Phase II trial of Linsitinib (anti-IGF-1R/IR) in patients with relapsed and/or refractory Ewing Sarcoma

Published: 05-03-2015
Last updated: 21-04-2024

Primary ObjectivesTo determine the pharmacodynamic effect of linsitinib in the tumourTo evaluate the safety and tolerability of linsitinibSecondary ObjectivesTo determine the clinical outcomeTo conduct pharmacokinetic assays with linsitinib...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Musculoskeletal and connective tissue neoplasms
Study type	Observational invasive

Summary

ID

NL-OMON43946

Source
ToetsingOnline

Brief title
Eurosarc Trial of Linsitinib in advanced Ewing Sarcoma (Lines)

Condition

- Musculoskeletal and connective tissue neoplasms

Synonym
Ewing sarcoma

Research involving
Human

Sponsors and support

Primary sponsor: University of Oxford
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: ewing sarcoma, insulin growth factor, oncology

Outcome measures

Primary outcome

Tumor and plasma biomarkers

Toxicity according to CTC version 3.0

Secondary outcome

Tumor measuremnt according to RECIST 1.1

PK data of linsitinib

Study description

Background summary

The most innovative development in ES has been the identification of the IGF1 receptor pathway deregulation, and early Phase I/II trials using agents that target only IGF1R (R1507 and Figitumumab) have shown 10-15% partial response rates and a number of patients with prolonged disease stabilisation [1, 2].
The antibody therapies have been well tolerated with some patients still being maintained on therapy years after initial trial enrolment.
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.
In terms of the former, the correlation of tumour response with high IGF-1 levels (>0.95ng/ml) maybe a reflection of variable (sub) therapeutic antibody levels in some patients.
Overall, these agents are only going to result in tumour regression if the ES cells undergo cell death, as these agents are not cytotoxic in themselves. Here we aim to establish pharmacodynamic responses in ES tumours using functional imaging
18FDG-PET-CT and repeat post treatment biopsies, toxicity and clinical outcome to the dual anti-Insulin-like growth factor I / Insulin receptor kinase

blocking agent, linsitinib.

Study objective

Primary Objectives
To determine the pharmacodynamic effect of linsitinib in the tumour
To evaluate the safety and tolerability of linsitinib
Secondary Objectives
To determine the clinical outcome
To conduct pharmacokinetic assays with linsitinib treatment

Study design

International, multi-centre, single arm phase II study utilising Bayesian analysis

Study burden and risks

2 tumor biopsies with associated risk
however chances of antitumor response are real given the experience with similar drugs in this setting

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

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 6 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 18FDG uptake positive
14. Cardiac Ejection Fraction (Echocardiogram or MUGA) >=45%.
15. Fasting glucose <= 150 mg/dL (8.3 mmol/L) with no history of diabetes. Concurrent use of non-insulinotropic anti-hyperglycaemic therapy for diabetes 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 as below:
* Haemoglobin (Hb) >=9 g/dL (Previous transfusion is allowed)
* Absolute neutrophil count (ANC) >=1.0 x 109/L without growth factor support
* Platelet count > 80.x 109/L (Previous transfusion is allowed)

* Bilirubin <1.5 times the upper limit of normal (ULN)
* Serum alanine aminotransferase (ALT) <2.5 x ULN for age and <= 5 x ULN if liver metastasis
* Aspartate aminotransferase (AST) <2.5 x ULN for age
* Alkaline phosphatase <2.5 x ULN for age
* CPK <2.5 x ULN for age
* Serum creatinine <=1.5 x ULN for age
* Potassium, magnesium and calcium within normal limits (supplementation and re-testing is permitted)

Exclusion criteria

Females: Pregnant or breast-feeding, or of childbearing potential unless effective methods of contraception are used (see section 5.1 for definition.) Males: Unless effective methods of contraception are used (see section 5.1 for definition).
2. Significant active cardiac disease including: History (within last 6 months) of significant cardiovascular disease unless the disease is wellcontrolled. 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.
LINES Confidential
LINES_Protocol_V4.0_13Jan2014 Protocol Template V2.0_20Mar2012
Page 11 of 71
4. Mean QTcF interval >= 450 msec based on analysis of screening visit and pre-dose ECGs.
5. Use of drugs that have a known risk of causing Torsades de Pointes (TdP) (*Torsades List* on www.azcert.org/medical-pros/druglists/bycategory.cfm, see Appendix 4) 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 cone-biopsied in situ carcinoma of the cervix uteri and non-melanoma 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 postive for Hepatitis B, Hepatitis C or HIV

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-05-2015
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Linsitinib

Ethics review

Approved WMO Date:	05-03-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-05-2015
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	04-06-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	28-04-2016
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2012-000616-28-NL
ISRCTN	ISRCTN94236001NCTO2546544
CCMO	NL51440.058.14