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

Published: 28-09-2020
Last updated: 08-04-2024

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...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Skin neoplasms malignant and unspecified
Study type	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 icnluding changes in lab values, vital signs, cardic assessments dose interuptions, reductions and permanent discontinuation.
- Evaluation of efficiacy 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 adiministered orally and continously.

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 additinol assessments (ECG/blooddraws) planned. Duration of a visit may extend from minimally 2 to max 6 ours.

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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Scientific
Novartis

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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 >= 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 fo runresectable or metasttic melanoma with checkpoint inhibitors (CPIs) either an anti-PD-1/PD-L1 as as 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.
- Particitpants must have documented confirmed progressive dissease 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 metatstic 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. additionall pts must have receied 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 progresssed 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 therapy systemic immunotherapy for unresectable or metatstatic 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 neitrosourea 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	ID
EudraCT	EUCTR2020-000873-26-NL

Register	ID
ClinicalTrials.gov	NCT04417621
CCMO	NL74783.056.20