A phase I dose finding study of oral LTT462 in adult patients with advanced solid tumors harboring MAPK pathway alterations

Published: 11-10-2016
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Primary: To characterize safety and tolerability of LTT462 and identify a recommended dose and regimen for future studies in adult patients with advanced solid tumors harboring MAPK pathway alterations. Secondary: Preliminary anti-tumor activity,...

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

Summary

ID

NL-OMON46853

Source
ToetsingOnline

Brief title
A phase I study with LTT462 in tumors with MAPK pathway alterations

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
metastatic cancer, Solid tumor

Research involving
Human

Sponsors and support

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

Intervention

Keyword: ERK inhibitor, LTT462, MAPK pathway, Phase I

Outcome measures

Primary outcome

Safety:

Incidence and severity of adverse events (AEs) and serious AEs (SAEs).

Incidence and nature of DLTs (dose escalation only)

Tolerability:

Dose interruptions, reductions, and dose intensity

Secondary outcome

Overall response rate, disease control rate, duration of response, progression

free survival, PK, changes from baseline of the PD marker DUSP6 in tumor tissue

and in blood.

Study description

Background summary

MAPK pathway is frequently activated in human cancers with RAS genes (KRAS, NRAS and HRAS) being the most frequently mutated oncogenes in all cancers (>30%) with KRAS mutations being the most prevalent in 20% of all cancers. However, no effective therapies exist for KRAS mutant cancers.
Inhibitors against BRAF or MEK suppress MAPK signaling and have demonstrated efficacy in BRAF mutant tumors, but these effects are almost always short-lived due to multiple acquired resistance mechanisms which commonly reactivate ERK1/2

signaling. In this setting, inhibition of ERK1/2, which are the most distal kinases in the MAPK signaling cascade, effectively inhibits MAPK signaling and demonstrates anti-tumor effects in preclinical studies. LTT462 has shown efficacy in a wide range of MAPK pathway-driven human cancer cell lines and in vivo tumor xenografts including models harboring activating lesions in the KRAS, NRAS, MEK and BRAF oncogenes. Therefore it is expected that the ERK1/2 inhibitor LTT462 will result in anti-tumor activity in adult patients with advanced solid tumors harboring documented MAPK pathway alterations.
The purpose of this first-in-human trial is to characterize safety and tolerability of the ERK1/2 inhibitor LTT462 and identify a recommended dose and regimen for future studies in adult patients with advanced solid tumors harboring mitogen activated protein kinase (MAPK) pathway alterations.

Study objective

Primary:
To characterize safety and tolerability of LTT462 and identify a recommended dose and regimen for future studies in adult patients with advanced solid tumors harboring MAPK pathway alterations.

Secondary:
Preliminary anti-tumor activity, pharmacokinetic profile, pharmacodynamic profile

Study design

Multicenter phase I open-label dose finding study with a dose escalation part and a dose expansion part. Treatment with LTT462 until disease progression or unacceptable toxicity.
Food effect sub-study in a subset of subjects in expansion phase. Follow-up for survival in expansion part/
21 subjects in escalation part and 50 in expansion part. If needed enrolment may be increased up to 250 subjects

Intervention

LTT462
Daily oral dosing. Fixed dose

Study burden and risks

- Risk: Adverse effects of LTT462 (first in humans study).
- Burden: Cycles of 4 weeks. Cycle 1: 7-8 visits, cycle 2: 4 visits, cycle 3-6: 2 visits and thereafter 1 visit per cycle. Duration mostly 1-4 hours. Two visits (cycle 10 will take 7-9, resp. 11-13hrs.
- Physical examination: once per cycle.

- Blood draws/tests (mostly 15-30 ml/occasion): nearly every visit. Additional blooddraws for Pk and biomarkers.
- ECG: multiple ECG's at screening and pre- / post intake of LTT462 for the first 6 cycle and at End of Treatment.
- MUGA scan (or echocardiography): 3 times.
- CT-/MRI scan: every 8 weeks.
- Eye examinations (incl. OCT and fundoscopy with dilatation of the pupil): 5 times.
- maximal 3 tumor biopsies.
- Optional storage and use of tumor tissue and blood for future research.

Contacts

Public
Novartis

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NL
Scientific
Novartis

Raapopseweg 1
Arnhem 6824 DP
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. >=12 years of age (in Netherlands: >=18 years of age)
2. Must have progressed following standard therapy, or, in the opinion of the Investigator, no effective, tolerated or appropriate standard therapy.
3. ECOG performance status 0, 1.
4. Presence of at least one measurable lesion (RECIST v1.1).
5. Archival tumor tissue or fresh tumor tissue at screening.
6. Patients must be willing to undergo study required biopsies.;Dose escalation part:
• Advanced solid tumors harboring at least one of the MAPK pathway alterations.;Dose expansion part:
• Group 1: confirmed KRAS and/or BRAF-mutated NSCLC.
• Group 2: confirmed KRAS and/or BRAF-mutated ovarian cancer.
• Group 3: BRAFV600 mutated melanoma. Initial response to, or stable disease for at least 6 months on a BRAFi and/or MEKi but then relapse. BRAFi and/or MEKi as the last line of treatment prior to entry into the study, or only one immunotherapy agent (e.g. anti-CTLA-4, anti PD-1, anti-PD-L1) following BRAFi and/or MEKi failure.
• Group 4: other advanced solid tumors harboring documented MAPK pathway alteration(s) other than those defined in Group 1, 2 and 3. ;Other criteria may apply. See protocol page 39-40 for more details.

Exclusion criteria

1. Prior treatment with ERK inhibitors.
2. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO.
3. Other severe, acute or chronic medical condition that prevent the patient*s participation in the clinical study due to safety concerns
4. Treatment with strong inhibitors and/or inducers of CYP3A and CYP2C8; substrates of CYP3A with a narrow therapeutic index; and sensitive substrates of CYP3A, which cannot be discontinued 7 days prior to the start study treatment.
5. Proton pump inhibitors which cannot be discontinued 3 days prior to the start of study treatment.
6. Clinically significant cardiac disease.
7. Insufficient bone marrow function at screening: Absolute Neutrophil Count (ANC) < 1.5 x 109/L, Hemoglobin (Hgb) < 9.0 g/dL, Platelets < 75 x 109/L
8. Insufficient hepatic and renal function at screening: total bilirubin > 1.5 x upper limit of normal (ULN), AST or ALT > 3 x ULN or > 5.0 x ULN if liver metastases are present, creatinine > 1.5 x ULN
9. Pregnancy, lactation, insufficient contraception for females of childbearing potential.;Other criteria may apply. See protocol page 40-43 for more details.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-12-2016
Enrollment:	6
Type:	Anticipated

Ethics review

Approved WMO Date:	11-10-2016
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-01-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-07-2017
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-08-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-09-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-10-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-01-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-07-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	30-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-10-2018
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	EUCTR2015-003614-24-NL
ClinicalTrials.gov	NCT02711345
CCMO	NL57739.031.16