The NEMO trial (NRAS melanoma and MEK inhibitor): A randomized Phase III, open label, multicenter, two-arm study comparing the efficacy of MEK162 versus dacarbazine in patients with advanced unresectable or metastatic NRAS mutation-positive melanoma

Published: 12-03-2013
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To determine whether treatment with MEK162 prolongs PFS as compared to dacarbazine in patients with previously untreated, advanced unresectable, or metastatic NRAS mutation-positive melanoma who are previously untreated or who have progressed on or...

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

Summary

ID

NL-OMON47339

Source
ToetsingOnline

Brief title
NEMO: NRAS melanoma and MEK inhibitor

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Array Biopharma
Source(s) of monetary or material Support: Array BioPharma Inc

Intervention

Keyword: DTIC, MEK inhibitor, Melanoma, NRAS

Outcome measures

Primary outcome

PFS, defined as the time from the date of randomization to the date of the

first documented disease progression or death due to any cause, whichever

occurs first. PFS will be determined based on tumor assessment (RECIST V1.1

criteria) as per BIRC and survival information.

The local Investigator*s assessments will be used as supportive analyses.

Secondary outcome

OS, calculated as the time from date of randomization to date of death due to

any cause

Study description

Background summary

Cutaneous melanoma is the most aggressive skin cancer. Although it accounts for only 4 percent of all dermatologic cancers, it is responsible for 80 percent of skin cancer deaths. The median age at diagnosis is 57 years, and up to 75% of patients are younger than 70 years.

dacarbazine is considered the standard of care for most patients with unresectable advanced or metastatic melanoma. However, the response rate with dacarbazine is modest (7-15%), these responses are short-lived (e.g. median

duration of response of 6 months) and there is no associated increase in survival.

Recently ipilimumab has obtained the FDA approval for the treatment of unresectable or metastatic melanoma and the EMA approval for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

There are no targeted therapies approved specifically for the treatment of the subset of patients with NRAS mutated melanoma (15-20% of melanoma). NRAS activating mutations result in an aberrant downstream signaling, leading to malignant transformation and tumor progression.
To date, MEK162 is the only MEK inhibitor of which the antitumor activity has prospectively been assessed in patients with NRAS mutant advanced cutaneous melanoma

Study objective

To determine whether treatment with MEK162 prolongs PFS as compared to dacarbazine in patients with previously untreated, advanced unresectable, or metastatic NRAS mutation-positive melanoma who are previously untreated or who have progressed on or after prior first-line immunotherapy for metastatic disease.

To compare Overall Survival (OS) between treatment arms

Study design

This is a two-arm, randomized, prospective, open-label, multi-center, phase III study to compare the efficacy and safety of MEK162 (45 mg BID) versus dacarbazine (1000 mg/m2 IV every 3 weeks) in patients with, advanced unresectable or metastatic NRAS mutation-positive melanoma as confirmed by central assessment.

A total of 393 patients will be randomized 2:1 to MEK162 or dacarbazine and stratified according to AJCC stage ,ECOG Performance status and previously treated or not

Intervention

MEK162 tablets of 15mg, Orally, continuous, daily
Startdose: 45mg / BID

or DTIC, 1000mg/m2 once every 3 weeks

Study burden and risks

Possible side effects of MEk162 are:
* skin irritation (acne-like rash or redness which may be itchy)
* diarrhea
* headache
* abdominal pain
* nausea (with or without vomiting)
* eye disorders with may include mild to moderate changes in vision, 'floaters" or swelling in and around the eye
* increases in the blood levels of proteins (called creatinine kinase proteins)
* heartburn of indigestion
* mucositis (sores in the mouth or throat)
* edema (swelling or puffiness of parts of the body)
* loss of appetite
* muscle ache

Other risks:
Taking blood and tumorbiopsies may cause pain, bleeding, and/or bruising.
Patients will be exposed to radiation (CT-scan, MUGA-scan and/or X-rays). The radiation exposure will not exceed the maximum ranges that are set within the Netherlands.
Allergic reaction on contrast used for CT-scan.

Possible toxicities due to Dacarbazine

Contacts

Public
Array Biopharma

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Cambridge. MA 02140
US
Scientific
Array Biopharma

Cambridge park Drive 100
Cambridge. MA 02140
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1 Male or female patients, age * 18 years
2 Histologically confirmed diagnosis of locally advanced, unresectable or metastatic cutaneous or unknown primary melanoma AJCC Stage IIIC or IV (Uveal and mucosal melanoma are excluded)
3 Presence of NRAS Q61 mutation in tumor tissue prior to randomization, as determined by a central laboratory
4 Naïve untreated patients or patients who have progressed on or after prior treatment with any number of lines of immunotherapy for unresectable or metastatic melanoma;
5 Evidence of at least one measurable lesion as documented by radiological or photographic methods according to RECIST (version 1.1)
6 ECOG performance status of 0-1
7 Adequate bone marrow and organ function and laboratory parameters:
* ANC * 1.5 x 109/L
* Hemoglobin (Hgb) * 9 g/dL without transfusions
* Platelets (PLT) * 100 x 109/L without transfusions
* AST and/or ALT * 2.5 × upper limit of normal (ULN); patients with liver metastases * 5 ×ULN
* Total bilirubin * 2 × ULN
* Creatinine * 1.5 mg/dL
8 Adequate cardiac function:
* left ventricular ejection fraction (LVEF) * 50% as determined by a multigated acquisition (MUGA) scan or echocardiogram
* QTc interval * 480 ms
9 Negative serum * HCG test (female patients of childbearing potential only) performed locally within 72 hrs prior to first dose

Exclusion criteria

1 Any active central nervous system (CNS) lesion (i.e., those with radiographically unstable, symptomatic lesions). However, patients treated with radiotherapy or surgery are eligible if the patient remained without evidence of CNS disease progression * 3 months. Patients must be off corticosteroid therapy for * 3 weeks.

2 Uveal or mucosal melanoma
3 History of leptomeningeal metastases
4 History or current evidence of central serous retinopathy (CSR) or retinal vein occlusion (RVO) or predisposing factors to RVO or CSR
5 History of allogeneic bone marrow transplantation or organ transplantation
6 History of Gilbert*s syndrome
7 Previous or concurrent malignancy with the following exceptions:
* adequately treated basal cell or squamous cell carcinoma
* in situ carcinoma of the cervix, treated curatively and without evidence of recurrence for at least 3 years prior to the study
* a primary malignancy which has been completely resected and in complete remission for *5 years
8 Prior therapy with a MEK inhibitor
9 Patients with washout period < 12 weeks from the last dose of ipilimumab or other immunotherapy;
10 Impaired cardiovascular function or clinically significant cardiovascular diseases
11 Uncontrolled arterial hypertension, despite medicial treatment
12 Known positive serology for HIV, active Hepatitis B, and/or active Hepatitis C infection
13 Patients who have neuromuscular disorders that are associated with elevated CK
14 Impairment of gastrointestinal function or gastrointestinal disease
15 Pregnant or nursing (lactating) women
16 Women of child-bearing potential, unless they are using highly effective methods of contraception during dosing and for 8 weeks after stopping study treatment.
17 Sexually active males, unless they use a condom during intercourse while taking drug and for 8 weeks after stopping study medication.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-03-2019
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	DTIC
Generic name:	Dacarbazine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	MEK162
Generic name:	binimetinib

Ethics review

Approved WMO Date:	12-03-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-05-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	23-07-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-10-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	25-11-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-12-2013
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-05-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	20-05-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	14-11-2014
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-11-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	09-12-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	24-12-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	16-06-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	26-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	31-05-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	21-11-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	14-12-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	28-05-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	14-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van

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	EUCTR2012-003593-51-NL
ClinicalTrials.gov	NCT01763164
CCMO	NL42858.031.13

Study results

Results posted: 27-03-2020

First publication
29-01-2020