A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Pembrolizumab (MK-3475) in Combination With Epacadostat or Placebo in Subjects with Unresectable or Metastatic Melanoma (KEYNOTE-252 / ECHO-301).

Published: 11-04-2016
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The objective of this study is to test the safety, tolerability and anti-tumor activity of the combination of the investigational products epacadostat and pembrolizumab, compared to pembrolizumab as mono therapy, in patients with unresectable or...

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

Summary

ID

NL-OMON45831

Source
ToetsingOnline

Brief title
MK3475-252

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Incyte Corporation
Source(s) of monetary or material Support: Incyte Corporation,industrie,Merck

Intervention

Keyword: epacadostat, melanoma, pembrolizumab

Outcome measures

Primary outcome

The dual primary endpoints are PFS and OS.

* Progression-free survival, defined as the time from date of randomization

until the

earliest date of disease progression, as determined by independent central

review of

objective radiographic disease assessments per RECIST 1.1, or death from any

cause,

whichever comes first.

* Overall survival, defined as the time from date of randomization to date of

death due to

any cause.

The study is considered to have met its study objective if the combination is

superior to

pembrolizumab and placebo in either PFS or OS.

Secondary outcome

Objective response rate, defined as the proportion of subjects who have best

response as

complete response (CR) or partial response (PR). Responses are based on

independent

central review using RECIST 1.1.

Duration of response (DOR) determined by disease assessment defined as the time

from

the earliest date of qualifying response until earliest date of disease

progression or death

from any cause, whichever comes first. Response will be determined by

independent

central review using RECIST 1.1.

Study description

Background summary

Melanoma is the most serious form of skin cancer and exists in adults of all ages. In the EU alone, 41000 new cases are diagnosed every year and yearly, approximately 11000 patients within the EU die from the disease. Average 5-year survival for advanced melanoma is a mere 15% and therefore an important medical need exists to identify new, effective treatments. Surgical excision with a wide margin is the standard of care for early-stage melanoma, and most patients with in situ melanoma or early-stage melanoma will be cured by primary excision alone. Metastatic melanoma, however, is very unlikely to be curable wby surgery because of the likelihood of micrometastases too small to be found by CT, MRI or PET imaging. Therefore, an adjuvant treatment is indicated. Radiation therapy plays a role in the treatment strategy, in particular after resection of primary melanomas that are associated with a high rate of local recurrence, and in patients with positive excision margins. Secondly, blockade of immuno-inhibitory pathways are currently in focus as important therapeutic strategy for cancer treatment. Proof of this is observed in the clinical response to therapy with antibodies targeted against CTLA-4 and PD-1/PD-L1. Pembrolizumab is a potent and highly selective monoclonal antibody that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

Even though these agents show anti-tumor activity in a monotherapeutic setting, there are more immuno-inhibitory mechanisms present in the tumor microclimate. This suggests that combination therapies might have a more optimal therapeutic effect. Recent research has focused on the role of indoleamine 2,3-dioxygenase (IDO1) as a mechanism inducing tolerance to the malignity. IDO1 activity results in a strong inhibition of the T-cell mediated immune respons by blocking T-cell activation and inducing T-cell apoptosis. Additionally, IDO1 activity induces the differentiation of naive T-cells to cells with a regulatory phenotype (Treg). Studies showed that an elevated Treg activity promotes tumor growth. In reverse, Treg depletion showed to induce an antitumor immune response. Within the context of cancer, there are a number of indications that IDO1 is an important regulator of immunosuppressive mechanisms at the basis of the evasion of the immune response by tumors. It is expected that combined inhibition of the IDO1 and the PD-1 pathway will have a complimentary therapeutic effect and will lead to a greater suppression of antitumor immunity.

Study objective

The objective of this study is to test the safety, tolerability and anti-tumor activity of the combination of the investigational products epacadostat and pembrolizumab, compared to pembrolizumab as mono therapy, in patients with unresectable or metastatic melanoma.

Study design

This is a randomised, double blind, placebo controlled phase 3 trial of pembrolizumab in combination with epacadostat or placebo.

Intervention

Both treatment groups will receive pembrolizumab (200 mg per IV over 30 mins), on day 1 of every 3-week treatment cycle.
Additionally, patients will receive 100 mg epacadostat, bid, orally, or placebo. See also C16.

Study burden and risks

Treatment cycles will take three weeks, of which pembrolizumab will be administered on day 1 and epacadostat will be taken orally twice daily. At every visit, a physical examination will be performed, vital signs will be measured, ECGs made and blood samples will be collected. At some selected sites, additional ECGs (day 1 of cycli 1 and 2 as well as additional PK sampling is planned. Subjects who consent to these additional PK samples will have to remain in the hospital for an extended period of time, as these are taken 4-10 hours after administration of pembrolizumab. These additional PK

samples are optional and trial subjects will be specifically asked for their consent for this, in the consent form.
The subjects will also be asked to complete questionnaires on their health and symptoms (EuroQol EQ-5D-3L [Health], EORTC QLQ-C30 [Quality of Life], WPAI: Melanoma [Work productivity and activity impairment].
There will be a tumor biopsy at screening (this can be omitted in case there is adequate tumor tissue available). If the subject consents, a tumor biopsy may be performed at week 12 and week 24, and after disease progression. At several timepoints during the study, photographs are taken of the skin lesions.
Trial subjects may experience physical and/or psychological discomfort with some of the study procedures, such as blood sampling, administration of the IV line, ECGs, CT/MRI scans, and tumor biopsy. The main side effects reported with the trial medication include fatigue, itching, rash, frequent or irregular bowel movements, pain in joints, muscles, or bones, stomach ache and nausea.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

- Have histologically or cytologically confirmed melanoma.
- Have unresectable Stage III or Stage IV melanoma, not amenable to local therapy.
- Have been untreated for advanced or metastatic disease - with exceptions as outlined in the protocol.
- Have documentation of V600-activating BRAF mutation status or consent to BRAF V600 mutation testing during the screening period.
- Have laboratory parameters within Protocol-defined range.
- Have the presence of at least one measurable lesion by CT or MRI per RECIST 1.1 criteria.
- Provide a baseline tumor biopsy
- Have resolution of toxic effect(s) of the most recent prior therapy to Grade 1 or less (except alopecia).
- Have an Eastern Cooperative Oncology Group (ECOG) performance status 0 to 1.
subject.

Exclusion criteria

- Has received prior systemic treatment for unresectable or metastatic melanoma (except therapy as noted in inclusion criteria #3).
- Has received prior therapy with an anti*PD-1, anti*PD-L1, anti*PD-L2, anti*CD137, or IDO1 inhibitor or any other antibody or drug specifically targeting checkpoint pathways other than anti-CTLA-4 which is permitted in the adjuvant setting.
- Has received prior adjuvant therapy, monoclonal antibody, chemotherapy or an investigational agent or device within 4 weeks or 5 half-lives (whichever is longer) before administration of study drug or not recovered (* Grade 1 or at baseline) from AEs due to previously administered agents. Exception to this rule would be use of denosumab, which is not excluded.
Note: Subjects with * Grade 2 neuropathy are an exception and may enroll.
- Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy or any other form of immunosuppressive therapy within 7 days before the first dose of study treatment.
- Has a known additional malignancy that is progressing or requires active treatment. Exceptions are described in the protocol.
- Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.
- Has ocular melanoma.
- Has an active autoimmune disease that has required systemic treatment in past 2 years.
- Has an active infection requiring systemic therapy.
- Has known history of human immunodeficiency virus (HIV)
- Has known history of or is positive for Hepatitis B or Hepatitis C
- Has history of (noninfectious) pneumonitis that required steroids, or current pneumonitis.
- Has received prior radiotherapy within 2 weeks of therapy. Subjects must have recovered

from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
- Is pregnant or breastfeeding or expecting to conceive or father children within the projected duration of the study.
- Has received live vaccine within 30 days before the first dose of study treatment.
- Has received monoamine oxidase inhibitors within the 21 days prior to starting study treatment.
- Has any history of Serotonin Syndrome after receiving serotonergic drugs.
- Has presence of a gastrointestinal condition that may affect drug absorption.
- Has a history or presence of an abnormal electrocardiogram (ECG) that, in the investigator's opinion, is clinically meaningful.
- Has clinically significant cardiac disease, including unstable angina, acute myocardial infarction within 6 months from Day 1 of study drug administration, New York Heart Association Class III or IV congestive heart failure, and arrhythmia requiring therapy. Medically controlled arrhythmia would be permitted.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	23-11-2016
Enrollment:	14
Type:	Actual

Medical products/devices used

Product type:	Medicine

Brand name:	INCB024360
Generic name:	epacadostat
Product type:	Medicine
Brand name:	Keytruda
Generic name:	pembrolizumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	11-04-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-06-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-11-2016
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-04-2017

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-10-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-08-2018
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	EUCTR2015-004991-31-NL
CCMO	NL56546.056.16