A phase 1 multicenter, open label, dose-escalation study of oral LEE011 in patients with advanced solid tumors or lymphomas.

Published: 19-11-2010
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Primary To determine the maximum tolerated dose (MTD) and characterize the dose-limiting toxicities (DLT) of LEE011 when administered orally once daily for 21 consecutive days followed by a 7 day break.Secondary *Safety and tolerability of LEE011.*...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON39139

Source
ToetsingOnline

Brief title
A phase I study with LEE011, a CDK4/6 inhibitor

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer, Solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: LEE011, Lymphoma, Phase I, Solid tumors

Outcome measures

Primary outcome

Frequency of Dose Limiting Toxicities.

Secondary outcome

- Safety and tolerability: type, grade and frequency of adverse events (AEs), serious adverse events (SAEs), changes in hematology and chemistry values (especially those associated with hepatic and bone marrow function), assessment of physical examinations, vital signs and ECGs

- Pharmacokinetics: AUClast, area under the curve from time zero to infinity (AUCinf), Cmax, tmax, Css, t1/2 will be estimated for LEE011, LEQ803 and/or additional clinically significant metabolites that may be identified. For LEE011, CL/F and the apparent volume of distribution during terminal phase after oral administration (associated with *z) (Vz/F) will be calculated as well.

- Pharmacodynamics: changes from baseline in biomarkers associated with the pharmacologic activity of LEE011 (e.g., p-pRb and Ki67, in surrogate tissues and tumor tissue).

- Antitumor activity: CT/MRI Response Evaluation Criteria for Solid Tumors

(RECIST Criteria v1.0) or Cheson Criteria 2007 for lymphomas.

Study description

Background summary

The D-cyclin-CDK4/6-INK4a-pRb pathway is universally disrupted in cancer to favor cellproliferation. Eighty percent of human neoplasms maintain functional pRb but harbor aberrations that effectively inactivate pRb function. These aberrations include genetic or epigenetic changes that directly increase CDK4/6 kinase activity or that deactivate upstream regulators.
LEE011 is an orally bioavailable small molecule inhibitor of CDK4/6. LEE011 exhibits highly specific inhibitory activity against CDK4/cyclinD1 and CDK6/CylinD3 complexes. It is inactive against the majority of other kinases.
In Jeko-1 mantle cell lymphoma (MCL) cells that overexpress cyclin D1, LEE011 inhibits the phosphorylation of pRb at CDK4/6-specific sites. In nude rats bearing Jeko-1 subcutaneous xenografts, LEE011 demonstrates dose-dependent target inhibition in the tumors. LEE011 doses that induce >75% inhibition of pRb phosphorylation in this model are associated with complete tumor regression. LEE011 also inhibits the growth of many other tumor types in vitro and in vivo, including liposarcoma, melanoma, rhabdoid cancer, and carcinomas of the esophagus, breast, lung and pancreas. Regardless of the various genetic aberrations that may be present in the cancer cells, the anti-tumor activity of LEE011 requires the presence of functional pRb.

Study objective

Primary
To determine the maximum tolerated dose (MTD) and characterize the dose-limiting toxicities (DLT) of LEE011 when administered orally once daily for 21 consecutive days followed by a 7 day break.

Secondary
*Safety and tolerability of LEE011.
*Pharmacokinetic profiles of LEE011, LEQ803 and any other clinically significant metabolites
*Pharmacodynamic effects of LEE011
*To characterize antitumor activity that may be associated with LEE011

Study design

A phase I, multi-center, open label dose escalation study of LEE011,

administered orally daily on a continuous 21-day dosing schedule. Followed by a 7 days rest period.
At the time of the MTD declaration for initially planned dosing schedule, if safety and PK data support it, a continuous dosing regimen will be evaluated to establish an MTD for that regimen.
Enrollment to this study is restricted to patients with tumors that are pRb-positive, determined by immunohistochemical analysis (ICH).
After MTD has been declared, The dose expansion phase will limit enrollment to patients whose tumors are not only pRb-positive but that also contain defects in the D-cyclin-CDK4/6-INK4a-pRb pathway identified by IHC.

Intervention

LEE011, oral,
Formulations:
- Capsules 10mg, 50mg and 200mg
- Bottles with powder 1200mg and 1800mg
Start dose: 150 mg/day
21 days adminsitration followed by 7 days rest or continuous (daily)

Study burden and risks

Side effects from LELEE011 seen in animals that might happen in human:
- Infection, bleeding, anemia
- Liver damage
- QT prolongation, rhythm disturbance
- Nausea, vomiting, diarrhea,
- Impairment of the thyroid function

Taking blood and tumorbiopsies may cause pain, bleeding, and/or bruising. Patients will be exposed to radiation (CT-scan, and X-rays). The radiation exposure will not exceed the maximum ranges that are set within the Netherlands.

Contacts

Public
Novartis

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NL
Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Patients with a histologically or cytologically confirmed diagnosis of a solid tumor or lymphoma for which no further effective standard treatment is available
1) dose escalation phase: pRb-positive tumor tissue (immunohistochemical analysis)
2) dose expansion phase: tumors known to have aberrant activation of the D-cyclin-CDK4/6-INK4a-pRb pathway or whose tumors can be shown to harbor such an abnormality identified by IHC, by mutation analysis or by FISH. Patients with MCL, liposarcoma, HPVnegative HNSCC, melanoma, ER+ breast cancer and neuroblastoma are permitted to be enrolled in the study without documented pRb status.
A representative tumor specimen must be available for molecular testing. An archival tumor sample may be submitted; however, if one is not available, a newly obtained tumor biopsy specimen must be submitted instead.
- WHO performance status 0 or 1.
- Required baseline laboratory values:
o Absolute Neutrophil Count *1.5 x 109/L
o Hemoglobin * 9 g/dl <= 5.58 mmol/l
o Platelets * 100x109/L
o AST/SGOT and ALT/SGPT* 3 x Upper Limit of Normal (ULN) or * 5.0 x ULN if liver metastases are present
o Serum bilirubin * 1.5 x ULN
o Serum creatinine * 1.5 x ULN or 24-hour clearance * 50 ml/min.
o Potassium, magnesium and calcium within clinical relevant limits
- A sufficient interval must have elapsed between the last dose of prior anti-cancer therapy (including cytotoxic and biological therapies and major surgery) and enrollment in this study, to allow the effects of prior therapy to have abated.

- Patients enrolled in the dose expansion phase must have at least one measurable lesion as defined by RECIST criteria for solid tumors or measurable nodal disease at baseline as defined by Cheson criteria for lymphoma.
- A negative serum pregnancy test * 72 hours before starting study treatment

Exclusion criteria

- Patients with primary CNS tumors or brain metastases. However, if over a minimum of 3 months the disease is stable (confirmed by MRI) and if the patient remains asymptomatic, then the patient may be enrolled. Such patients must have no need for treatment with steroids or anti-epileptic medications.
-Impairment of gastro-intestinal (GI) function or GI disease that may significantly alter the absorption of LEE011 and clinically significant gastroparesis, nausea, vomiting, or diarrhea of CTCAE grade > 1
- Autologous stem cell transplant within 3 months before the first dose of LEE011 or prior allogeneic stem cell transplant at any time
- Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
1) Left ventricular ejection fraction (LVEF) <45%
2) Complete left bundle branch block
3) Obligate use of a cardiac pacemaker or implantable cardioverter defibrillator
4) Congenital long QT syndrome or family history of unexpected sudden cardiac death
5) History or presence of ventricular tachyarrhythmia
6) Presence of unstable atrial fibrillation
7) Clinically significant resting bradycardia
8) QTcF >450 ms for males and >470 ms for females on screening ECG
9) Right bundle branch block and left anterior hemiblock (bifascicular block)
10) Acute MI or angina pectoris * 3 months prior to starting study drug
11) Other clinically significant heart disease
- The use of agents that are known to cause QTc prolongation
- Treatment with agents including vitamins, supplements, and herbal supplements that are either (i) metabolized solely through CYP3A4/5, CYP1A2 or BSEP and have a narrow therapeutic window or (ii) are strong inhibitors of CYP3A4/5, CYP1A2 or BSEP
- Concurrent severe and/or uncontrolled concurrent medical conditions e.g., uncontrolled hypertension and/or diabetes mellitus, clinically significant pulmonary disease, clinically significant neurological disorder, active or uncontrolled infection.
- Pregnant or lactating women.
- Women of childbearing potential and men with reproductive potential unwilling to use adequate contraception whilst on study therapy and for 3 months thereafter

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-07-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	niet van toepassing
Generic name:	niet van toepassing

Ethics review

Approved WMO Date:	19-11-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-02-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	31-05-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-07-2011
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	21-07-2011
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	11-07-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	19-11-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-06-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-07-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	09-10-2013
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	10-10-2013
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	25-03-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	17-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	28-09-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	EUCTR2009-017017-30-NL
ClinicalTrials.gov	NCT01237236
CCMO	NL34087.041.10