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Phase 2 study of tefinostat in chronic myelomonocytic leukaemia (CMML)

Submission date 24/09/2015	**Recruitment status** No longer recruiting	[_] Prospectively registered [X] Protocol
Registration date 25/09/2015	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 18/10/2022	**Condition category** Cancer	[_] Individual participant data

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-of-tefinostat-for-chronic-myelomonocytic-leukaemia-monocle

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2015-002281-23

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
SPON 1345-14

Study information

Scientific Title
A phase 2 study of the monocyte-targeted histone deacetylase inhibitor tefinostat (CHR-2845) in chronic myelomonocytic leukaemia (CMML)

Acronym
MONOCLE

Study objectives
The dual primary objectives of the study are:
1. To evaluate the safety and tolerability of tefinostat (CHR-2845) in chronic myelomonocytic leukaemia
2. To evaluate the overall clinical response rate to tefinostat in patients with chronic myelomonocytic leukaemia (according to Wattel and modified IWG criteria)

Ethics approval required
Old ethics approval format

Ethics approval(s)
Wales REC 3, 15/01/2016, REC ref: 15/WA/0391

Study design
Single-arm phase 2 trial

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See additional files

Health condition(s) or problem(s) studied
Chronic myelomonocytic leukaemia is a myelodysplastic / myeloproliferative neoplasm with a high median age of presentation (>70yrs) and poor prognosis; the median survival from diagnosis remains only 11-17 months and very few clinical studies have addressed the disease in isolation.

Interventions
All patients will receive tefinostat (CHR-2845) which is a novel monocyte/macrophage-targeted HDAC inhibitor that is cleaved to an active acid (CHR-2847) by an intracellular esterase (hCE-1) that is found only in cells of monocytoid lineage. CHR-2847 selectively accumulates within hCE-1 expressing cells resulting in a 20 to 100-fold increase in potency of tefinostat for monocytic tumour cells, which make up the majority of the disease cells in CMML. In a previous first-in-man study of tefinostat in patients with refractory haematological malignancies treated with continuous doses of 20 to 640mg, tefinostat was well-tolerated with no 'maximum tolerated dose' being defined. Selective targeted increases in protein acetylation in monocytoid cells were demonstrated between 40 and 320mg. Of 2 CMML patients treated in that study, one achieved a bone marrow complete response at relatively small doses (20-80mg).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Tefinostat

Primary outcome measure
1. Safety and tolerability of tefinostat defined as the proportion of patients experiencing CTC grade 3-4 non-haematological toxicity or death thought to be at least possibly related to tefinostat
2. Overall clinical response rate (according to Wattel and modified IWG criteria)

Patients will receive tefinostat continuously for 6 continuous 4-week cycles (24 weeks). Primary outcome measures will be assessed continuously over this period, including fortnightly peripheral blood assessment (full blood count, blood film/differential) and bone marrow assessments performed after 12 and 24 weeks of therapy.

Secondary outcome measures
1. Incidence and duration of CR/PR/haematological improvement
2. Achievement of red blood cell and platelet transfusion independence
3. Overall survival
4. Progression-free survival
5. Incidence of transformation of CMML to acute myeloid leukaemia (AML), and the time to AML transformation
6. Duration of tefinostat therapy
7. BIological correlates including hCE-1 expression, changes in protein acetylation

Patients will receive tefinostat continuously for 6 continuous 4-week cycles (24 weeks). Secondary outcome measures will be assessed continuously over this period, including fortnightly peripheral blood assessment (full blood count, blood film/differential) and bone marrow assessments performed after 12 and 24 weeks of therapy.

Overall study start date
01/03/2015

Completion date

26/07/2019

Eligibility

Key inclusion criteria
1. All CMML-2 patients are eligible
2. For patients classified as CMML-1, the following must be present:
2.1. Symptomatic bone marrow failure / myeloproliferation defined as one or more of: red cell transfusion dependence with pre-transfusion Hb <90g/l symptomatic anaemia (Hb <115g/l) thrombocytopenia (platelets <50 x 109/l) symptomatic bleeding due to platelet function defect or DIC/fibrinolysis white blood cell count >50 x 109/l
and/or
2.2. CMML-specific Prognostic Score (CPSS) of intermediate-2 or high risk (16)
(details of derivation of CPSS score given below)
and/or
2.3. Systemic symptoms including weight loss with no alternative explanation (10% of baseline weight
within previous 6 months)
2.4. Symptomatic splenomegaly
2.5. Symptomatic extrameduallary involvement, eg. skin infiltration, serous effusions
3. Subject is able and willing to sign the informed consent form
4. Age greater than or equal to 18 years at the time of signing the informed consent form
5. Willingness to undergo scheduled assessments as per the study protocol including bone marrow assessments
6. ECOG performance status of 0-2 at study entry
7. Women of childbearing potential must have a negative urine pregnancy test within 7 days prior to starting study drug
8. Women of childbearing potential must use at least two effective contraceptive methods throughout the study and for three months following the date of the last dose of study drug
9. Men whose partner is a woman of childbearing potential must use at least two effective contraceptive

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
20 (previously 40; however, there were an insufficient number of objective clinical responses seen in part 1 of the study to reach the threshold required to trigger the opening of part 2. Therefore the trial never opened to the second stage and did not fulfil the overall study recruitment target of 40 patients)

Total final enrolment

Key exclusion criteria
1. CMML with eosinophillia and 5q33 abnormality
2. Previous chemotherapy for CMML except Hydroxycarbamide and 5-azacitidine
3. Creatinine concentration > 2x the institutional upper limit of normal range
4. Liver transaminases (AST / ALT) > 3x the institutional upper limit of normal range or serum bilirubin > 4x the institutional upper limit of normal range
5. Pregnant or lactating females
6. Use of experimental drug or therapy within 28 days of registration
7. Other malignancy within the last 3 years other than curatively-treated basal cell or squamous cell skin cancer, carcinoma in situ of the cervix, organ-confined or treated non-metastatic prostate cancer with negative prostate-specific antigen, in situ breast carcinoma after complete surgical resection, or superficial transitional cell bladder carcinoma
8. Known seropositivity for HIV infection or infectious hepatitis (type B or C)
9. Uncontrolled inter-current illness including, but not limited to, ongoing infection, psychiatric illness or social situation that the treating physician judges would limit compliance with study requirements

Date of first enrolment
01/09/2015

Date of final enrolment
21/09/2017

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

Study participating centre
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Study participating centre

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Study participating centre
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Study participating centre
Freeman Hospital
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University/education

ROR
https://ror.org/03kk7td41

Funder(s)

Funder type
Charity

Funder Name
Leukaemia and Lymphoma Research

Alternative Name(s)

Funding Body Type

Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Precise publication plans will be confirmed at a later date. Following completion of study treatment and follow-up it is our intention to initially present the findings from this study at a high profile international haematology meeting (American Society of Hematology or European Haematology Association) prior to publication in high impact peer-reviewed journal.

Intention to publish date
01/09/2020

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet		23/10/2018	23/10/2018	No	Yes
Plain English results			23/06/2020	No	Yes
Abstract results	results presented at ASH	29/11/2018	21/07/2020	No	No
Protocol file	version 3.0	28/03/2017	18/10/2022	No	No
HRA research summary			28/06/2023	No	No