Adjuvant immunotherapy with anti-PD-1 monoclonal antibody Pembrolizumab (MK-3475) versus placebo after complete resection of high-risk Stage III melanoma: A randomized, double-blind Phase 3 trial of the EORTC Melanoma Group.

Published: 27-05-2015
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This study has been transitioned to CTIS with ID 2023-509136-25-00 check the CTIS register for the current data. To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves recurrence-free survival (RFS) as compared...

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

Summary

ID

NL-OMON56050

Source
ToetsingOnline

Brief title
Immunotherapy with anti-PD in stage III melanoma

Condition

- Skin neoplasms malignant and unspecified

Synonym
serious type of skin cancer caused especially by the light of the sun

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: EORTC-1325-MG, KEYNOTE 054, MK-3475, Pembrolizumab

Outcome measures

Primary outcome

Primary endpoint:

* Recurrence-free survival (RFS)

* RFS for patients with PD-L1-positive expression

* Progression/recurrence-free survival 2 (PRFS2)

Secondary outcome

Secondary endpoints:

* Distant metastases-free survival (DMFS)

* DMFS for patients with PD-L1-positive expression

* Overall survival (OS)

* OS for patients with PD-L1-positive expression

* Pharmacokinetics (PK) of pembrolizumab

Adverse events will be scored according to the CTCAE version 4.0

* Quality of life

* Health economics

* Predictive biomarkers (e.g. immune-related gene signatures, genetic

variation, SPDL1) for treatment difference in outcome

* To assess for development of anti-drug antibodies (ADA).

Study description

Background summary

The last decades we see an increase of melanoma being diagnosed across the globe with regional positive lymph nodes (stage III). Most patients with stage III melanoma have a high risk of relapse and early decease. Surgery alone is insufficient to achieve a cure in most patients with stage III melanoma. Current available treatments have marginal impact on overall survival; there is a large unmet medical need. Earlier results in research with Pembrolizumab (MK-3475; anti-PD1 monoclonal antibody) are optimistic and show improved overall survival. Until 30 November 2014 about 5000-6400 patients have been treated with Pembrolizumab. Pembrolizumab has been generally well tolerated. Various oncology indications are currently being studied for treatment with Pembrolizumab, outlined in the Investigator's Brochure.

Study objective

This study has been transitioned to CTIS with ID 2023-509136-25-00 check the CTIS register for the current data.

To prospectively assess whether post-operative adjuvant therapy with pembrolizumab improves recurrence-free survival (RFS) as compared to placebo in high-risk patients with complete resection of Stage IIIA (> 1 mm metastasis), IIIB and IIIC melanoma.
To prospectively assess whether in the subgroup of patients with PD-L1-positive tumor expression, pembrolizumab improves recurrence-free survival as compared to placebo.

* To compare quality of life between the two arms (pembrolizumab versus placebo).
* To compare health outcomes evaluation between the two arms (pembrolizumab versus placebo).
* To evaluate predictive biomarkers (e.g., immune-related gene signatures, genetic variation, SPDL1)
for treatment difference in outcome.
* Progression/recurrence-free survival 2 (PRFS2)

Study design

This is an international, double-blinded, placebo-controlled randomized phase III trial. Enrollment will be a multi-step process. Randomization (placebo vs.

pembrolizumab) will be performed centrally and will be stratified for the following factors: stage (IIIA (> 1 mm metastasis) vs. IIIB vs. IIIC 1-3 positive lymph nodes vs. IIIC >= 4 positive lymph nodes) and region (North America, European countries, Australia and other countries as designated)). Data will be unblinded in case of recurrence and at any time during the trial in case of a safety concern affecting an individual patient.

Intervention

1) Adjuvant therapy:Pembrolizumab/Placebo at a dose of 200 mg fixed dose, will be administered by IV, every 3 weeks.
Study drugs will be administered for 1 year unless one of the withdrawal criteria applies (Section 5.4.1.2)

2) after 1st recurrence
Upon documented recurrence, patients assigned to pembrolizumab adjuvant arm who experience disease recurrence more than six months after completing one year of therapy may be re-treated with pembrolizumab 200 mg IV every 3 weeks if clinically indicated.
Pembrolizumab will be administered for 2 years unless one of the withdrawal criteria applies (Section 5.4.2.4)

Study burden and risks

Patients may or may not receive any direct medical benefit from being in this study. Their condition may get better, it may get worse, or it may stay the same. Information learned from this study may help in the future to better treat patients.

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

Please see protocol summary section Diagnosis and main criteria for inclusion, for full description
- At least 18 years of age.
- written informed consent must be given
- Complete resection of Stage III melanoma (AJCC R0) with histologically confirmed cutaneous melanoma metastatic to lymph node, classified as (AJCC, 2010): Stage IIIA with metastasis > 1 mm; any Stage IIIB or IIIC. No past or current in-transit metastases or satellitosis..
- Melanoma with unknown origin of the primary is eligible
- Mandatory to ship tumor sample for evaluation of PD-L1 expression.
- The maximum duration from surgery to first study drug treatment is 13 weeks. Treatment should start only after complete wound healing from the surgery.
Note: If there is a delay of 1-7 days exceeding 13 weeks due to extreme unforeseen circumstances, the eligibility should be discussed with the medical monitor.
- Disease status for the post-surgery baseline assessment must be documented by full Chest/Abdomen/Pelvis CT and/or MRI with Neck CT and/or MRI (for Head and Neck primaries) and complete clinical examination after the informed consent and prior to enrollment.
Note: if a patient had laboratory/imaging tests as part of local routine guidelines (standard of care) prior to signing informed consent, the procedures will be acceptable for screening purpose if they are within the window required by the protocol.
- Disease-free (no loco-regional relapse or distant metastasis); no clinical evidence for brain metastases.
- BRAF mutation status (known or not done)
- ECOG performance status of 0 or 1.
- Patient demonstrates adequate organ function as defined in the protocol

- Women of child bearing potential (WOCBP) must have a negative serum (or urine) pregnancy test within 72 hours prior to the first dose of study treatment.
- Patients of childbearing / reproductive potential should use adequate birth control methods.
- Female patients who are breast feeding should discontinue nursing prior to the first dose of study treatment and until 120 days after the last dose of study drug .
- Patients who have been disease-free for 5 years, or patients with a history of completly resected non-melanoma skin cancer or succesfully treated in situ carcinoma are eligible, for example cervical cancer is situ. , Please refer to the Diagnosis and Main Criteria for Inclusion in the Protocol for the full list of inclusion criteria.

Exclusion criteria

Please see protocol summary section Diagnosis and main criteria for inclusion, for full description
- Mucosal or ocular melanoma.
- Prior therapy for melanoma including surgery for primary melanoma lesions.
- history of (non-infectious) pneumonitis that required steroids or current pneumonitis. History of or current interstitial lung disease.
- history of another malignancy or a concurrent malignancy. Exceptions include patients who have been disease-free for 5 years, or patients with a history of completely resected non-melanoma skin cancer or succesfully treated in situ carcinoma are eligible, for example cervical cancer in situ.
- active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
- active infection requiring therapy.
- diagnosis of immunodeficiency, no systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment
- known history of human immunodeficiency virus (HIV), active Hepatitis B or Hepatitis C.
- treatment with live vaccines within 30 days prior to the first dose of study medication are not eligible.
- prior treatment with any anti-CTLA4 monoclonal antibody or anti-PD-1, or PD-L1 or PD-L2 agent.
- Patient is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigation device within 4 weeks prior to the first dose of treatment

- patient is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or Sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.
- female patients who are Breast feeding

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-11-2015
Enrollment:	108
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pembrolizumab (MK-3475)
Generic name:	Keytruda

Ethics review

Approved WMO

Date:	27-05-2015
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	01-06-2015
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-11-2015
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-03-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-05-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-01-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-04-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-09-2017
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	26-10-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-11-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-06-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-08-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-09-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-02-2019
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	28-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-12-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-10-2020
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-06-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-12-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-12-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-02-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-03-2023
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	18-09-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-02-2024
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
EU-CTR	CTIS2023-509136-25-00
EudraCT	EUCTR2014-004944-37-NL
ClinicalTrials.gov	NCT02362594
CCMO	NL52995.031.15