A phase II, multi-center, open-label study of sequential LGX818/MEK162 combination followed by a rational combination with targeted agents after progression, to overcome resistance in adult patients with locally advanced or metastatic BRAF V600 melanoma

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To assess the anti-tumor activity of LGX818/MEK162 in combination with third targeted agents after progression on LGX818/MEK162 combination therapy.

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

Summary

ID

NL-OMON45032

Source
ToetsingOnline

Brief title
LOGIC-2

Condition

- Skin neoplasms malignant and unspecified
- Skin neoplasms malignant and unspecified

Synonym
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: BRAFV600, LOGIC-2, Melanoma

Outcome measures

Primary outcome

Overall response rate (ORR) of LGX818/MEK162 in combination with third targeted

agents after progression on LGX818/MEK162 combination therapy.

Secondary outcome

Incidence of Dose Limiting Toxicities (DLTs) in Cycle 1 of Combination Part

(Part II)

Adverse Events (AEs), serious AEs (SAEs), changes in hematology and chemistry

values, vital signs, electrocardiograms (ECGs), dose interruptions, reductions

and dose intensity.

Study description

Background summary

Melanoma is one of the most aggressive human malignancies. Its incidence has rapidly increased throughout the world in the last few decades faster than that of all solid tumors. Although the majority of early stage patients can be treated with surgical resection, and have excellent survival rates, many will develop disseminated disease. The prognosis for patients with distant

metastasis is, by contrast, very poor.

Currently, the existing therapeutic options for patients with melanoma comprise of 6 FDA approved therapies: dacarbazine (DTIC), interleukin-2 (IL-2), ipilimumab (anti-CTLA-4) ,vemurafenib and dabrafenib (BRAF inhibitors) as well as trametinib (MEK inhibitor).

In addition to approved therapies, the concept of a simultaneous, dual, vertical pathway inhibition of the RAF/MEK/ERK pathway to prevent the emergence of resistance to single agent is currently being explored by the combination treatment of a selective BRAF- and a MEK1/2-inhibitor.

Despite the demonstrated clinical efficacy of BRAF and MEK inhibitors, in most cases tumors become resistant to treatment.

activation of survival pathways have also been demonstrated to confer resistance to BRAF inhibitors, and by extension are likely to promote resistance to combinations of BRAF and MEK inhibitors as well. It is important of identifying mechanisms of resistance in real time in order to initiate rational combination therapy soon after progression. By comparing the set of genetic alterations present in a progressing tumor at the time of relapse to the alterations present in the tumor prior to treatment, it should be possible to identify the likely molecular mechanisms underlying resistance. This comparison could then be used to direct the selection of a drug combination therapy for an individual patient that is most likely to overcome resistance.

In this CLGX818X2109 study, a rational combination treatment approach informed by comparing the genetic profiles of relapsed and treatment naive tumors will be taken to expand and improve the therapeutic options for patients with BRAF-mutant advanced or metastatic melanoma

Study objective

To assess the anti-tumor activity of LGX818/MEK162 in combination with third targeted agents after progression on LGX818/MEK162 combination therapy.

Study design

multicenter, open-label, phase II

two parts:
Part I, patients naïve to selective BRAF and MEK inhibitors will be treated with the LGX818/MEK162 combination Based on the genetic assessment of a tumor biopsy obtained at progression of disease (PD), patients will enter Part II of the study for tailored combination treatment in one of four arms: LGX818/MEK162 + BKM120, BGJ398, INC280 or LEE011

New triple combination arms will be introduced in the study via substantial protocol amendment

During Part I, patients will be treated with LGX818/MEK162 at RP2D of the dual combination.
In Part II, dose escalation for the triple combination will occur unless a RP2D for the respective combination is already established.
Non-naïve patients for BRAF and/or MEK inhibitor treatment who are relapsing will be enrolled into Part II. Depending on the previous treatment, patients may receive a brief Run-in with LGX818/MEK162 combination.

Intervention

Part I : dual combination LGX818 (QD) and MEK162 (BID)

Part II: triple combination of MEK162 and LGX818 (see above) and logic third compound

• LGX818 (QD) and MEK162 (BID) and BKM120 (QD)
• LGX818 (QD) and MEK162 (BID) and BGJ398 (QD)
• LGX818 (QD) and MEK162 (BID) and INC280 (BID)
• LGX818 (QD) and MEK162 (BID) and LEE011 (QD)

Study burden and risks

Risks and burden are stronlgly depended on the group (Part I) en treatment arm (Part II) the patient will be treated in. Also the cycle number is relevant.
Below this has not been indicated specifically:

Risks: toxicities of the medication

BurdenL cycles of 21 days or 28 days, with 1,2,3,4 or 5 visites per cycle.
Blooddraws as specified in section J, inclusive PK sampling
ECGs
MUGA scan and CT scan (see section J)
Tumor biopsies
Ophthamological assessments
skintest

Contacts

Public
Array Biopharma

Walnut Street, 3200
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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. Age >= 18 years at the start of dosing
2. Histologically confirmed diagnosis of unresectable stage III or metastatic melanoma (stage IIIC to IV per American Joint Committee on Cancer [AJCC]).
3. Documented evidence of BRAF V600 mutation
4. Evidence of measurable disease, as determined by RECIST v1.1.
5. ECOG Performance Status <= 2.
6. Negative serum pregnancy test within 72 hours prior to the first dose of study treatment in all women of childbearing potential.
7. For Group A only: patients who are naïve to selective BRAF and MEK inhibitors and might have received other allowed treatments
8. For Group A only: Patients must provide either archival or newly obtained tumor sample at baseline. In addition, patients must agree to a mandatory biopsy at the time of progression from LGX818/MEK162 combination, if not medically contraindicated.
9. For Group B only: Patients with progressive disease following any single or double-agent BRAF and MEK inhibitors other than LGX818/MEK162
10. For Group B only: The most recent biopsy sample collected after progression from any BRAF and/or MEK inhibitor (other than LGX818 and MEK162 combination) must be available before entering the Run-in. In addition, patients must agree to a biopsy at the time of

progression from LGX818/MEK162 combination if necessary and not medically contraindicated.
11. For Group C only Progressive disease documented per RECIST v 1.1 and determined using radiological assessments, following prior treatment with LGX818/MEK162 combination.
12. For Group C only A pre-LGX818/MEK162 combination archival tumor sample must be available.
13. For Group C only A biopsy sample at disease progression, post-LGX818/MEK162 combination, must be either already available from previous studies or collectable at screening/baseline of this study..
14 Able to understand and voluntarily sign the informed consent form prior to any screening procedure, and ability to comply with the study visit schedule and other protocol requirements.
15. For Group B only: Patients who progressed after treatment with single agent BRAF or MEK inhibitor or the combination of BRAF/MEK inhibitors (excluding LGX818/MEK162 combination) and patients who did not progress on their prior BRAF and/or MEK inhibitor regimen (including LGX818 and/or MEK162 inhibitor), but did not tolerate this treatment, may enter the Run-in (Group B) upon consultation with Sponsor.

Exclusion criteria

Part I and Run-in
1. Symptomatic or untreated leptomeningeal disease.
2. Symptomatic brain metastasis.
3. Known acute or chronic pancreatitis.
4. History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO
5 Patients who have undergone any major surgery within the last 2 weeks prior to starting study drug or who would not have fully recovered from previous surgery.;PART II
Patients are NOT eligible for enrollment in Part II of this study if they meet any exclusion criteria listed above, and all the applicable additional exclusion criteria listed below.
1. Patients who discontinued LGX818/MEK162 for more than 6 weeks prior to the scheduled first dose of triple combination (Part II), and AEs related to the above treatment are not resolved to at least grade 2.;Additional Exclusion Criteria for Part II for selected triple combination may apply. Please refer to the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-02-2015
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BGJ398
Generic name:	BGJ398
Product type:	Medicine
Brand name:	binimetinib
Generic name:	binimetinib
Product type:	Medicine
Brand name:	BMK120
Generic name:	BMK120
Product type:	Medicine
Brand name:	encorafenib
Generic name:	encorafenib
Product type:	Medicine
Brand name:	INC280
Generic name:	INC280

Ethics review

Approved WMO

Date:	25-04-2014
Application type:	First submission
Review commission:	METC NedMec

Approved WMO

Date:	25-04-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	10-07-2014
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-07-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-09-2014
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-09-2014
Application type:	Amendment
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-10-2014
Application type:	Amendment
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Approved WMO Date:	24-10-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-01-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-01-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-02-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-02-2015
Application type:	Amendment

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Approved WMO Date:	19-02-2015
Application type:	Amendment
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-08-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-08-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-09-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-11-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-11-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	12-02-2016
Application type:	Amendment
Review commission:	METC NedMec
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-04-2016
Application type:	Amendment
Review commission:	METC NedMec
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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	07-07-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC NedMec
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
Review commission:	METC NedMec
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-02-2017
Application type:	Amendment
Review commission:	METC NedMec
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-02-2017
Application type:	Amendment
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-05-2017
Application type:	Amendment
Review commission:	METC NedMec
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Application type:	Amendment
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Approved WMO Date:	31-05-2017
Application type:	Amendment

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Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC NedMec
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Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
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Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-12-2017
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	EUCTR2013-004552-38-NL
CCMO	NL48488.031.14

Study results

Results posted: 07-09-2023

First publication
12-07-2023