

LINEs: Eurosarc trial of LINsitinib in advanced Ewing Sarcoma

Submission date 05/03/2014	Recruitment status No longer recruiting	☒ Prospectively registered ☐ Protocol
Registration date 05/03/2014	Overall study status Completed	☐ Statistical analysis plan ☒ Results
Last Edited 08/08/2019	Condition category Cancer	☐ Individual participant data

Plain English summary of protocol

<http://www.cancerresearchuk.org/about-cancer/trials/a-trial-looking-linsitinib-advanced-ewings-sarcoma-lines>

Contact information

Type(s)

Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)

NCT02546544

Clinical Trials Information System (CTIS)

2012-000616-28

Protocol serial number

14859

Study information

Scientific Title

Phase II trial of Linsitinib (anti-IGFR/IR) in patients with relapsed and/or refractory Ewing Sarcoma

Acronym

LINES

Study objectives

An important development in ES has been the identification of IGF-1R pathway dependency. The reasons for the remarkable single agent efficacy observed in a small subset of patients remains unknown, as is the relative lack of efficacy in the majority of patients. There may be heterogeneity in response due to partial signal pathway inhibition at the tumour level, inherent resistance in ES cells or the presence of alternative pathway activation through IR-A receptor signalling.

Here we aim to establish pharmacodynamic responses in ES tumours using functional imaging 18FDG-PET-CT and repeat post treatment biopsy for biomarker responses, toxicity and clinical outcome to the dual anti-IGF-1R/IR kinase blocking single agent linsitinib.

This is a single arm phase 2 study utilising adaptive Bayesian analysis. Approximately 40 patients will be recruited the national bone sarcoma centre in 5 EU countries over 18 months.

Eligible patients will take 4x 150 mg tablets once a day, days 1-3 of the week followed by 4 days off - repeated for 3 weeks = one treatment cycle. Patients can remain on treatment for as long as they gain clinical benefit.

The primary objectives are to determine the effect of linsitinib on the patients tumours in terms of changes in biomarker and PET scans and to establish the safety of the trial drug (linsitinib) in Ewing sarcoma at the dose and treatment schedule being used in the trial.

More details can be found at: <http://public.ukcrn.org.uk/search/StudyDetail.aspx?StudyID=14859>

Ethics approval required

Old ethics approval format

Ethics approval(s)

South Central Oxford C, 22/08/2013, ref: 13/SC/0330

Primary study design

Interventional

Study design

Non-randomised; Interventional; Design type: Treatment

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Topic: National Cancer Research Network; Subtopic: Sarcoma; Disease: Bone

Interventions

Linsitinib, Linsitinib is to be administered orally once a day on days 1-3, 8-10 and 15-17 on a 21 day cycle.

The starting dose is 600 mg.

Treatment should continue in patients with either radiological confirmed stable or responding disease until disease progression, unacceptable toxicity or at the patients request.

Study Entry : Registration only

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

Linsitinib

Primary outcome(s)

FDG uptake (SUV) responses; Timepoint(s): FDG uptake (SUV) responses, measured using PET-CT at baseline, during cycles 1, 3, and 6

Key secondary outcome(s)

Safety and tolerability of Linsitinib; Timepoint(s): Adverse events and lab abnormalities (CTCAE v4 grade, timing, seriousness & relatedness) - all visit

Completion date

28/02/2015

Eligibility

Key inclusion criteria

1. Histological or cytological confirmed original (no new biopsy required) diagnosis of Ewing sarcoma, preferably with EWSR in situ hybridisation break apart probe.
2. First, second or any relapse or refractory disease to conventional treatment.
3. Current disease state for which there either is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.
4. Has recovered from prior chemotherapy-related toxicity to $\leq$ grade 2.
5. Male or female, Age $\geq$ 18 and $\leq$ 70 years.
6. Life expectancy of at least 4 months.
7. WHO performance score of 0-2.
8. Must be able to take oral medication.
9. Is willing and able to comply with the protocol for the duration of the study, and scheduled visits and examinations, including biopsies and PET-CT scans.
10. Written (signed and dated) informed consent.
11. Tumour at biopsy accessible site; in the case of lung metastases, accessible with VATS procedure.
12. Tumour progression documented with imaging in the 3 months prior to study entry.
13. At least one measurable lesion on CT scan performed in past 14 days of minimum size 1 cm and 18 FDG uptake positive
14. Cardiac Ejection Fraction (Echocardiogram) $\geq$ 45%.
15. Fasting glucose $\leq$ 150 mg/dL (8.3 mmol/L) with no history of diabetes mellitus. Concurrent

use of non-insulinotropic anti-hyperglycemic therapy is permitted if the dose has been stable for ≥ 4 weeks at the time of enrolment.

16. Haematological and biochemical indices within the specified ranges.

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 Years

Sex

All

Total final enrolment

16

Key exclusion criteria

1. Females: Pregnant or breast-feeding, or of childbearing potential unless effective methods of contraception are used. Males: Unless effective methods of contraception are used.

2. Significant active cardiac disease including: History (within last 6 months) of significant cardiovascular disease unless the disease is well-controlled.

Significant cardiac disease includes second/third degree heart block; clinically significant ischemic heart disease; superior vena cava (SVC) syndrome; poorly controlled hypertension; congestive heart failure of New York Heart Association (NYHA) Class II or worse (slight limitation of physical activity; comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea).

3. History of arrhythmia (multifocal premature ventricular contractions [PVCs], bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) that is symptomatic or requires treatment ($\geq$ grade 3), left bundle branch block (LBBB), or asymptomatic sustained ventricular tachycardia are not allowed. Patients with atrial fibrillation controlled by medication are not excluded; uncontrolled high blood pressure (no greater than 2 SD above the mean for age for SBP and DBP), unstable angina, congestive heart failure, myocardial infarction within the previous 6 months, or serious cardiac arrhythmias.

4. Mean QTcF interval ≥ 450 msec based on analysis of screening visit ECGs;

5. Use of drugs that have a known risk of causing Torsades de Pointes (TdP) within 14 days prior to registration.

6. Use of the potent CYP1A2 inhibitors ciprofloxacin and fluvoxamine within 7 days prior to registration. Linsitinib is primarily metabolized by CYP1A2 and inhibitors/inducers of CYP1A2 could alter the pharmacokinetics of linsitinib.

Other less potent CYP1A2 inhibitors/inducers are not excluded.

7. Other psychological, social or medical condition, physical examination finding or a laboratory abnormality that the

Investigator considers would make the patient a poor trial candidate or could interfere with protocol compliance or the interpretation of trial results.

8. Any other active malignancy, with the exception of adequately treated conebiopsied in situ carcinoma of the cervix uteri and nonmelanoma skin lesions.
9. History of cerebrovascular accident (CVA) within 6 months prior to entry that resulted in ongoing neurologic instability.
10. Patients with symptomatic brain metastases. Patients with previously diagnosed brain metastases are eligible if they have completed their CNS treatment and have recovered from the acute effects of radiation therapy or surgery prior to the start of study medication, have discontinued corticosteroid treatment for these metastases for at least 4 weeks, and are neurologically stable.
11. Major surgery within 4 weeks prior to study treatment.
12. Prior anti-IGF-1R treatment.
13. Treatment with any other investigational agent, or participation in another clinical trial within 28 days prior to enrolment.
14. Patients who are known to be serologically positive for Hepatitis B, Hepatitis C or HIV.

Date of first enrolment

30/04/2014

Date of final enrolment

28/02/2015

Locations

Countries of recruitment

United Kingdom

England

France

Germany

Italy

Netherlands

Study participating centre

Oncology Clinical Trials Office (OCTO) - Department of Oncology

Oxford

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Sponsor information

Organisation

University of Oxford

ROR

<https://ror.org/052gg0110>

Funder(s)

Funder type

Government

Funder Name

European Commission - The Directorate-General for Research and Innovation; Grant Codes: 278742

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Basic results			08/08/2019	No	No
HRA research summary			28/06/2023	No	No