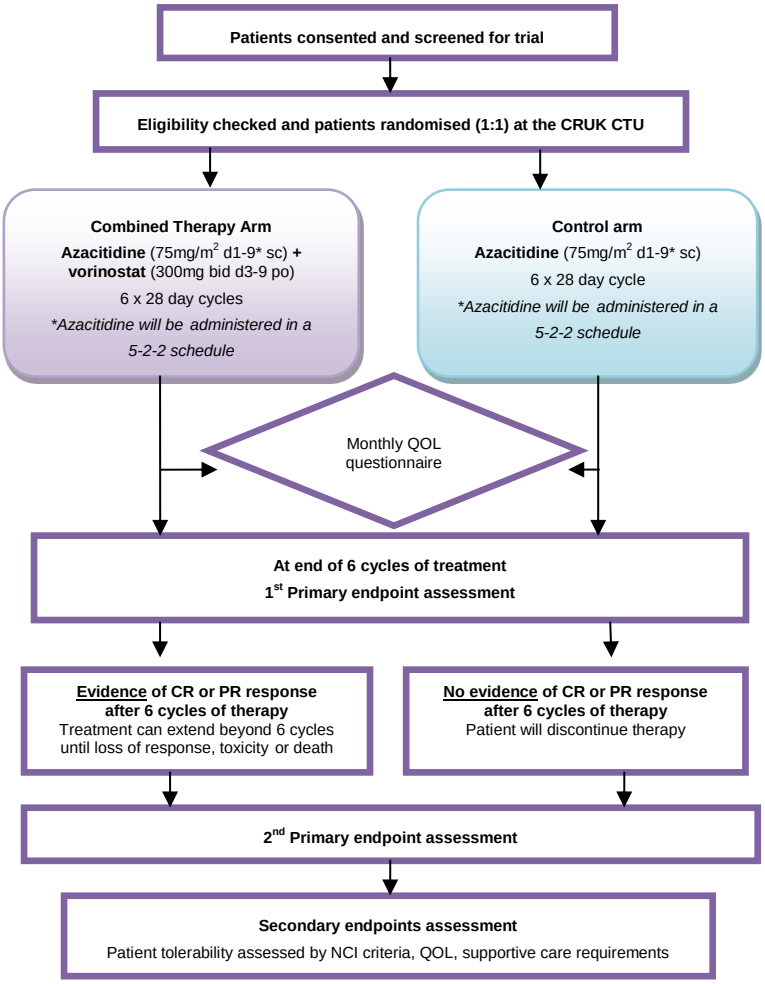
Epigenetic therapies, including DNA methyltransferases inhibitors (DNMTi), such as 5-azacitidine and histone deacetylase inhibitors (HDACi), such as sodium valproate and vorinostat, demonstrate significant clinical activity in adults with high risk AML/MDS.

Phase II trials have documented higher Complete Remission (CR) rates when azacitidine is combined with a HDACi in newly diagnosed and relapsed AML/MDS. However no randomised trials have yet examined the important question of whether concurrent HDACi administration increases the clinical activity of Azacitidine.

Trial Design

This is a multicentre, open-label randomised phase II trial comparing azacitidine monotherapy with combined azacitidine and vorinostat in patients with newly diagnosed, relapsed or refractory AML/ high risk MDS.

Patients ineligible for intensive chemotherapy will be randomised to treatment with monthly cycles of azacitidine or combined azacitidine and vorinostat. Clinical response will be assessed after 3 and 6 cycles of therapy.



Objectives

Primary: To evaluate the activity of azacitidine and vorinostat combined therapy, in terms of Overall Response Rate (CR, CRi, PR) as defined by modified Cheson criteria for AML and the IWG response criteria for MDS and OS in patients with newly diagnosed, relapsed or refractory AML or high risk MDS who are ineligible for intensive chemotherapy.

Secondary: To determine whether the combination therapy has an acceptable side effect profile, improves quality of life and does not significantly increase the supportive care requirements (blood product support/red cell and platelet transfusion requirements/days on antibiotics/days of hospitalisation).

Trial duration

The aim is to recruit over 32 months. Patients will be followed up for a minimum of 24 months or until death.

Entry Criteria

Inclusion Criteria:

1. Adults with AML (except Acute Promyelocytic Leukaemia (APL) as defined by WHO classification or high risk MDS categorised as INT-2 or high risk according to IPSS who are deemed ineligible for intensive chemotherapy on the grounds of age or co-morbidities with ONE of the following disease status:
   i. Newly diagnosed OR
   ii. Relapsed Disease* OR
   iii. Refractory Disease*

* refer to protocol for definitions

2. Patients who are able to receive treatment as an out-patient
3. Adequate renal and hepatic function
4. Patients that have given written informed consent
5. ECOG performance status ≤2

Exclusion criteria:

1) Patients with greater than class III New York Heart Association cardiac impairment

2) Blastic transformation of Chronic Myeloid Leukaemia (CML)

3) Prior allogeneic haematopoietic stem cell transplant

4) Pregnant or lactating women or adults of reproductive potential not willing to use appropriate effective contraception during the trial and for 12 months post treatment

5) Patients who have received prior HDAC inhibitor-like treatment as anti-tumour therapy. (Patients who have received HDACi treatment for other indications e.g valproic acid for epilepsy may enrol after a 30-day washout period).

6) Previous anti-tumour therapies, including prior experimental agents or approved anti-tumour small molecules and biologics, within 30 days before the start of protocol treatment. (Patients receiving anti-tumour therapies to control blood counts may enrol into the trial and receive trial treatment simultaneously).

7) Patients who have received prior treatment with demethylating agents such as 5-azacitidine or decitabine.

8) Patients with contraindications to receiving azacitidine or vorinostat

9) Any co-morbidity that in the Investigators opinion will affect the patient's participation in this study

Sample Size

260 eligible patients to be randomised to receive either azacitidine alone (control arm n=130) or azacitidine + vorinostat (combined therapy arm n=130)

Treatment plan

Control arm: Patients will receive azacitidine (75mg/m^2) by SC injection on 7 consecutive days (excluding weekends), for up to 6 cycles

Combined therapy arm: Patients will receive (75mg/m^2) azacitidine by SC injection on 7 consecutive days (excluding weekends), for up to 6 cycles

*It is recommended Azacitidine is administered in a 5-2-2 schedule at the convenience of the treatment centre.

Translational Science

All sites will participate in *Leukaemic Stem Cell Quantification Studies*. Bone marrow aspirate samples (EDTA) will be collected at baseline (pre-treatment), and after cycles 1, 3 and 6, and on relapse.

A punch skin biopsy (sterile saline) will also be requested at baseline (pre-treatment). This sample will be optional for patients.

All of these samples will be sent to the Weatherall Institute of Molecular Medicine (WIMM), Oxford in boxes provided by the WIMM.

In addition to this, 20mls of peripheral blood (EDTA) will be collected at baseline (pre-treatment), on days 1, 8 and 22 of cycle 1, day 1 of cycle 2 and on relapse.

These Samples will be sent to the School of Cancer Sciences, University of Birmingham in Royal Mail Safe Boxes provided by the Trials Office.

Haematology Trials Team (RAvVA), CR UK Clinical Trials Unit, School of cancer Sciences, University of Birmingham, B15 2TT
Tel: 0121 414 92735 **Fax: 0121 414 6061** **Email: RAVVA@trials.bham.ac.uk**