A Phase II, open-label study to assess the safety and efficacy of oral MEK162 in adults with locally advanced and unresectable or metastatic malignant cutaneous melanoma, harboring BRAFV600 or NRAS mutations

Published: 01-02-2011
Last updated: 27-04-2024

To find out if MEK162 is safe and what effects (good of bad) it has on the patient.. To understand what MEK162 does in the patient and assess what the patient does to clear the studymedication from the system. And last but not least to find out what...

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

Summary

ID

NL-OMON47322

Source
ToetsingOnline

Brief title
Phase II study of MEK162 for melanoma harboring BRAFV600 of NRAS mutations

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: Array BioPharma Inc.

Intervention

Keyword: BRAFV600 gene, malignant melanoma, MEK162, NRAS gene

Outcome measures

Primary outcome

To estimate the objective response rate (ORRs) of MEK162 in adult patients with advanced, unresectable, cutaneous malignant melanoma, i) harboring BARFV600 of ii) harboring NRAS mutations

Secondary outcome

* To assess the effect of oral MEK162 on time-related efficacy parameters (progression free survival (PFS) and duration of response)

* To characterize the safety and tolerability of oral MEK162

* To assess the effect of MEK162 on MEK/MAPK signaling, (PD changes of molecular status of ERK, DUSP6, MEK) in pre- vs. post-dose tumor biopsies

* To characterize the baseline status of molecules relevant to MEK/MAPK signaling (PTEN, p53) in tumor tissue and potential correlation with clinical outcomes

* To measure plasma concentrations of MEK162 and the pharmacologically active metabolite, AR00426032

Study description

Background summary

Cutaneous malignant melanoma is a highly invasive form of skin cancer. The incidence of malignant melanoma is rapidly increasing throughout the world. Clinical outcome is dependent on the extent of disease at diagnosis with excellent survival rates (approximately 90% at 5 years) described for patients with stage I disease. By contrast, very poor survival rates (ranging from 6.7% to 18% at 5 years) with median survival of 6 to 9 months are reported for those patients with metastatic (stage IV) disease. The poor survival of patients with metastatic melanoma appears to result from the disease*s chemoinsensitivity. Recent advances in the understanding of the genetic basis of melanoma have motivated the development of new therapies for this disease. Previous studies implicated mutations in NRAS in the pathogenesis of melanoma. More recently, activating somatic mutations in the BRAF gene have been observed in a wide variety of human tumors, most notably melanoma. Somatic mutations in BRAF have been detected in approximately two-thirds of melanoma tumors and cell lines. BRAF is a member of the Ras/Raf/MEK/ERK pathway. This pathway plays a prominent role in controlling several key cellular functions including growth, proliferation, and survival. These findings suggest that inhibition of the Ras/Raf/MEK/ERK pathway would have therapeutic benefit in melanoma patients. Specifically, the high frequency of BRAF (V600E) mutations in patients with melanoma has led to the development of new drugs targeting this mutant BRAF protein. Mek162 is a novel, orally active molecule with potent inhibitory activity against mutant BRAF and NRAS kinase and additional anti-angiogenic activity through inhibition of vascular endothelial growth factor receptor type 2 (VEGFR-2).

MEK162 is an experimental drug that could be an alternative for patients with advanced melanoma, whose tumors have a mutation of the NRAS or BRAF gene and who do not repond to the current therapy or for who no standard therapy exists.It is expected that because of the selective profile less toxicity could occur.

Study objective

To find out if MEK162 is safe and what effects (good of bad) it has on the patient.. To understand what MEK162 does in the patient and assess what the patient does to clear the studymedication from the system. And last but not least to find out what effects MEK162 is having on the cancer.

Study design

This is a multi-center, open-label, 2-arm, Phase II study to determine the

anti-tumor efficacy of oral MEK162 in adults with advanced BRAFV600E / NRAS mutated cutaneous malignant melanoma. Patients will be assigned according to their mutation status at baseline:
Arm 1: BRAFV600 (n=28) MEK162 45 mg BID
Arm 2: NRAS (n= 96) MEK162 45mg BID
Arm 3: BRAFV600 (n=28) MEK162 60 mg BID

Intervention

MEK162 tablets 15mg
Orally, daily, continue
Startdosis: 45mg / twice daily or 60 mg / twice daily, depending on the arm

Study burden and risks

Possible side effects of MEk162 are:
Most likely side effects (greater than 20% incidence) are:
• Rash, acne or skin irritation including redness, raised bumps, dryness or itching
• 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, arms, legs, hands, feet, face or eyes.
• Alteration of the light sensing part of the back of the eye that may effect your vision
• Feeling weak, tired, or lacking in energy

Less likely side effects (greater than 10% up to 20% incidence):
• Blurred or impaired vision
• Fever
• High blood pressure
• Increase in lab test results that check how well the liver is working
• Muscle spasms, muscle pain or inflammation
• Stomach pain

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.

Contacts

Public
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US
Scientific
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Cambridge park drive 100
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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 or metastatic cutaneous melanoma AJCC Stage IIIB to IV, not potentially curable with surgery
3. Must have documented presence of somatic BRAFV600 or NRAS mutation in tumor tissue
4. All patients enrolled should provide sufficient fresh or archival tumor sample at baseline to enable central confirmation of BRAF or NRAS mutations and the additional analyses described in the protocol
5. Evidence of measurable tumor disease as per RECIST
6. WHO performance status of 0-2
7. Adequate organ function and laboratory parameters:
•ANC >= 1.5 x 109/L
•Hemoglobin (Hgb) >= 10 g/dL
•Platelets (PLT) >= 75 x 109/L
•AST and/or ALT <= 2.5 × upper limit of normal (ULN); patients with liver metastases <= 5 ×ULN

•Bilirubin <= 2 × ULN
•Calculated or directly measured creatinine clearance >= 60 mL/min/1.73m2
8. LVEF >= 50% as determined by MUGA scan or TTE

Exclusion criteria

1. History or current evidence of central serous retinopathy (CSR), retinal vein occlusion (RVO) or ophthalmopathy visible at screening that would be considered a risk factor for CSR or RVO
2. Patients with symptomatic CNS metastasis.
3. Prior therapy with a MEK- inhibitor
4. Impaired cardiovascular function or clinically significant cardiovascular diseases, including any of the following:
• History/evidence of acute coronary syndromes (including MI, unstable angina, CABG, coronary angioplasty, or stenting) <6 months prior to screening
• Symptomatic CHF, history or current evidence of clinically significant cardiac arrhythmia and/or conduction abnormality
• Uncontrolled arterial hypertension, defined as BP > 140/100 mmHg
5. Known positive serology for HIV, active Hepatitis B, and/or active Hepatitis C infection
6. Any other condition that would, in the Investigator*s judgment, contraindicate patient*s participation in the clinical study due to safety concerns or compliance with clinical study procedures , e.g., infection/inflammation, intestinal obstruction, unable to swallow medication, social/ psychological issues, etc.
7. Patients who have received prior systemic anti-cancer treatment within the following time frames:
•Patients who have received cyclical chemotherapy within a period of time that is shorter than the cycle length used for that treatment (e.g., 6 weeks for nitrosourea, mitomycin-C) prior to starting study drugs
•Patients who have received biologic therapy (e.g., antibodies) within 4 weeks prior to starting study drug
•Patients who have been treated with continuous or intermittent small molecule therapeutics within <= 5 t1/2 of the agent, or <= 4 weeks prior to starting study drug where half life is unknown
•Patients who have received any other investigational agents within a period of time that is less than the cycle length used for that treatment or <= 4 weeks (whichever is shorter) prior to starting study drugs
•Treatment with prior radiotherapy within 28 days of the first dose of study drug; however, if the radiation portal covered <= 10% of the bone marrow reserve, the patient may be enrolled irrespective of the end date of radiotherapy
8.Patients who have undergone major surgery <= 4 weeks prior to starting study drug or who have not recovered from side effects of such procedure
9.Pregnant or nursing (lactating) women.
10.Women may not become pregnant. Reliable contraception should be maintained throughout the study and for 3 months after study drug discontinuation

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):	30-03-2011
Enrollment:	31
Type:	Actual

Ethics review

Approved WMO Date:	01-02-2011
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-03-2011
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	10-10-2011
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	25-10-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-12-2011
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-05-2012
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-09-2012
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-12-2012
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-03-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	06-05-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	10-06-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-06-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-08-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-09-2014
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-10-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-12-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-02-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-02-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	10-05-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-05-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	14-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-05-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-05-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO	

Date:	09-04-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-08-2022
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2010-023412-13-NL
ClinicalTrials.gov	NCT01320085
CCMO	NL35299.031.11