A phase I dose finding study of oral LXH254 in adult patients with advanced solid tumors harboring MAPK pathway alterations.

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Primary: To characterize the safety and tolerability of LXH254 single agent and to identify recommended doses for future studies in adult patients with advanced solid tumors harboring MAPK pathway alterations.To characterize the safety and...

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

Summary

ID

NL-OMON50657

Source
ToetsingOnline

Brief title
CLXH254X2101

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
advanced solid tumors harboring MAPK pathway

Research involving
Human

Sponsors and support

Primary sponsor: Novartis Pharma BV

Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: BRAF (v-raf Murine Sarcoma Viral Oncogene Homolog B1), CRAF (v-raf-1 Murine Leukemia Viral Oncogene Homolog 1), LXH254, MAPK (Mitogen-Activated Protein Kinase), PDR001

Outcome measures

Primary outcome

Adverse events, DLTs.

Secondary outcome

Overall response rate, disease control rate, progression free survival,

duration of response, overall survival. PK parameters of LXH254 and PDR001.

DUSP6 (as PD marker) for LXH254, Emergence of anti-PDR001 antibodies: Presence

and/or concentration of anti-PDR001 antibodies. BA of a new LXH254 tablet

formulation compared to the current LXH254 formulation

Study description

Background summary

Dysregulation of the MAPK pathway is a common event in many malignancies. RAS genes are amongst the most frequently mutated oncogenes (9-30%) in all cancers with KRAS mutations being the most prevalent (86%) of all RAS-driven cancers. BRAF inhibitors, which are efficacious in melanomas with the BRAF V600E mutation, are found to be ineffective in RAS-mutant cancers. MEK inhibition has not demonstrated robust clinical efficacy in patients with tumors harboring RAS mutations. Thus, (K)RAS-mutant tumors remain a high unmet medical need for which no effective treatment exists.
CRAF has been demonstrated to be the critical mediator of mutant KRAS-driven development in many cancers including NSCLC and plays an essential role in mediating paradoxical activation following BRAF inhibition.
LXH254 is a pan-RAF inhibitor. Taking into account published data on the importance of CRAF in MAPK pathway regulation and based on promising preclinical anti-tumor activity in in vitro and in vivo models, we have a

strong rationale to evaluate the safety, tolerability and the preliminary anti-tumor activity of LXH254 in adult patients with advanced solid tumors harboring documented MAPK pathway alterations, including RAS and/or BRAF mutated NSCLC, ovarian cancer and BRAF mutated melanoma resistant to BRAF and/or MEK inhibition.

Study objective

Primary:
To characterize the safety and tolerability of LXH254 single agent and to identify recommended doses for future studies in adult patients with advanced solid tumors harboring MAPK pathway alterations.
To characterize the safety and tolerability of LXH254 in combination with PDR001 and identify a recommended dose and regimen for future studies in adult patients with advanced NSCLC harboring KRAS mutations.

Secondary:
To evaluate the preliminary anti-tumor activity of LXH254 single agent and LXH254 in combination with PDR001.
To evaluate the pharmacokinetic (PK) profile of LXH254 single agent and LXH254 in combination with PDR001.
To assess the pharmacodynamic (PD) effect of LXH254 single agent and LXH254 in combination with PDR001.
To assess emergence of anti-PDR001 antobodies following one or more intravenous (i.v.) infusions of PDR001.

Study design

Multicenter phase I open-label dose escalation and dose expansion study of LXH254.

The dose escalation part will be performed in adult patients with advanced solid tumors harboring documented MAPK pathway alterations. Primarily a once daily regimen will be tested. If needed a twice daily regimen will be investigated as well. Once the MTD/RP2D of LXH254 is achieved, the dose expansion part will commence with selected indications (melanoma, NSCLC and ovarian cancer). NSCLC patients may be treated with LXH254 in combination with PDR001. Rare MAPK pathway alterations are also planned to be investigated in the dose expansion phase.
For 12 patients the bioavailabiltiy of the LXH254 100mg and LXH254 200mg will be compared.
The study treatment will be administered as oral tablets in cycles of 28 days. Tablets will be taken in the fasting state. However in the dose expansion phase the effect of a high fat high calorie meal will be assessed in the first patients (n=12 evaluable patients) prior to the start of the treatment phase.

In case a food effect is observed, the effects of a low fat meal will also be investigated.
Treatment until disease progression or unacceptable side effects.
Follow-up for survival in the expansion cohort.
Dose escalation approx. 21 subjects.
Dose expansion approx. 50 (max. 171) subjects.

Intervention

Treatment with LXH254 or LXH254+PDR001

Study burden and risks

-Risk:
Adverse effects of LXH254. Especialliy occurrences of several cases of polyneuropathies (PNP) and similar
events occurring in a subset of patients after stopping or interrupting treatment with LXH254.
Adverse effects of PDR001: Risk of Stevens-Johnson Syndrome (SJS)which mandates stopping with PDR001
- First-in-human study with LXH254.
-Burden: Cycles of 4 weeks. Cycle 1 7 visits, cycle 2 4 visits, cycle 3-6 2 visits, from cycle 7 onwards 1 visit per cycle. Duration mostly 1-4 hours. Two visits during cycle 1 with a duration of 7-9 hours and 11-13 hours, respectively.
-Physical examination: once per cycle.
-Blood tests for safety (approx. 10-40 ml/occasion): nearly every visit.
Additional blood draws for PK, biomarkers.
-ECG: 4 times during cycle 1 (2 times multiple ECGs), 2 times during cycle 2 and once during cycles 3-6.
-Echocardiogram (or MUGA scan): 3 times in total.
-Ophthalmological examination: cycle 2, 3, 4 and final visit.
-2-3 tumor biopsies.
-CT-/MRI-scan: every 8 weeks.
-Optional storage and use of the remaining blood and tissue for future research.
- baseline neurological exam

Contacts

Public
Novartis Pharma BV

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Amsterdam 1101 BX

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Scientific
Novartis Pharma BV

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

** 18 years old.
*Progressed following standard therapy, or, in the opinion of the Investigator, no effective standard therapy exists, is tolerated or appropriate.
*Dose escalation part: Advanced solid tumors, harboring at least one MAPK pathway alteration (see protocol Table 5-1) when enrolled in cohorts testing LXH254 single agent or NSCLC patients and NRAS mutant melanoma patients with specific mutations in the MAPK pathways for cohorts testing LXH254 in combination with PDR001.
*Dose expansion part: other advanced solid tumors harboring documented MAPK pathway alteration (protocol Table 5-1). These include but are not limited to:
-Confirmed KRAS and/or BRAF-mutated NSCLC.
-Confirmed KRAS and/or BRAF-mutated ovarian cancer.
-BRAF V600-mutated melanoma patients who are refractory to or relapsed on prior BRAFi/MEKi combination therapy, NRAS-mutated melanoma
LXH254 in combination with PDR001: NSCLC patients with specific mutations in the MAPK pathway and patients with NRAS mutated melanoma
-NRAS- mutated solid tumors,
*ECOG performance status 0-1

Exclusion criteria

*Prior treatment with a BRAF, MEK and/or pan-RAF inhibitor in patients with confirmed KRAS and/or BRAF-mutated NSCLC and ovarian cancer in dose expansion part.
*Prior treatment with any of the following (see protocol page 37 for details incl. time frames): radiation, chemotherapy, cytotoxic agents with major delayed toxicities, major surgery, immunotherapy.
*History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO.
*Gilbert*s syndrome or other heritable diseases of bile processing.
*Clinically significant cardiac disease, see protocol page 38 for details.
*Out of range laboratory values. See protocol page 38-39 for details.
*Sexually active males unless they use a condom during intercourse.
*Pregnancy, lactation, insufficient contraception for females of childbearing potential.

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):	29-03-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	spartalizumab
Generic name:	nog niet bekend

Ethics review

Approved WMO Date:	21-12-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-01-2016
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-03-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-06-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	27-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	27-10-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-11-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	01-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-02-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	09-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-06-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

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Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-10-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-12-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-05-2018

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-08-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-09-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-10-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-11-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-05-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	18-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-06-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-07-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-11-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-12-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-03-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-03-2020
Application type:	Amendment

Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-05-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-06-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-07-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	18-08-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-09-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO	

Date:	23-10-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Application type:	Amendment
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Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
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Approved WMO Date:	15-12-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

(Rotterdam)

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	EUCTR2015-003421-33-NL
ClinicalTrials.gov	NCT02607813
CCMO	NL55506.078.15