Multicenter phase 3 trial comparing NeoADjuvant Ipilimumab + Nivolumab versus standard Adjuvant nivolumab in macroscopic stage III melanoma - NADINA

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This study has been transitioned to CTIS with ID 2024-513519-28-00 check the CTIS register for the current data. Primary objective • To compare the event-free survival (EFS) of neoadjuvant ipilimumab + nivolumab (followed by adjuvant nivolumab or...

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

Summary

ID

NL-OMON54313

Source
ToetsingOnline

Brief title
NADINA

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: BMS,Bristol-Myers Squibb

Intervention

Keyword: Ipiplimumab, Neoadjuvant, Nivolumab, stage III melanoma

Outcome measures

Primary outcome

Primary endpoint:

• EFS, defined as time from randomization to melanoma progression (irresectable stage III or stage IV disease), melanoma recurrence, treatment-related death, or melanoma-related death, whichever occurs first.

Secondary outcome

Key secondary endpoint

• OS, defined as time between date of randomization and date of death from any cause;

Secondary endpoints:

• RFS, defined as time between date of surgery and date of melanoma recurrence, treatment-related death or melanoma-related death, whichever occurs first;

• DMFS, defined as time between date of randomization and date of first distant metastasis, treatment-related death or melanoma-related death, whichever occurs first;

• EFS including new primary melanoma, defined as time from randomization to a new primary melanoma (excluding melanoma in situ), melanoma progression

(irresectable stage III or stage IV disease), melanoma recurrence,

treatment-related death, or melanoma-related death, whichever occurs first;

• Pathologic response rate (categorized into pCR, near-pCR, MPR, pPR, pNR,

according to INMC criteria) in the neoadjuvant arm;

• Correlation of pathologic response in the neoadjuvant arm to RFS, DMFS, and

OS;

• Frequency and duration of all grade and grade 3-5 treatment-related adverse

events according to CTCAE 5.0;

• Surgical complication rates according to Clavien-Dindo surgical

classification;

• Quality of life as measured by EORTC QLQ C30, the Melanoma Subscale and

Melanoma Surgery Subscale of FACT-M, the Cancer Worry Scale, HADS

questionnaire, EQ-5D-5L, the immunotherapy-specific questionnaire, an

assessment of work performance, sexual health, and Amsterdam Cognition Scan;

• Performing health technology assessments comparing the neoadjuvant arm with

the standard adjuvant arm.

Study description

Background summary

Immunotherapy
Ipilimumab and nivolumab are antibodies (human proteins) that can help the body's natural defenses (immune system) attack tumor cells. These agents are also called "immunotherapy".

Adjuvant Immunotherapy
The standard treatment for patients with stage III melanoma (where there is only metastasis to the lymph nodes) is surgery in which the lymph nodes are

removed, followed by one year of immunotherapy with nivolumab, pembrolizumab or targeted treatment with dabrafenib + trametinib (in patients with BRAFV600E / K melanoma).
By the time patients are diagnosed with stage III melanoma, they often already have small metastases to other parts of the body that are so small that they cannot be seen with scans. If you only performed an operation without additional immunotherapy, this would allow the tumor to come back after the operation in more than half of these patients. Immunotherapy after surgery (also called "adjuvant" immunotherapy) can reduce the chance of disease recurrence by 20%.

Neoadjuvant Immunotherapy
By administering the combination of ipilimumab and nivolumab prior to surgery ("neoadjuvant" immunotherapy), we hope to further reduce the chance that the tumor will come back. In previous studies, led by the AvL, which were carried out in the Netherlands (including the AVL) and Australia (the OpACIN and OpACIN-neo study), melanoma patients with metastases to the lymph nodes only were treated with immunotherapy prior to surgery for 6 years. weeks. These studies showed that the risk of disease recurrence after surgery was greatly reduced in patients who respond well to the immunotherapy (1 of 71 subjects got the disease back). The correct dose of immunotherapy was also found that is effective (in 61% of the subjects the immunotherapy had a good effect on the tumor in 13% a partial effect) and thereby gives as little chance of side effects as possible (20% of the subjects treated with this scheme developed one or more more serious side effects).
This dose of the combination ipilimumab and nivolumab was subsequently tested in a follow-up study (the PRADO study), in which an additional 99 subjects were treated. This study confirmed the effectiveness and safety of the combination immunotherapy; 61% of the subjects achieved a good effect and 11% a partial effect on the combination ipilimumab and nivolumab and 22% of the subjects developed one or more serious adverse reactions.

Additional treatment
The OpACIN and OpACIN-neo studies also showed that patients who do not respond well to the neoadjuvant immunotherapy have a higher chance of the tumor coming back. The PRADO study showed that patients who have partially responded to the immunotherapy also have a higher chance of a tumor coming back, although this is to a lesser extent than in patients who have not responded well.
If it appears in this study that your tumor has not or partially responded well to the neoadjuvant immunotherapy prior to the operation, you will therefore receive additional treatment after the operation in consultation with your doctor. This is possible with nivolumab, which is currently the standard treatment for your disease. Your tumor may also contain a BRAF mutation. BRAF is a protein that can change (mutate) and is found in about 50% of patients with melanoma. If your tumor contains a BRAF mutation, you will be treated with the combination of dabrafenib and trametinib after surgery. You might also be advised to have the operating area irradiated afterwards.

The administration of ipilimumab and nivolumab prior to surgery is still under investigation and has not yet been approved as standard treatment. If other treatments become available during the study, we will always look at what is the best treatment for you at that time. Your doctor will tell you more about this.

Study objective

This study has been transitioned to CTIS with ID 2024-513519-28-00 check the CTIS register for the current data.

Primary objective
• To compare the event-free survival (EFS) of neoadjuvant ipilimumab + nivolumab (followed by adjuvant nivolumab or dabrafenib + trametinib in patients not achieving a pathologic response) versus standard adjuvant nivolumab.

Study design

This is an international (Australia, Europe, and USA) open-label two-arm randomized phase 3 trial including 420 stage III (<=3 resectable in-transit metastases allowed) cutaneous or unknown primary melanoma patients. Patients will be randomized 1:1 to receive either 2 cycles of neoadjuvant ipilimumab 80 mg + nivolumab 240 mg every 3 weeks followed by a total lymph node dissection (TLND) and, if applicable, resection of in-transit metastases (arm A) versus standard upfront TLND +/- resection of in-transit metastases followed by 12 cycles adjuvant nivolumab 480 mg every 4 weeks (arm B). Patients in arm A achieving only a pathologic partial response (10-50% viable tumor) or having no response (>50% viable tumor) will receive additional adjuvant therapy: in case of BRAF wildtype melanoma nivolumab 480 mg every 4 weeks for 46 weeks (11 cycles) and in case of BRAF V600E/K mutation-positivity, adjuvant dabrafenib plus trametinib for 46 weeks. Patients will be treated in the study in both arms until melanoma progression to irresectable stage III or stage IV disease, disease recurrence, unacceptable toxicity, subject withdrawal of consent or until end of study treatment.
Patients will be stratified according to BRAF status, continent, and the presence/absence of in-transit metastases. An interim analysis will be performed after 60 events have occurred. The data safety monitory board (DSMB) will be ad hoc consulted when unexpected toxicities are reported. Patients will be followed by 12 weekly CT scans until end of year 3 and then until year 5 according to the institute*s standards.

Intervention

In the NADINA trial, patients will be randomized to either neoadjuvant ipilimumab 80 mg + nivolumab 240 mg q3w for 6 weeks (2 cycles), followed by

TLND (+ excision of in-transit metastases, if present), followed by 11 cycles adjuvant nivolumab 480 mg q4w (BRAF wt) or dabrafenib 150 mg bid + trametinib 2 mg qd (BRAF V600E/K-mutated) for 46 weeks in patients not achieving a MPR (arm A) or to TLND (+ excision of in-transit metastases) followed by standard adjuvant nivolumab 480 mg q4w 12 cycles (arm B). In each arm 210 patients will be included. After week 60 the patients will be followed every 12 weeks for the first 2 years (year 2 and 3), and subsequently according to institute*s standard in year 4 and 5.
Medication: 2 cycles ipilimumab 80 mg + nivolumab 240 mg q3w, followed by adjuvant nivolumab 480 mg q4w (11 cycles) or dabrafenib 150 mg bid + trametinib 2 mg qd for 46 weeks in pathologic partial and non-responders (arm A) versus adjuvant nivolumab 480 mg q4w for 52 weeks (12 cycles) (arm B).
Lab testing (including collection of serum, plasma and 1 vial of EDTA blood) will be performed during screening. Lab testing (including collection of serum and plasma) will be performed at baseline (week 0), week 3 (arm A only), week 6, week 9 (arm A only), at week 12 and every 12 weeks until end of year 3.
Tumor biopsies are required at baseline (4x14g: 1x FFPE, 2x fresh frozen, 1x for tumor fragments (frozen in DSMO) or another fresh frozen sample according to technique present at the study center). Surgical material should be preserved as FFPE material, as fresh frozen (if lymph node >2cm) and as fragments (if lymph node >5cm, in experienced centers (see Appendix D)).
Optionally, tumor biopsies (4x 14g: 2x fresh frozen, 1x FFPE, 1x for tumor fragments (frozen in DMSO) or another fresh frozen sample) in week 2 for translational research (window +/- 3 days).
CT scans will be required during screening and at week 6 and week 12.
Follow-up will start at week 12 with 12-weekly CT scans for patients achieving a MPR in arm A. Adjuvant therapy should start no later than week 12 for patients achieving no MPR in arm A and for all patients in arm B. During adjuvant therapy radiologic evaluation will also be performed every 12 weeks.
Subsequent follow-up will be by CT scans in both arms every 12 weeks in year 2 and 3, and according to the institute*s standard follow-up schedules in year 4 and 5.
QoL (BL, week 6, 12, then every 12 weeks in year 1, and every half year in year 2 and 3), the Amsterdam Cognition Scan (ACS, BL, year 1 and year 2), and ePROs with urgency algorithms (continuously) will be collected using the KAIKU app.
In case of recurrence, tumor biopsies (4x14g: 1x FFPE, 2x fresh frozen, 1x for tumor fragments (frozen in DSMO) or another fresh frozen sample according to technique present at the study center), serum and plasma collection are required.

Study burden and risks

Recently, adjuvant systemic targeted therapy with dabrafenib and trametinib in BRAFV600E/K mutation-positive patients has shown to improve RFS (significantly) and OS (not significantly). Grade 3-4 toxicities were reported to occur in 41% of the patients. Adjuvant systemic treatment with ipilimumab has been approved by the FDA due to RFS and OS benefit, but was not filed for approval outside

the US due to the high grade of adverse events (41.6% grade 3-4 adverse events in patients treated with ipilimumab 10 mg/kg adjuvant). Both anti-PD-1 antibodies nivolumab and pembrolizumab have been approved as adjuvant therapies based on two phase 3 trials investigating pembrolizumab versus placebo and nivolumab versus ipilimumab that showed RFS benefit in favor of the anti-PD-1 antibody, while OS benefit data are still pending. Treatment-related grade 3-4 adverse event rates were 14.7% and 14.4%, respectively.
Adjuvant nivolumab 240 mg q2w + ipilimumab 1 mg/kg q6w versus adjuvant nivolumab in completely resected, stage IIIB/C/D or stage IV melanoma (according to AJCC 8th edition) tested in the Checkmate 915 trial, failed to achieve its primary objective. The IMMUNED trial that investigated adjuvant placebo versus nivolumab versus standard dosing of ipilimumab 3 mg/kg + nivolumab 1 mg/kg every 3 weeks for 4 cycles followed by nivolumab consolidation up to 1 year in resectable stage IV melanoma patients already showed a promising 24-months RFS of 70%. The grade 3-4 toxicity rate was high, with 70.9% grade 3-4 adverse events for the combination treatment and 26.8% for nivolumab monotherapy. These high toxicity rates combined with promising RFS data support the idea of less systemic immune suppression in patients with low tumor load, and result in the requirement of alternative lower dosing schemes for combination therapy.
Participants of the NADINA trial will be exposed to two immunotherapeutic agents (ipilimumab and nivolumab) known to induce immune-related adverse events at a higher percentage when combined together. This has also been observed in the OpACIN trial in which 90% of all patients receiving ipilimumab and nivolumab at standard dosing developed grade 3-4 toxicities independent of neoadjuvant or adjuvant application.
However, the OpACIN-neo trial that compared different dosing regimens, identified two cycles of neoadjuvant ipilimumab 1 mg/kg + nivolumab 3 mg/kg as dosing scheme that was effective (77% pRR, 57% pCR) and had a manageable toxicity profile (20% grade 3-4 adverse events). Responding patients seem to achieve long term benefit, as only one out of 71 responders in the OpACIN and OpACIN-neo trial has recurrenced so far with a median follow-up of 48.0 and 24.6 months, respectively. These safety and efficacy data were confirmed in the PRADO extension cohort that showed a pathologic response rate of 72%, a MPR of 61% and grade 3-4 adverse event rate of 22% for 2 cycles neoadjuvant ipilimumab 1 mg/kg + nivolumab 3 mg/kg (data update 10/2020).
These observations have led to the design of this phase 3 NADINA trial that will test the dosing scheme of 2 cycles ipilimumab 80 mg + nivolumab 240 mg flat-dose compared to standard adjuvant therapy.
Patients achieving no pathologic response upon neoadjuvant immunotherapy have a high chance of early recurrence. To date, 16 out of 23 patients (69.6%) in the OpACIN and OpACIN-neo trial without pathologic response recurred. Patients that achieve a partial response may also be at risk for early recurrence, as in the PRADO trial (and in contrast to the previous neoadjuvant trials where no relapses were observed) 4 out of 11 partial responders (36,4%) had a recurrence within the first two years. Interestingly, only 8 out of 21 non-responders (38,1%) recurred, suggesting that the additional adjuvant therapy that

non-responders received in this trial, improves the outcome for this subgroup with an initial poor prognosis (historic data from OpACIN-neo suggested 69,6% relapses in non-responders). For patients achieving a partial or no response, we hope to improve the RFS by adding adjuvant nivolumab or dabrafenib + trametinib, and also allowing parallel adjuvant radiotherapy.
*

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

• Men and women, at least 16 years of age;
• World Health Organization (WHO) Performance Status 0 or 1;
• Cytologically or histologically confirmed resectable stage III melanoma of cutaneous or unknown primary origin with one or more macroscopic lymph node metastases (clinical detectable), that can be biopsied and a maximum of 3 additional resectable in-transit metastases. A concurrent resectable primary melanoma is allowed. Clinical detectable lymph nodes are defined as either:

o a palpable node, confirmed as melanoma by pathology,or;
o a non-palpable but enlarged lymph node according to RECISTv1.1 (at least 15 mm in short axis), confirmed as melanoma by pathology, or;
o a PET scan positive lymph node of any size confirmed as melanoma by pathology;
• No other malignancies, except adequately treated and with a cancer-related life-expectancy of more than 5 years;
• No prior immunotherapy targeting CTLA-4, PD-1, PD-L1 or LAG-3;
• No prior targeted therapy targeting BRAF and/or MEK;
• No immunosuppressive medications within 6 months prior study inclusion (steroids equivalent to prednisolone <=10 mg are allowed);
• Screening laboratory values must meet the following criteria: WBC >=2.0x109/L, neutrophils >=1.5x109/L, platelets >=100x109/L, hemoglobin >=5.5 mmol/L, creatinine <=1.5xupper limit of normal (ULN), AST <=1.5x ULN, ALT <=1.5x ULN, bilirubin <=1.5x ULN (except for subjects with Gilbert syndrome who must have a total bilirubin <3.0 mg/dL);
• LDH level <1.5x ULN;
• Women of childbearing potential (WOCP) must use appropriate method(s) of contraception, i.e. methods with a failure rate of <1% per year when used consistently and correctly, to avoid pregnancy during and until 23 weeks post last ipilimumab + nivolumab infusion;
• Males who are sexually active with WOCP are not required to use contraception during treatment with nivolumab +/- ipilimumab, but must use appropriate method(s) of contraception, i.e. methods with a failure rate of <1% per year when used consistently and correctly, to avoid pregnancy during and until 17 weeks post last dabrafenib + trametinib administration;
• Patient willing and able to understand the protocol requirements and comply with the treatment schedule, scheduled visits, electronic patient outcome reporting, tumor biopsies and extra blood withdrawal during screening and in case of relapse, and other requirements of the study;
• Patient has signed the Informed Consent document.

Exclusion criteria

• Distantly metastasized melanoma;
• Uveal/ocular or mucosal melanoma;
• Subjects with any active autoimmune disease or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications. Subjects with vitiligo, resolved childhood asthma/atopy type I diabetes mellitus, residual hypothyroidism due to autoimmune thyroiditis only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment are permitted to enroll;
• Prior radiotherapy; targeting the affected lymph node region(s);
• Subjects will be excluded if they test positive for hepatitis B virus surface antigen (HBsAg) or hepatitis C virus ribonucleic acid (HCV antibody),

indicating acute or chronic infection. Subjects treated and being at least one year free from HCV are allowed to participate;
• Subjects will be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS);
• Subjects with history of allergy to study drug compononents or history of severe hypersensitivity reaction to monoclonal antibodies.
• Subjects with underlying medical conditions or active infection that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity or adverse events;
• Women who are pregnant or breastfeeding;
• Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids >10 mg prednisolone daily equivalent;
• Use of other investigational drugs before study drug administration 30 days or 5 half-times before study inclusion;
• Psychological, familial, sociological, or geographical conditions that potentially hamper compliance with the study protocol and follow-up schedule; those conditions should be discussed with the subject before registration in the trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-08-2021
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	01-06-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-06-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	10-02-2022
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	16-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-09-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	26-03-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-05-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	CTIS2024-513519-28-00
EudraCT	EUCTR2021-001492-16-NL
ClinicalTrials.gov	NCT04949113
CCMO	NL76979.031.21