ROMAZA

TRIAL SYNOPSIS

Title

Phase I trial of combination therapy with Romidepsin and Azacitidine in patients with newly diagnosed, relapsed or refractory Acute Myeloid Leukaemia ineligible for conventional chemotherapy (ROMAZA)

Acute Myeloid Leukaemia (AML) is a common haematological malignancy whose incidence rises from 3:100,000 in young adults to greater than 20:100,000 in older adults. Acquired abnormalities in chromatin structure are commonly observed in AML and are thought to play an important role in disease pathogenesis. Epigenetic therapies, including DNA methyltransferase inhibitors (DNMTIs) such as Azacitidine and histone deacetylase inhibitors (HDACis) such as Sodium Valproate, Vorinostat and Romidepsin, have the capacity to reverse the abnormalities in chromatin structure and selectively induce apoptosis of AML blasts *in vitro* and demonstrate clinical activity in AML.

Trial Design

This is a phase I/II study examining the MTD of Romidepsin and Azacitidine combination therapy and to determine its tolerability in patients with newly diagnosed, relapsed or refractory AML who are deemed ineligible for conventional chemotherapy. This will represent the first trial, to our knowledge, in this patient population determining the MTD of Romidepsin and Azacitidine combination therapy with the aim of determining whether there is potential clinical benefit in this patient population.

The MTD of Romidepsin in combination with Azacitidine will be determined using an escalating, de-escalating 3+3 cohort design.

Objectives

Primary objectives:

- To determine the maximum tolerated dose (MTD) of Romidepsin in combination with Azacitidine
- To determine the clinical activity of combined Romidepsin and Azacitidine treatment in patients with high risk AML

Secondary objective:

- To determine the tolerability and safety of Romidepsin in combination with Azacitidine

Outcome Measures

Primary outcome measures:

- Phase 1 component
  - Assessment of MTD of Romidepsin when administered in combination with Azacitidine
- Expansion cohort
  - Major response rate (CR, CRi and PR), as defined by modified Cheson criteria (Appendix 1) and assessed at the end of cycles 3 and 6 of treatment

Secondary outcome measures:

- Assessment of tolerability and safety of Romidepsin in combination with Azacitidine (graded according to NCI Common Toxicity Criteria for Adverse Events (CTCAE) version 4) from the date of commencing treatment until 28 days following treatment discontinuation

Patient Population

Patients with newly diagnosed, relapsed or refractory AML whom are ineligible for conventional chemotherapy will be recruited to this trial.

Sample Size

Up to 18 patients will be recruited to determine the MTD. Once the MTD has been determined an additional 35 patients will be recruited and treated at the MTD in order to gain further safety and efficacy data.

Main Inclusion and Exclusion Criteria

Inclusion criteria:

1. Adults (aged ≥16 years) with newly diagnosed, relapsed or refractory AML (except Acute Promyelocytic Leukaemia (APML) as defined by the World Health Organisation (WHO) Classification)
2. Patients deemed ineligible for conventional chemotherapy on the grounds of age or co-morbidities
3. Patients are able to receive treatment as an out-patient
4. Patients must have adequate renal and hepatic function
5. Patients have given written informed consent
6. Be willing to comply with the protocol for the duration of the study
7. ECOG performance status ≤2

Exclusion criteria:

1. Patients with allergies or contraindications to Romidepsin or Azacitidine
2. Patients with class III or IV of the New York Heart Association (NYHA) cardiac impairment
3. Blastic transformation of Chronic Myeloid Leukaemia (CML)
4. Pregnant or lactating women
5. Patients of reproductive potential not willing to use appropriate, effective, contraception during the trial and for 3 months following treatment discontinuation
6. Patients with unstable angina, congenital long QT syndrome or a history of myocardial infarction (MI) within the last 6 months
7. Patients with concurrent active malignancy
8. Any co-morbidity that could limit compliance with the trial
9. Patients who have taken any other investigational medicinal product within 4 weeks of study entry
10. Active symptomatic fungal, bacterial and/or viral infection including known HIV or known viral (A, B or C) Hepatitis
11. Patients who are high medical risks due to non-malignant systemic disease as well as those with active uncontrolled infection
12. Patient who have received prior treatment with demethylating agents such as 5-azacitidine or decitabine
13. Previous anti-tumour therapies, including prior experimental agents or approved anti-tumour small molecules and biologics, within 30 days before study entry. (Patients receiving anti-tumour therapies to control blood counts may enol into the trial and receive trial treatment simultaneously)

Trial Duration

This trial will plan to recruit up to 18 patients within 18 months. It is anticipated that the additional 35 patients in the extension phase will be recruited within 18 months.

Trial Office Contact Details

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