ISRCTN94236001 https://doi.org/10.1186/ISRCTN94236001

# LINES: Eurosarc trial of LINsitinib in advanced Ewing Sarcoma

| Submission date | Recruitment status | [X] Prospectively registered |
|---|---|---|
| 05/03/2014 | No longer recruiting | [_] Protocol |
| **Registration date** | **Overall study status** | [_] Statistical analysis plan |
| 05/03/2014 | Completed | [X] Results |
| **Last Edited** | **Condition category** | [_] Individual participant data |
| 08/08/2019 | Cancer | |

**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

**Contact name**
Ms Hannah Johnson

**Contact details**
Oncology Clinical Trials Office (OCTO) - Department of Oncology
Old Road Campus
Roosevelt Drive Headington
Oxford
United Kingdom
OX3 7DQ
-
octo-eurosarc@oncology.oc.ac.uk

## Additional identifiers

**Clinical Trials Information System (CTIS)**
2012-000616-28

**ClinicalTrials.gov (NCT)**
NCT02546544

**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

## Study design
Non-randomised; Interventional; Design type: Treatment

## Primary study design
Interventional

## 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 oally 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, unaccetable 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 ≤ grade 2.
5. Male or female, Age ≥ 18 and ≤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) ≥45%.
15. Fasting glucose ≤ 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 (≥ 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
United Kingdom
OX3 7DQ

## 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 |
| Participant information sheet | Participant information sheet | 11/11/2025 | 11/11/2025 | No | Yes |