



Phase I/II study to determine the maximum tolerated dose and activity of the combination of romidepsin and carfilzomib in relapsed or refractory peripheral T-cell lymphoma

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Sponsor: University of Birmingham

Trial Design

Phase I: Continual Reassessment Method (CRM) to determine the Maximum Tolerated Dose (MTD) of the combination of romidepsin and carfilzomib.

Phase II: A'Hern's single stage design to assess the activity of the combination of romidepsin and carfilzomib

Objectives

- Determine the MTD of the combination of romidepsin and carfilzomib based on a CRM with target Dose Limiting Toxicity (DLT) set at 25%
- Assess the activity of the combination at the MTD in terms of overall response
- An exploratory objective is to determine whether the expression of the protein HR23B can be used as a predictive biomarker of response to this combination

Primary Outcome Measures

Phase I

- MTD of the combination of romidepsin and carfilzomib as determined by the CRM with a predefined target Dose Limiting Toxicity (DLT) probability of 25%.

Phase II

- Best overall response rate (PR + CR) during the first 8 cycles of treatment at the MTD using International response criteria

Secondary Outcome Measures

Phase I

- Toxicity of the combination of romidepsin and carfilzomib using CTCAE v4
- Best overall response during the first 8 cycles of treatment at the MTD
- Maximum % change in the radiological sum of the product of the diameters from baseline
- Duration of response from time of first documented response until relapse or progression

Phase II

- Best overall response rate post 8 cycles of treatment until the end of the trial
- Toxicity of the combination of romidepsin and carfilzomib using CTCAE v4
- Maximum % change in the radiological sum of the product of the diameters from baseline
- Duration of response from time of first documented response until relapse or progression
- Progression free survival
- Overall survival

Trial Duration

Patients will be recruited over 36 months from the 13 Trials Acceleration Programme (TAP) centres with the potential to expand to further non-TAP centres.

Following registration, patients will receive a minimum of 8 cycles (each of 28 days duration) of the combination of romidepsin and carfilzomib. At the end of 8 cycles, cycles of either the combination or romidepsin alone (at the investigators discretion) will be delivered until disease progression, unacceptable toxicity or patient choice. Patients will continue to be followed up for progression and survival until the end of trial or a minimum of 12 months.

Inclusion criteria

- Age \geq 16 years of age
- Life expectancy $>$ 12 weeks
- ECOG performance status \leq 2 (Appendix 5)
- Relapsed or refractory* peripheral T-cell lymphoma including the following histologies: peripheral T-cell lymphoma not otherwise specified, angioimmunoblastic T-cell lymphoma, anaplastic large cell lymphoma, enteropathy associated T-cell lymphoma, extranodal NK/T-cell lymphoma, transformed mycosis fungoides, hepatosplenic T-cell lymphoma
- Failed at least 1 prior therapy (but no upper limit of prior regimens)
- Patients MAY have had a prior allogeneic stem cell transplant but must not require systemic immunosuppression for graft-versus-host disease (local treatments are permitted)
- Adequate haematopoietic reserve (Hb \geq 9g/dl, neutrophils \geq $1.0 \times 10^9/l$ and platelets \geq $100 \times 10^9/l$ or \geq $75 \times 10^9/l$ if marrow involvement documented)
- Adequate liver function (bilirubin \leq 1.5 x upper limit of normal (ULN) (unless due to Gilbert's syndrome), AST / ALT \leq 2x ULN)
- Adequate renal function (creatinine clearance \geq 20ml/min as assessed by Cockcroft and Gault calculation)
- Serum potassium \geq 3.8 mmol/l, calcium \geq 2.2 mmol/l and magnesium \geq 0.85 mmol/l prior to trial entry (supplements permitted – see Appendix 7)
- CT measurable disease with at least 1 lesion having short axis $>$ 1.5cm or splenomegaly $>$ 14cm in cranio-caudal length attributable to relapsed lymphoma
- Ability to give informed consent

* For all relapsed patients, relapse must be confirmed by tissue biopsy (or bone marrow trephine if no other tissue available). For refractory patients, a biopsy must have been obtained within the last 6 months and preferably to confirm refractory disease.

Exclusion Criteria

- Persistent treatment related toxicities of CTCAE v4.0 grade \geq 2
- Previous treatment with histone deacetylase inhibitor or proteasome inhibitor
- Need for any other concurrent anti-cancer drug (apart from corticosteroids at a dose equivalent to prednisolone \leq 7.5mg daily). A steroid prephase may be used but should be stopped by the first day of cycle 1.
- Concurrent medical illness deemed by the investigator as uncontrolled and/or clinically significant
- Previous systemic malignancy within the last 3 years unless treated with curative intent with no sign of recurrence. Other exceptions include non-melanotic skin cancer or carcinoma in-situ of the uterine cervix
- Co-existing active infection requiring parenteral antibiotics
- Patients unable to swallow oral medication
- Active infection with HIV, hepatitis B or hepatitis C
- Radiotherapy* (except for palliative reasons), endocrine therapy, immunotherapy or use of other investigational agents within 28 days prior to trial entry (or a longer period depending on the defined characteristics of the agents used, please contact the trials office for confirmation).
*Limited field radiotherapy to an isolated lesion in bone or soft tissue must be completed 2 weeks prior to trial entry
- Major surgery within 4 weeks of trial entry
- Patients with proven CNS involvement
- QTc interval of \geq 480ms or patients taking medications that significantly prolong the QT interval (Appendix 6)
- Clinically significant cardiac disease \geq NYHA Class III (see Appendix 8), symptomatic ischaemia, conduction abnormalities uncontrolled by conventional intervention or myocardial infarction within 6 months of trial entry

- Pregnant and lactating patients (patients of childbearing potential must have a negative pregnancy test prior to study entry and within 7 days prior to the start of treatment. Postmenopausal females (> 45 years old and without menstruation for > 1 year) and surgically sterilised females are exempt from a pregnancy test)
- Patients and partners of childbearing potential not willing to use effective contraception during and for 3 months after therapy
- Concurrent Pulmonary Hypertension
- Left Ventricular Ejection Fraction (LVEF) of $\leq 40\%$

Contact details

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