

# A randomized, open-label, multi-arm, two-part, phase II study to assess the efficacy and safety of multiple LXH254 combinations in patients with previously treated unresectable or metastatic BRAFV600 or NRAS mutant melanoma

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Primary objective of this study: evaluate the efficacy of each combination arm, as measured by confirmed objective response rate (ORR) by local investigator's assessment per RECIST v1.1secondary objectives: - Safety & tolerability of each...

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

## Summary

### ID

NL-OMON55115

### Source

ToetsingOnline

### Brief title

CLXH254C12201

### Condition

- Skin neoplasms malignant and unspecified

### Synonym

BRAFV600 and NRAS mutant melanoma

### Research involving

Human

## Sponsors and support

**Primary sponsor:** Novartis

**Source(s) of monetary or material Support:** Farmaceutische industrie

## Intervention

**Keyword:** BRAFV600 mutation, Melanoma, NRAS mutation, Phase II

## Outcome measures

### Primary outcome

Objective response rate as determined by local assessment through (i)RECIST

v1.1

### Secondary outcome

Safety, tolerability, efficacy through duration of reponse, progression free

survival, disease control rate and overall survival.

## Study description

### Background summary

Optimal treatment for irresectable and/or metastatic BRAFV600 and NRAS mutant melanoma is unknown, the proposed combination of therapy (LXH453 backbone with two combination drugs) is hoped to overcome intrinsic and / or acquired resistance to previous therapy.

### Study objective

Primary objective of this study: evaluate the efficacy of each combination arm, as measured by confirmed objective response rate (ORR) by local investigator's assessment per RECIST v1.1

secondary objectives:

- Safety & tolerability of each combination arm through incidence and severity of AE's including changes in lab values, vital signs, cardiac assessments dose interruptions, reductions and permanent discontinuation.
- Evaluation of efficiency in each combination arm by duration of response,

progression free survival, and disease control rate using RECIST v1.1  
- evaluation of overall survival of each combination arm.

## **Study design**

A randomized open label multi-center two-part phase II study, assessing two combinations of therapy.

Part 1: selection part, part 2: expansion.

## **Intervention**

Three possible combination therapies:

LXH254, 400 mg BID in combination with LTT462, 200 mg QD

LXH254, 400 mg BID in combination with trametinib, 0.5 mg QD => updated in PAM5  
to: LXH254 200 mg BID in combination with trametinib 1 mg QD

LXH254, 400 mg BiD in combination with ribociclib 400 mg QD => discontinued as  
of PAM5

Cycles of 28 days, all current study drug administered orally and continuously.

## **Study burden and risks**

Risks and side-effects associated with the treatment provided.

Risks associated with the study assessments such as blooddraws, imaging and tumor biopsy.

Burdens: 4 week cycles. Cycle 1 and 2: 3 visits.

From Cycle 3 onward: 1 visit.

Duration of visits: usually 1-2 hours unless additional assessments  
(ECG/blooddraws) planned. Duration of a visit may extend from minimally 2 to  
max 6 hours.

Risks associated with assessments during visits, depending on combination  
therapy and type of visit: physical exam, blooddraws, ECG's /  
vital signs, imaging, pregnancy testing, tumor biopsy.

## **Contacts**

### **Public**

Novartis

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NL  
**Scientific**  
Novartis

Haaksbergweg 16  
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NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

### Inclusion criteria

Protocol language states : Male or female must be  $\geq 12$  years, in the Netherlands only adults 18 years or older will be included.

- Histologically confirmed unresectable or metastatic cutaneous melanoma
- Previously treated for unresectable or metastatic melanoma:
- Participants with NRAS mutation:
- Pts must have received prior systemic therapy for unresectable or metastatic melanoma with checkpoint inhibitors (CPIs) either an anti-PD-1/PD-L1 as a single agent or in combination with anti-CTLA-4, investigational agents, chemotherapy or locally directed anti-neoplastic agents.
- Prior CPI therapy in the unresectable or metastatic setting is not required for participants who have progressed on or within 6 months of adj. therapy with a CPI
- Prior therapy with T-VEC is allowed and will not be counted as a prior line of systematic therapy.
- A maximum of two prior lines of systemic CPI-containing immunotherapy for unresectable or metastatic melanoma are allowed. Additional agents administered with a CPI are permitted.
- Participants must have documented confirmed progressive disease as per iRecist v1.1 while on/after therapy with CPI. Confirmation is not required for

pts who remained on treatment > 6 months.

- Participants with BRAFV600 mutant disease:
  - Pts must have received prior systemic therapy for unresectable or metastatic melanoma with a checkpoint inhibitor (CPI) either an anti-PD-1/PD-L1 as single agent or in combination with anti-CTLA-4, investigational agents, chemotherapy or locally directed anti-neoplastic agents. Additionally, pts must have received targeted therapy with a RAFi as a single agent or in combination with a MEKi (+/- CPI allowed) as the last prior therapy.
  - Prior CPI therapy in the unresectable or metastatic setting is not required for participants who have progressed on or within 6 months of adjuvant CPI.
  - Prior therapy with T-VEC is allowed and will not be counted as a prior line of systemic therapy.
  - A maximum of two lines of CPI-containing systemic immunotherapy for unresectable or metastatic melanoma are allowed, additional agents with CPI are permitted.
  - A maximum of one line of targeted therapy is allowed, and it must be the most recent line of therapy.
  - If a participant discontinued targeted therapy for reasons other than disease progression, a switch to another targeted therapy regimen is allowed.
  - Pts must have documented progressive disease as per RECIST v1.1 while on/after treatment with targeted therapy.
- Other protocol-defined inclusion criteria may apply.

## Exclusion criteria

Treatment with any of the following anti-cancer therapies prior to the first dose of study treatment within the stated timeframes:

- \* ≤ 4 weeks for radiation therapy or ≤ 2 weeks for limited field radiation for palliation prior to the first dose of study treatment.
- \* ≤ 2 weeks for small molecule therapeutics.
- \* ≤ 4 weeks for any immunotherapy treatment including immune checkpoint inhibitors.
- \* ≤ 4 weeks for chemotherapy agents, locally directed anti-neoplastic agents or other investigational agents.
- \* ≤ 6 weeks for cytotoxic agents with major delayed toxicities, such as nitrosourea and mitomycin C.
- Participants participating in additional parallel investigational drug or medical device studies.
- All primary central nervous system (CNS) tumors or symptomatic CNS metastases that are neurologically unstable,
- History or current evidence of retinal vein occlusion (RVO) or current risk factors for RVO (e.g. uncontrolled glaucoma or ocular hypertension, history of hyperviscosity or hypercoagulability syndromes).
- Patients receiving proton pump inhibitors (PPI) which cannot be discontinued

3 days prior to the start study treatment and for the duration of the study.  
- Any medical condition that would, in the investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns or compliance with clinical study procedures.  
-Other protocol-defined inclusion/exclusion criteria may apply

## 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):	06-04-2021
Enrollment:	18
Type:	Actual

### Medical products/devices used

Product type:	Medicine
Brand name:	Kisqali
Generic name:	Ribociclib
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Mekinist
Generic name:	Trametinib
Registration:	Yes - NL outside intended use

## Ethics review

Approved WMO

Date: 28-09-2020

Application type: First submission

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 23-11-2020

Application type: First submission

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 01-12-2020

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 20-01-2021

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 29-03-2021

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 28-05-2021

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 17-06-2021

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	19-07-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	13-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	20-10-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	02-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	23-02-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	10-06-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	10-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO	
Date:	28-12-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek



(Assen)

Approved WMO

Date: 20-01-2023

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 04-03-2023

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 14-09-2023

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date: 13-10-2023

Application type: Amendment

Review commission: BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

## 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**

EudraCT

**ID**

EUCTR2020-000873-26-NL

**Register**

ClinicalTrials.gov

CCMO

**ID**

NCT04417621

NL74783.056.20