T-Cell Mediated Plaque Inflammation and Atherosclerosis in Stage III Melanoma Patients on (neo-)adjuvant Immune Checkpoint Inhibitors: a prospective matched cohort study

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To investigate the effects of ICIs (anti-CTLA4, anti-PD1, combination anti-CTLA4/PD1) on vascular inflammation (PET-CT) in stage III melanoma patients. We hypothesize that the increase in vascular inflammation will be greater in the exposure group...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Observational non invasive

Summary

ID

NL-OMON51479

Source
ToetsingOnline

Brief title
CHECK-FLAME II

Condition

- Cardiac disorders, signs and symptoms NEC
- Skin neoplasms malignant and unspecified
- Arteriosclerosis, stenosis, vascular insufficiency and necrosis

Synonym
melanoma, skin cancer

Research involving

Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: cardiotoxicity, immune checkpoint inhibitors, melanoma, plaque inflammation

Outcome measures

Primary outcome

The primary endpoints of the study are:

- The absolute and relative change in 18F-FDG uptake in prespecified arterial segments defined by maximum target-to-background-ratio (TBRmax) between baseline, 6 months (exposure group only) and 18 months (PET-CT).

- The absolute and relative change of total plaque volume in respectively mm3 and % in the coronary arteries between baseline and 18 months in the exposure group (CCTA).

Secondary outcome

The secondary endpoints will be:

- Incidence of major adverse cardiac events at follow up: Acute coronary syndrome (ACS), Ischemic stroke, Cardiac death, Peripheral arterial disease requiring interventional treatment

- The change plaque composition and in the coronary arteries determined by Hounsfield units (HU) between baseline and after 18 months in the exposure group.

- The change between baseline and after 18 months in the levels of biochemical

markers of inflammation and atherosclerosis (e.g. GDF 15, PCT, OPN, Copeptin,

ET-1, MPO, Ang-2, Relaxin-1, NT-proBNP, Troponine-T)

Study description

Background summary

In the past decade immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment as they lead to unprecedented response rates in many types of cancer - in particular lung cancer and melanoma - and they significantly improved the prognosis of cancer patients. Due to the success of ICI therapy, prescription rates have substantially increased and currently more than 40% of all new malignancies meet the indication for a form of ICI therapy. ICIs are very potent to combat a variety of malignancies, but their cardiovascular toxicities are an emerging problem. Recently, studies have shown that T-cell mediated acceleration of atherosclerosis may be an important long-term complication of ICIs. The incidence of atherosclerotic cardiovascular adverse events in todays* practice is currently unknown as these agents only recently entered the clinics, but these toxicities are reported in an increasing number of studies. Statin therapy appeared to attenuate this increase in aortic atherosclerotic plaque.

How ICIs affect atherosclerosis in cancer patients is currently unknown. In hyperlipidemic mice, short-term ICI treatment induced hyper-inflammatory atherosclerotic plaque phenotype, thereby promoting atherosclerotic lesion progression towards clinically unfavorable unstable plaques. Although limited research has been performed on vascular inflammation after ICI therapy, several studies found an association between the F-FDG uptake as a measure of inflammation and cardiovascular events. The aforementioned improvement of long-term prognosis due to ICI therapy in patients with advanced malignancies- in conjunction and tremendous expansion of ICI therapy eligibility - thus leads to the formation of a substantial high-risk population for atherosclerotic cardiovascular events. There is an unmet clinical need to prospectively assess the effects of ICIs on atherosclerosis and the subsequent atherosclerotic cardiovascular events.

Study objective

To investigate the effects of ICIs (anti-CTLA4, anti-PD1, combination anti-CTLA4/PD1) on vascular inflammation (PET-CT) in stage III melanoma patients. We hypothesize that the increase in vascular inflammation will be greater in the exposure group than in the control group.

Study design

This pilot investigation - a single center prospective matched cohort study - will enroll both patients with stage III melanoma who are scheduled to receive (neo-)adjuvant ICI therapy and a control group of patients with stage IB/II melanoma who receive (non-ICI) anti-cancer treatment. Patients with melanoma stage III will be recruited from the medical oncology department of LUMC and patients with melanoma stage IB/II will be recruited from the dermatology department of LUMC.

Patients with melanoma stage III who are scheduled to receive ICI therapy (exposure group) will undergo a CCTA scan in addition to routinely performed PET-CT scans at baseline and 18 months follow-up. The control group consists of patients with melanoma stage IB/II who will not receive ICI therapy. The control group will undergo PET-CT scans at baseline and at 18 months follow up The total study duration will be 3 years.

Exclusion criteria are: inability to give informed consent, severe psychiatric disorder, history of cardiovascular disease, contra-indication for PET-CT or (in the exposure group) CCTA scan, use of cholesterol-lowering drugs (exposure group only), use of systemic prednisolone >10 mg/day and/or an equivalent dose of another systemic corticosteroid, uncontrolled diabetes.

Study burden and risks

The outcome of this study will indirectly give future benefit for the treatment of melanoma patients with ICIs, as we will gain knowledge about the process of atherosclerosis in patients treated with ICIs, which will possibly contribute to future prevention strategies. The blood samples are necessary to assess cardiovascular biomarkers, but could be a small burden for the patients. By undergoing CCTA, patients will be exposed to radiation, but, this concerns a very minimal amount of radiation (1.3 mSv). Furthermore, we do not expect any serious adverse outcomes related to these interventions. The results of this study will provide insight in vascular inflammation in melanoma patients treated with ICIs and will provide a framework for the identification of novel therapeutics of novel therapeutic strategies to limit the cardiovascular toxicity of ICIs, without compromising their anti-tumor efficacy. As treatment for cancer with ICIs improves, in the future the survival-rate will probably increase. For those patients, it is important to know the adverse effects of ICI treatment on inflammation, in order to prevent progressive atherosclerotic disease or even cardiac-related death. The PET-CT scans will expose the control group to additive radiation. However, these scans and their outcomes are also very relevant for this control patient group, as it is expected that treatment with ICI therapy will become available for melanoma stage IIB and IIC in the near future.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

Exposure group:
• The patient has a diagnosis of melanoma stage III.
• The patient is scheduled to be treated with (neo-)adjuvant ICI immunotherapy.
• The patient is 18 years or older.
• The patient has given written informed consent.

Control group:
• The patient has a diagnosis of melanoma stage IB or II.
• The patient will not be treated with ICI immunotherapy.
• The patient is 18 years or older.
• The patient has given written informed consent.
• If possible: the patient uses cholesterol-lowering drugs in the case that statins are initiated after baseline CCTA scan for a patient in the exposure

group to whom the patient can be matched

Exclusion criteria

The patient is unable to give informed consent.
The patient suffers from severe psychiatric disorder.
The patient has a history of cardiovascular disease.
The patient has a contra-indication for a PET or CT-scan. If female and fertile: signs and symptoms of pregnancy or a positive pregnancy test / breast-feeding, (severe) claustrophobia. Low dose benzodiazepines are allowed.
The patients uses cholesterol-lowering-drugs before baseline scans (only exposure group).
The patients actively uses or is scheduled to use > 10 mg prednisolone per day and/or treatment with an equivalent dose of other systemic corticosteroids.
The patient has uncontrolled diabetes/elevated blood glucose levels (>11.1 mmol/L). The use of short-acting insulins within 4 hours of the PET scan is not allowed
The patient is unable to understand, or unlikely to comply with, the study requirements.
The patient does not wish to be informed of incidental findings (e.g. cancer metastasis or other disease).

Study design

Design

Study type:	Observational non invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	29-09-2022
Enrollment:	50

Type:	Actual

Ethics review

Approved WMO Date:	20-06-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	09-02-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	31-05-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
CCMO	NL80375.058.22