An Open-Label, Non-Randomized, Single-Center Study to Determine the Metabolism and Elimination of 14C-E7080 in Patients with Advanced Solid Tumors or Lymphomas, who are Unsuitable For, or Have Failed, Existing Therapies

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Primary objective:To determine the pharmacokinetics of E7080 and its excretion balance in order to elucidate its metabolic profile in plasma, urine, and feces following a single oral dose of radiolabeled 14C-E7080 in patients with advanced tumors or...

Ethical review	Approved WMO
Status	Pending
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON33844

Source
ToetsingOnline

Brief title
NVT

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
Cancer, Drug Metabolism

Research involving

Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Eisai Limited

Intervention

Keyword: Advanced Cancer, Elimination, Metabolism, Radiolabelled

Outcome measures

Primary outcome

Plasma, urine, and fecal concentrations of 14C-E7080 related material, and its metabolites will be evaluated after the first dose of 14C E7080 to determine the timing, extent and pathway of elimination of the drug.

Secondary outcome

Baseline characteristics, adverse events, serious adverse events, laboratory parameters, and other safety parameters

Study description

Background summary

E7080 is a potent inhibitor of the split-kinase family of transmembrane growth factor receptors including Flt-1 and KDR. In addition, E7080 also potently inhibits fibroblast growth factor receptor 1 (FGFR1) and platelet-derived growth factor receptor beta (PDGFRBeta) tyrosine kinases. The primary focus for the development of this compound as an anticancer agent is in cell assays, E7080 inhibited VEGF-driven human umbilical vein endothelial cell (HUVEC) proliferation and tube formation.

Study objective

Primary objective:
To determine the pharmacokinetics of E7080 and its excretion balance in order to elucidate its metabolic profile in plasma, urine, and feces following a

single oral dose of radiolabeled 14C-E7080 in patients with advanced tumors or lymphomas who are unsuitable for, or have failed, existing therapies.
Secondary objectives:
To assess the safety and tolerability of E7080 when given continuously as a single daily dose of 24 mg.
To explore the anti-tumor activity of E7080.

Study design

Open Label, Single-Arm

Intervention

For each patient a screening visit will be conducted within 21 days prior to the start of treatment. Screening will include a tumor assessment, physical examination, vital signs, electrocardiogram (ECG), hematology, chemistry, and urinalysis. Except for the tumor assessment, these checks will be repeated pre-dose on Day 1 of the Study Phase. On Day 1 of the Study Phase following administration of a single oral dose of 14C-E7080, blood, urine, and fecal samples will be collected for PK analysis and determination of 14C-E7080 concentrations between Days 1 and 8. Patients will remain at the hospital until the Day 8 discharge visit. On Day 8, patients will be re-assessed prior to being discharged and will enter the Extension Phase of the study to continue to receive oral doses of E7080 study drug at a dose of 24 mg once daily. Each 28-day dosing period will be considered one treatment cycle. A Study Termination visit will occur as soon as possible following the final treatment dose, with a follow-up visit 30 days after the final treatment dose.

Study burden and risks

As of 31st January 2008, 133 individuals have taken E7080 (all in clinical trials). Approximately 1 in 10 of these patients experienced hypertension, the majority were symptomless and responded to anti-hypertensives; proteinuria; fatigue; nausea and vomiting; diarrhoea.

The additional radiation burden in this study due to the administration of 100 micro Curie 14C labelled E7080 is calculated to be 0.057mSv. This is about 3.5% of the average annual radiation burden. Patients will not receive any additional tumour assessments involving exposure to radiation than in routine care. Patients will be in-patients for a minimum of 8 days, during which time frequent blood samples will be taken and full urine and faeces collection is required. This is clearly a significant burden for the patient during the Study Phase.

It is not possible to determine whether a patient will benefit from receiving E7080. It is anticipated that patients may experience a response during the

Extension Phase of this study when they receive daily dosing with E7080. Very promising early indications of anti-cancer activity with a maximum tolerated dose identified at 25mg once daily dosing. The E7080-E044-101, a Phase I study of 39 evaluable patients with advanced solid tumours, demonstrated best responses of 5 partial responses, 25 stable disease, and 8 progressive disease. Of the 30 patients who had either a partial or stable response, the median time to progression is currently 38 weeks, with 6 patients still receiving treatment.

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. Patients with histologically and/or cytologically confirmed solid tumor or lymphoma who are resistant/ refractory to approved therapies or for whom no appropriate therapies are

available. Patients with measurable tumors according to RECIST are desirable but not essential for inclusion.
2. All previous treatment (including surgery and radiotherapy) must have been completed at least four weeks prior to study entry and any acute toxicity must have resolved
3. Aged >= 18 years
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0, 1, or 2
5. Able to take oral study medication
6. Give written informed consent to participate in the study
7. Willing and able to comply with the study protocol for the duration of the study.

Exclusion criteria

1. Patients with brain or subdural metastases, unless they have completed local therapy and have discontinued the use of corticosteroids for this indication for at least 4 weeks before starting treatment in this study. Any signs and/or symptoms of brain metastases must be stable for at least 4 weeks.
2. Patients with meningeal carcinomatosis
3. Any of the following values for laboratory parameters:
a) hemoglobin < 9 g/dl (5.6 mmol/L)
b) neutrophils <1.5 x 109/L
c) platelets <100 x 109/L
d) PT (or INR) and PTT > 1.5 x the upper limit of normal (ULN)
e) serum bilirubin >1.5 x ULN
f) other liver parameters >3 x ULN
g) creatinine clearance < 60 mL/min per the Cockcroft and Gault formula
4. Uncontrolled infections
5. Significant cardiovascular impairment (history of congestive heart failure > NYHA Class II, unstable ischemic heart disease including a myocardial infarction within six months of study start, or serious cardiac arrhythmia)
6. Patients with marked baseline prolongation of QT/QTc interval (QTc interval >= 500 msec) using the Fridericia method
7. Any treatment with an investigational drug within the last 30 days
8. Women who are pregnant or breast-feeding;women of childbearing potential with a positive pregnancy test at screening or no pregnancy test. Women of child-bearing potential unless (1) surgically sterile or (2) using adequate measures of contraception in the opinion of the Investigator (including two forms of contraception, one of which must be a barrier method). Perimenopausal women must be amenorrheic for at least 12 months to be considered of non-child-bearing potential. Fertile males with female partners of child-bearing potential who are not willing to use contraception, or whose female partners are not using adequate contraceptive protection, are excluded.
9. Proteinuria > 1+ on bedside testing
10. History of gastrointestinal malabsorption
11. Surgery within four weeks of start of study treatment
12. Bleeding or thrombotic disorders or use of an anticoagulant, such as warfarin, with a therapeutic international normalization ratio (INR). Aspirin, non-steroidal anti-inflammatory

drugs (NSAIDs), and low molecular weight heparin (LMWH) are permissible but should be used with caution.
13. Poorly controlled hypertension (defined as a change in hypertensive therapy within three months of study start) or patients diagnosed with hypertension (defined as a repeat blood pressure measurement of 160/90 mmHg or higher) at screening
14. Previous E7080 therapy
15. History of alcoholism, drug addiction, psychiatric or psychological condition, or social situation which, in the opinion of the investigator, would impair study compliance
16. History of allergic reactions attributed to compounds of similar chemical or biological composition to E7080
17. Other significant disease or disorder that, in the Investigator*s opinion, would exclude the patient from the study
18. Legal incapacity

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	24-03-2009
Enrollment:	10
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	14C- E7080
Product type:	Medicine
Brand name:	E7080
Generic name:	nvt

Ethics review

Approved WMO Date:	28-11-2008
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-03-2009
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-08-2010
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2007-004619-70-NL
CCMO	NL24438.031.09