A phase Ib/II, multicenter, open label, study of LEE011 in combination with MEK162 in adult patients with NRAS mutant melanoma

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Primary objective: Phase Ib (see study design): Maximum Tolerated Dose(s) and/or Recommended Phase II Dose (RP2D) of LEE011 and MEK162 in combination. Phase II (see study design): Assess the anti-tumor activity of the LEE011 and MEK162 combination...

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

Summary

ID

NL-OMON44775

Source
ToetsingOnline

Brief title
LEE011 with MEK162 in NRAS mutant melanoma (CMEK162X2114)

Condition

- Skin neoplasms malignant and unspecified

Synonym
malignant cutaneous melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Array Biopharma

Source(s) of monetary or material Support: Farmaceutische industrie Array Biopharma Inc.

Intervention

Keyword: LEE011, MEK162, NRAS melanoma

Outcome measures

Primary outcome

Phase Ib: Incidence of Dose Limiting Toxicities (DLT)

Phase II: Overall Response Rate (CR and PR) according to RECIST 1.1

Secondary outcome

Phase Ib: Plasma concentration-time profiles of LEE011 and MEK162, PK parameters

Phase II: Duration of response (DOR), Time to progression (TTP), Progression

Free Survival (PFS), Overall Survival (OS) and Best Overall

Response (BOR) according to RECIST 1.1

Both phase Ib and phase II: Incidence and severity of adverse drug reactions

and serious adverse drug reactions. Changes in hematology and chemistry values,

vital signs, ECGs, and dose interruptions, dose reduction and dose intensity.

Study description

Background summary

There are no established therapies for patients with NRAS mutant melanoma and their prognosis is poor. Targeting the RAS/RAF/MEK/ERK pathway and the CCND1/CDK pathway may be an effective strategy for treatment. MEK inhibitors can potentially block signal transduction that results from either mutations or activation through cell surface receptors. In a mouse model of NRAS-mutant melanoma, pharmacological MEK inhibition activated apoptosis but failed to trigger cell cycle arrest. This is in contrast to complete mutant NRAS

extinction by genetic means, which induced both apoptosis and cell cycle arrest. Microarray data demonstrated that the lack of cell cycle arrest with MEK inhibition centered on a CDK4-Rb axis. Accordingly, the combined pharmacological inhibition of MEK and CDK4 in vivo led to apoptosis, cell cycle arrest and tumor regression. Simultaneous, inhibition of MEK and CDK4/6 could ensure complete inhibition of activated pathways and lead to enhanced anti-tumor activity.
In clinical studies, MEK162 has demonstrated single agent anti-tumor activity in patients with NRAS cutaneous melanoma. So far 31 patients with NRAS mutant status were evaluable for efficacy. 7 patients (23%) had a partial response, 13 patients had stable disease (42%), and the disease control rate was 63%. The median PFS was 3.65 months.
LEE011 is a highly selective inhibitor of CDK4/6 which has shown in vitro and in vivo activity in models of NRAS melanoma both as single agent and in combination with MEK162. The combination of LEE011 and MEK162 has the potential to be effective in patients with NRAS mutant melanoma. The purpose of this study is to evaluate the safety of the combination of these agents, evaluate ORR and PFS in comparison to the single agent activity of MEK162 in the ongoing studies in the same patient population.

Study objective

Primary objective: Phase Ib (see study design): Maximum Tolerated Dose(s) and/or Recommended Phase II Dose (RP2D) of LEE011 and MEK162 in combination. Phase II (see study design): Assess the anti-tumor activity of the LEE011 and MEK162 combination at the RP2D.

Secondary objective: Phase Ib: safety and tolerability, PK. Phase II: safety, tolerability, clinical efficacy.

Study design

Open-label two part study with a phase Ib dose escalation part (fixed dose of MEK162 and increasing dose of LEE011), followed by a phase II part at the RP2D.
Approximately 58 patients.
Pre-Screening for NRAS mutation.
Cohorts of 3-6 patients. Cycle of 4 weeks.
Treatment until progression or unacceptable toxicity.
Follow-up for survival.

Intervention

Treatment with MEK162 and LEE011
LEE011 capsules, once daily first 3 weeks of each cycle and one week no intake.
Starting dose: 200mg

MEK162 tablets, twice daily , every day. Starting dose: 45mg

Study burden and risks

Risk: Adverse events of study medication (LEE011 and MEK162). This combination has not been tested in humans before.

The main side effects of MEK162 (single agent) sofar are:
* Rash, acne or skin irritation including redness, raised bumps, dryness or itching
* Diarrhea
* Swelling due to fluid retention or a worsening of pre-existing fluid retention in specific areas of the body. This can occur throughout your body or in specific areas such as your abdomen or arms, legs, hands, feet or face.
* Increase in a lab test called creatine phosphokinase (an enzyme found in the blood that may indicate muscle inflammation or damage)
* Increase in lab test results that check how well the liver is working
* Feeling weak, tired or lacking in energy
* Nausea

* *Eye disorders, which may include
o Changes in vision (such as blurred vision) or
o Seeing *floaters* or
o Alteration of the light sensing part of the back of the eye or
o Dry eye or
o Increased pressure in the eye
* Itching
* Vomiting

The main side effects of LEE011 (single agent) so far are:
* Low white blood cell count which increases risk of infections (neutropenia, leukopenia or lymphopenia)
* Low red blood cell count which can lead to tiredness and weakness (anemia)
* Nausea
* Diarrhea
* Vomiting
* Constipation
* Mouth sore, or pain inflammation and/or infection of the mouth and throat
* Abdominal pain
* Tiredness or generalized weakness (fatigue or asthenia)
* Swelling of the arms or legs (peripheral oedema)
* Fever (pyrexia)
* Urinary tract infection
* Increase in the blood levels of liver parameters as indicated by liver tests (transaminases and/or bilirubin)
* Decreased appetite
* Back pain

* Headache
* Sleeplessness (insomnia)
* Shortness of breath (dyspnea)
* Hair thinning or loss (alopecia)
* Skin rash
* Itching of the skin (pruritus)

The risks related to some study assessments as taking blood and imaging as MUGA-scans and CT-scans.

Burden:
6 visits during course 1, 3 during course 2 and 2 during the subsequent courses. Visit duration 1-4 h.
4 times blood sampling during course 1, 2 during course 2 and once during the subsequent courses. 15 mL blood/occasion.
Additional PK: phase Ib: 2 sessions of 8 hours (6 samples, 2,5 mL each); phase II 2 sessions of 4 hours (4 samples).
4 times ECG during course 1, 2 during course 2 and once during the subsequent courses. Echocardiogram or MUGA-scan at screening and every 2nd cycle.
Ophthalmic evaluation (slit lamp, visual acuity, visual field testing, intra ocular pressure, OCT, fundoscopy and if indicated fluorescein angiography and/or electroretinogram)
Tumor evaluations at screening and every 2nd cycle thereafter until disease progression.
Tumor biopsy at screening and during treatment (phase II).
Follow-up for survival (phone call every 3 months).

Contacts

Public
Array Biopharma

Walnut Street, 3200
Boulder CO 80301
US
Scientific
Array Biopharma

Walnut Street, 3200
Boulder CO 80301
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Histologically or cytologically confirmed diagnosis of locally advanced or metastatic NRAS mutant melanoma (written documentation)
2. ECOG performance status of 0 * 1.
3. Phase Ib: evaluable disease only is allowed. For phase II expansion at least one measurable lesion as defined by RECIST 1.1.
4. Archival of fresh tumor biopsy specimen (if no archival tumor) for all patients.
5. A tumor biopsy at time of study entry and on day C1D15 in the phase II part of the study.
6. A sufficient interval must have elapsed between the last dose of prior anti-cancer therapy and the first dose of study drugs:
* > 2 weeks for systemic antineoplastic therapy or any experimental therapy
* > 6 weeks for nitrosoureas and mitomycin-C).
* * 4 weeks for biologic therapy (e.g., antibodies)
7. Laboratory values:
a. Absolute Neutrophil Count (ANC) * 1.5 x 109/L.
b. Hemoglobin (Hgb) * 9 g/dL (5,58 mmol/L)
c. Platelets * 75 x 109/L without tranfusions within 21 days before 1st treatment.
d. PT/INR and aPTT * 1.5 ULN
e. Serum creatinine *1.5 ULN.
f. Serum total bilirubin * 1.5 x upper limit of normal (ULN).
g. AST and ALT * 3 x ULN, except in patients with tumor involvement of the liver who must have AST and ALT * 5 x ULN.
8. A negative serum pregnancy test * 72 hours before starting study treatment

Exclusion criteria

1. Presence of any brain metastases detected by MRI or CT of the brain at screening.
2. Uncontrolled arterial hypertension despite medical treatment

3. Impairment of gastro-intestinal (GI) function or GI disease that may significantly alter the absorption of LEE011 or MEK162.
4. Impaired cardiac function or clinically significant cardiac diseases, including any of the following:
* Left ventricular ejection fraction (LVEF) * 50%
* Congenital long QT syndrome or family history of unexpected sudden cardiac death,
* QTcF or QTcB >450 ms for males and >470 ms for females at screening,
* Angina pectoris or acute myocardial infarction * 3 months prior to starting study drug, clinically significant bradycardia, history or presence of ventricular tachyarrhytmia, unstable atrial fibrillation, complete left bundle branch block, obligate use of pacemaker or implantable cardioverter defibrillator
5. Treatment with agents that are known to cause QTc prolongation.
6. Treatment with agents that are metabolized predominantly through CYP3A4 and that have a narrow therapeutic window. Agents that are known strong inducers or inhibitors CYP3A4 are prohibited. Enzyme inducing anti-epileptic drugs are not permitted.
7. Patients with concurrent severe and/or uncontrolled concurrent medical conditions
8. Major surgery <2 weeks before starting study treatment.
9. Known diagnosis of human immunodeficiency virus (HIV) or hepatitis C
10. Current evidence of retinal disease; history of CSR, RVO or ophthalmology as assessed by ophthalmologic examination at baseline that would be considered a risk factor for CSR/RVO.
11. Pregnant or nursing (lactating) women.

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):	25-07-2013
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Niet van toepassing
Generic name:	binimetinib
Product type:	Medicine
Brand name:	Niet van toepassing
Generic name:	Niet van toepassing

Ethics review

Approved WMO Date:	08-03-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-07-2013
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-04-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-06-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	17-10-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-11-2014
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-02-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-03-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-04-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-06-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	24-07-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	04-08-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-02-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	27-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-06-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-08-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	17-08-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-11-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-12-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-01-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-06-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-11-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-12-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2012-004104-35-NL
ClinicalTrials.gov	NCT01781572
CCMO	NL43662.091.13