Safe Stop IPI-NIVO Trial: Early discontinuation of nivolumab upon achieving a (confirmed) complete or partial response in patients with irresectable stage III or metastatic melanoma treated with first-line ipilimumab-nivolumab

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This study has been transitioned to CTIS with ID 2024-516938-34-00 check the CTIS register for the current data. The primary objective of this study is to evaluate the rate of ongoing response at 12 months after start of treatment in patients with...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON53859

Source
ToetsingOnline

Brief title
Safe Stop ipi-nivo

Condition

- Miscellaneous and site unspecified neoplasms benign
- Skin neoplasms malignant and unspecified

Synonym

malignant melanoma, Melanoma

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: NFU transformatiedeal

Intervention

Keyword: Ipilimumab-nivolumab, Melanoma, Nivolumab, Response

Outcome measures

Primary outcome

Primary endpoint of this study is response rate, defined as the rate of ongoing responses (CR and PR) according to RECIST v1.1 at 12 months after first start of first-line ipilimumab-nivolumab in patients with irresectable stage III or metastatic melanoma.

Secondary outcome

The secondary objectives of this study include the evaluation of:

A. Patient outcomes:

1. Ongoing response at 24 months after start of first-line treatment with ipilimumab-nivolumab

2. Response (CR/PR) at different time points

3. Duration of response (CR/PR) measured until progressive/recurrent disease

4. Melanoma specific survival measured from start of first-line treatment with ipilimumab-nivolumab until melanoma related death

5. Overall survival (OS) measured from start of first-line treatment with

ipilimumab-nivolumab until death by any cause

6. Impact of discontinuation treatment on (S)AEs

7. Overall Response Rate (ORR) per RECIST v1.1 in retreated patients

8. Need and feasibility of restarting (systemic) treatment for melanoma

9. Disease control (CR/PR/SD/not PD) after restarting (systemic) anti-melanoma treatment

B. Cost-effectiveness analysis

1. Impact on productivity with respect to paid and unpaid work

2. Impact on healthcare resource

3. Impact of early discontinuation of treatment on hours of informal care

C. Quality of life assessment in patients with irresectable stage III or metastatic melanoma who did not start nivolumab maintenance therapy or discontinued nivolumab maintenance therapy early. Patients will fill out the QoL questionnaires at inclusion, every 12 weeks in the first year of follow up, every 4 months in year 2, every 6 months in year 3 and one set of questionnaires in year 5.

Study description

Background summary

Based on the pivotal clinical trials, combination therapy with ipilimumab and nivolumab is usually discontinued in case of disease progression, severe toxicity, or after a treatment duration of maximum 2 years. However, durable tumor responses have been observed after early discontinuation of the

ipilimumab-nivolumab schedule in patients with irresectable stage III or metastatic melanoma who achieve a tumor response. In clinical practice, an increasing number of physicians discontinues treatment on an individual basis, for example at achieving complete response (CR) or partial response (PR), or on patients* request. From a toxicity, economic, and patient perspective, a shorter treatment duration is obviously to be preferred, however, the safety of early discontinuation of the ipilimumab-nivolumab schedule has not been prospectively evaluated in clinical practice.

Study objective

This study has been transitioned to CTIS with ID 2024-516938-34-00 check the CTIS register for the current data.

The primary objective of this study is to evaluate the rate of ongoing response at 12 months after start of treatment in patients with irresectable stage III or metastatic melanoma who are treated with first-line ipilimumab-nivolumab and who early discontinue treatment upon achieving a (confirmed) CR or PR according to RECIST v1.1.

Study design

This is a nationwide, multicentre, prospective, single-arm, intervention study in the Netherlands.

Intervention

Discontinuation of (maintenance) treatment with nivolumab at achieving CR

Study burden and risks

Patients are treated and evaluated according to standard of care in the Netherlands. As nivolumab will be discontinued early, participation in this trial may affect treatment efficacy, which will be evaluated as primary objective of this study. As a result, participation in this trial may affect clinical outcome and even survival of these patients. However, as an increasing number of physicians discontinues this treatment early (before 2 years) on an individual basis at achieving (confirmed) CR or PR, the additional risk of participation in this trial is considered limited as compared to daily clinical practice.

Contacts

Public

Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- 18 years of age or older
- irresectable stage III or metastatic melanoma
- Treated with at least one dose of first-line ipilimumab-nivolumab and considered to be a candidate for maintenance treatment with nivolumab.
o Previous systemic treatment, including ICIs, in (neo)adjuvant setting for resectable melanoma is allowed
o In this protocol, nivolumab maintenance is interchangeable with pembrolizumab maintenance therapy.
- Response evaluation according to RECIST v1.1 using a diagnostic CT documenting target lesions every 12 (-2/+6) weeks from the start of ipilimumab-nivolumab;
o For patients with CR on a diagnostic CT at response evaluation, a low-dose CT (which is usually part of 18FDG-PET/CT) is allowed at baseline
o For patients with PR on a diagnostic CT at response evaluation, a low-dose CT (which is usually part of 18FDG-PET/CT) is allowed if sufficient target lesions are measurable for response evaluation according to RECIST v1.1 criteria.

o In case of asymptomatic brain metastases prior to start of first-line ipilimumab-nivolumab, intracerebral tumor response should be confirmed using an MRI prior to inclusion
- Patients should be included after first CR/PR or first confirmed CR/PR according to RECIST v1.1
o Inclusion should take place no later than 5 weeks after first confirmed CR/PR
o In case of SD at first response evaluation, confirmed CR/PR is required for inclusion
o eligible and willing to discontinue nivolumab within 4(+1) weeks after inclusion, i.e. first CR/PR or first confirmed CR/PR
o no later than 9 months after start of treatment with ipilimumab-nivolumab
- Presence of MRI brain for the screening of brain metastases (prior to discontinuation of ipilimumab-nivolumab)
- Participants with previously locally treated brain metastases may participate in case they meet the following criteria:
o completely asymptomatic brain metastases at inclusion
o MRI of brain at baseline and for response evaluation during treatment
- Signed and dated informed consent form

Exclusion criteria

- Patients with SD/PD according to RECIST v1.1
- Malignant disease other than being treated in this study. Exceptions to this exclusion include the following: malignancies that were treated curatively and have not recurred within 2 years prior to start of study treatment; completely resected basal cell and squamous cell skin cancers and any completely resected carcinoma in situ.
- Presence of symptomatic brain metastases
* prior to first-line treatment with ipilimumab-nivolumab, or;
* when defined as new or progressive brain metastases at the time of study entry;
* brain metastases with need for steroid treatment in the last 8 weeks prior to study entry
Note: An incidental epileptic seizure caused by a brain lesion is not considered an exclusion criterion.
(provided that the other in- and exclusion criteria are met);
- Presence of leptomeningeal metastases;
- Systemic chronic steroid therapy (>10mg/day prednisone or equivalent) at inclusion or patients who need or needed any other second-line immunosuppressive therapy (e.g. infliximab, mycophenolate mofetil) for the treatment of irAEs. Note: local steroids such as topical, inhaled, nasal and ophthalmic steroids are allowed.
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before

registration in the trial. This comprises each and every condition or circumstance preventing the patient from showing up to the outpatient controls and/or undergoing the CT-scans, or preventing the patient from (adequately) filling out the questionnaires

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-06-2023
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	KEYTRUDA
Generic name:	pembrolizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	OPDIVO
Generic name:	nivolumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	YERVOY
Generic name:	ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-10-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-01-2023
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	CTIS2024-516938-34-00
EudraCT	EUCTR2022-002673-28-NL
CCMO	NL82177.078.22