Multicenter Phase 2 Study to Identify the Optimal neo-Adjuvant Combination Scheme of Ipilimumab and Nivolumab (OpACIN-neo) and Personalized Response-driven Adjuvant Combination (PRADO extension cohort)

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OpACIN-neo:Primary objectives: - To compare safety (immune related adverse events during the first 12 weeks) of three different neo-adjuvant combination schemes of ipilimumab + nivolumab - To compare radiological and pathologic response rates at...

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

Summary

ID

NL-OMON50672

Source
ToetsingOnline

Brief title
OpACIN-neo
PRADO

Condition

- Skin neoplasms malignant and unspecified

Synonym
melanoma, skin cancer

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: BMS,Bristol-Myers Squibb

Intervention

Keyword: Ipilimumab, Melanoma, Neo-adjuvant, Nivolumab

Outcome measures

Primary outcome

OpACIN-neo

- Safety as measured by the frequency of grade 3/4 immune-related adverse events (during the first 12 weeks).

- Response rate according to RECIST 1.1 at week 6

- Pathologic response according to central revision (pathology of NKI).

An interim analysis will be performed after 13 patients have been included in each arm (see 4.5), thus in total 39 patients have been included.

PRADO extension cohort:

- Pathologic response rate according to central revision (by a pathologist of the NKI or MIA) of the marked index lymph node

- RFS at 24 months in patients achieving pCR or pnCR in their marked index lymph node and did not undergo CLND. RFS will be calculated from date of resection of the marked lymph node.

- RFS at 24 months in patients with pNR and being subsequently treated with adjuvant nivolumab plus optional radiotherapy (or dabrafenib/trametinib if

BRAFV600E positive and treatment is approved). RFS will be calculated from day of resection of marked lymph node.

Secondary outcome

Opacin neo

- Recurrence Free Survival (RFS)
- Description of late adverse event (up to 3 years after treatment initiation) according to CTCAE v4.03
- Description of associations of mutational load, RNA tumor signatures, and surface marker expression with tumor immune infiltrates and response
- Alteration in magnitude or breadth of the neo-antigen specific T cell responses in peripheral blood from baseline to surgery at week 6 in each 10 randomly chosen patients per arm.

Prado

- Response rate according to RECIST 1.1 at week 6
- RFS at 2, 3 and 5 years
- DMFS at 2, 3 and 5 years
- OS at 2, 3 and 5 years
- Grade 3/4 immune-related adverse event rate according to CTCAE v4.03 within the first 12 weeks
- Surgical complication rates according to Clavien-Dindo surgical classification of only marked index lymph node resection vs. CLND
- Description of late adverse event (up to 3 years after treatment initiation) according to CTCAE v4.03

- Description of associations of mutational load, RNA tumor signatures (e.g. T

cell, TiS, and IFN), and surface marker expression with tumor immune

infiltrates and pathologic response

- Alteration in expansion/induction of tumor-resident TCR clones in peripheral

blood from baseline to surgery at week.

- Quality of life as measured by EORTC QLQ C30 and the melanoma and the surgery

subscale of FACT-M

Study description

Background summary

T cell checkpoint blockade by anti-CTLA and/or anti-PD1 is currently the most promising therapy in late stage melanoma to induce long-term benefit or even cure. Particularly the combination of ipilimumab and nivolumab induces high response rates and promising response depth. This raises the question whether ipilimumab and/or nivolumab could also become standard therapy in adjuvant treatment of melanoma. Ipilimumab as adjuvant therapy significantly improves recurrence free survival. Recently overall survival data were published and demonstrated a significant overall survival benefit for patients in the ipilimumab group with a 5-year overall survival rate of 65% compared to 54% in the placebo group. Nivolumab and pembrolizumab have been tested in large phase 3 randomized trials showing improved relapse free survival (RFS) compared to placebo and ipilimumab at excellent tolerability, but overall survival (OS) data are pending from both trials. In addition, adjuvant targeted therapy by the BRAF+MEK inhibitor combination of dabrafenib + trametinib in BRAFV600E/K mutation positive patients has been shown to improve RFS and OS (only RFS significant).
In contrast to chemotherapeutic approaches, immunotherapeutic approaches depend on sufficient activation of the immune system. To become fully activated, T cells require two signals. The first signal is provided by the interaction of the (tumor-) antigen presented in the major histocompatibility complex (MHC) on the antigen-presenting cell (APC) to the T cell receptor (TCR) on the T cell (signal 1). In parallel, a large number of co-inhibitory and co-stimulatory interactions - so-called T cell checkpoints - modulate the outcome of the TCR - pMHC interaction. Antibody-based interference with the T cell checkpoints CTLA-4 and PD-1 has been shown to improve tumor-specific T cell responses and to result in a significant clinical benefit in patients with melanoma and other

cancers.
The notion that T cell checkpoint inhibition is of greatest value at the moment of TCR triggering has potentially significant consequences for the use of checkpoint targeting antibodies as adjuvant therapies. Specifically, as the amount of antigen that can provide this signal 1 will correlate with tumor load, adjuvant immunotherapy can be assumed to work most efficiently, when adjuvant treatment is initiated prior to surgery. A phase 1 study testing neo-adjuvant and adjuvant application of 4 courses of ipilimumab + nivolumab in stage III melanoma (OpACIN, CA209-278, NCT02437279) showed that neo-adjuvant immunotherapy was feasible, but with the current standard regimen (4 courses ipilimumab 3mg/kg + nivolumab 1mg/kg) to toxic for (neo)adjuvant application. Pathologic responses after only 6 weeks of neoadjuvant ipilimumab + nivolumab were high with 78%, and all responders are free of relapse with a median follow-up of 25 months.
The observed feasibility and pathologic responses, combined with the observed toxicity, form the rationale for the design of the subsequent phase 2 trial, OpACIN-neo, that will compare safety and efficacy of neo-adjuvant ipilimumab + nivolumab of three different schemes combining ipilimumab and nivolumab. Aim is to identify a combination scheme that maintains the high rate of clinical responses observed, but at lower toxicity. The interim analysis after 39 patients having undergone the complete lymph node dissection (CLND) confirmed the high pathologic response rates of more than 60% in all arms, while toxicity was lower with 38%, 15%, and 50% for arm A, B, and C respectively (unplanned interim analysis at 62 patients due to one severe toxicity observed in Arm C). These interim data indicate that it is likely that OpACIN-neo will meet its primary objective to identify a neoadjuvant combination scheme that is less toxic, but similar effective. Thus, one of the coprimary objectives of the PRADO extension cohort will be to confirm the safety and efficacy of the winner combination. None of the patients with pathologic response in OpACIN and OpACIN-neo has relapsed so far. Interestingly, in stage IV melanoma long-term benefit is observed in patients achieving complete response upon nivolumab or ipilimumab + nivolumab with 88% and 80% PFS at 3 years (Robert et al. ESMO 2017). Even after discontinuation of checkpoint inhibition responses are ongoing in the vast majority of patients. Recently updated data from the KEYNOTE 006 trial demonstrated that for patients with CR as best overall response that stopped pembrolizumab after 2 years, the estimated progression free survival rate at 18 months after stop of therapy was 96% (Long et al presented at ASCO 2018). These observations question the benefit of CLND in patients achieving deep pathologic response after neoadjuvant ipilimumab + nivolumab. Therefore, additional coprimary objectives of PRADO will be to test response-driven intensities of subsequent therapy (surgery and adjuvant immunotherapy) after neoadjuvant ipilimumab + nivolumab.

Study objective

OpACIN-neo:
Primary objectives:

- To compare safety (immune related adverse events during the first 12 weeks) of three different neo-adjuvant combination schemes of ipilimumab + nivolumab
- To compare radiological and pathologic response rates at week 6 of the three neo-adjuvant combination schemes
Secondary objectives:
- To describe relapse free survival
- To describe rate and type of late adverse events (up to 3 years)
- To determine immune activating capacity of the alternative combination schemes
- Antigen specific T cell responses in peripheral blood from baseline to surgery at week 6.
PRADO extension cohort:
Primary objectives:
- To confirm the pathologic response rate (index lymph node, at week 6) of the winner neoadjuvant ipilimumab + nivolumab combination scheme identified in OpACIN-neo
- To show that patients with pathologic complete response (pCR) or pathologic near complete response (pnCR) in the index lymph node can be spared safely a CLND without affecting their prognosis
- To improve RFS at 24 months for patients achieving no pathologic response (pNR) by intensifying the subsequent adjuvant therapy
Secondary objectives:
- To confirm radiologic response rate at week 6 of the winner neo-adjuvant combination scheme identified in OpACIN-neo
- To describe RFS and distant metastasis free survival (DMFS), for pCR, pnCR, pPR, and pNR patients
- To describe event free survival (EFS) for the total population
- To describe OS for the total population and for pCR/pnCR, pPR and pNR patients
- To describe the grade 3/4 immune related adverse event rate within the first 12 weeks
- To describe rate and type of late adverse events (up to 3 years)
- To determine differences in surgical morbidity for only marked index lymph node resection versus CLND.
- To explore the immune activating capacity of the different response-driven treatment schemes
- To identify baseline biomarkers predictive for pCR/pnCR
- To evaluate health related quality of life

Study design

This is an open-label three-arm phase 2 trial (including a Simon stage 2 design) consisting of 90 stage III melanoma patients randomized 1:1:1 to receive either 2 courses 3 mg/kg ipilimumab + 1 mg/kg nivolumab every 3 weeks (Arm A), 2 courses 1 mg/kg ipilimumab + 3 mg/kg nivolumab every 3 weeks (Arm B), or 2 courses ipilimumab 3 mg/kg, directly followed by 2 courses nivolumab 3 mg/kg every 2 weeks (Arm C). All three treatment arms are applied prior to surgery at week 6, and are neo-adjuvant (30 patients per arm, Figure 1).

Patients will be stratified according to treatment center. An interim analysis will be performed after 13 patients have been included in each arm (see 4.5), thus in total 39 patients have been included. After inclusion of the 90 patients OpACIN-neo will transiently closed for analysis of the toxicity and response rate, and together with DSMB and BMS the study team will pick the winner scheme. Subsequent the extension cohort (PRADO) will be opened to confirm the response rates observed from the winner scheme in OpACIN-neo and to analyze the requirement of CLND after achieving pCR or pnCR in the index lymph node.
The extension cohort will consist of about 100-110 patients (inclusion will stop when 50 patients have achieved pCR or pnCR in their index lymph node). All patients in the extension cohort will receive (after marker placement into the largest lymph node metastasis) the same neoadjuvant ipilimumab + nivolumab combination scheme (the OpACIN-neo winner scheme). After 6 weeks of treatment, the patients will undergo a solitary lymph node removal of the marked index lymph node. Patients achieving pCR or pnCR will not undergo a subsequent CLND and will not receive any adjuvant therapy. Patients achieving pPR will undergo CLND and start follow-up thereafter in line with OpACIN-neo without any adjuvant therapy. Patients achieving pNR will undergo CLND and start at week 12 adjuvant radiotherapy (at patient*s and treating physician*s discretions) and adjuvant nivolumab 480mg q4wks for 52 weeks. In case of commercially available pNR patients that are BRAF V600E/K mutation positive may also receive adjuvant dabrafenib + trametinib (then after radiotherapy when indicated) instead of nivolumab according to the patient*s and the treating physician*s decision

Intervention

In OpACIN-neo patients will be treated pre-surgically for 6 weeks with the combination of ipilimumab + nivolumab at three different combination schemes (30 patients per arm).
Medicine tested: 2 courses ipilimumab 3 mg/kg plus nivolumab 1 mg/kg q3wks, versus 2 courses ipilimumab 1 mg/kg plus nivolumab 3 mg/kg q3wks, versus 2 courses ipilimumab 3 mg/kg q3wks, directly followed by 2 courses nivolumab 3 mg/kg every 2 weeks.
Lab testing (incl. collection of PBMC and EDTA blood for plasma and thrombocyte isolation) will be performed during screening, at baseline, week 6 pre-surgery and directly post-surgery, and at week 12.
Tumor biopsies/material preservation is required at baseline and during surgery.
CT scans will be required at baseline and at week 6.
Follow-up will start at week 12 with a CT or PET /CT scan according to the individual center*s standard. Subsequent follow-up will be by PET/CT or CT scans according to the national/institutional standards for high-risk melanoma (CT 3 monthly in the first years in the extension cohort).
Collection of another PBMC and EDTA blood (for plasma and thrombocyte isolation) sample, and collection of tumor biopsies will be performed at the time point of relapse.

In the PRADO extension cohort patients will be treated pre-surgically for 6 weeks with the winner combination of ipilimumab + nivolumab (about 100-110 patient, stopping inclusion when 50 patients have achieved pCR or pnCR).

Study burden and risks

Until recently, there was no standard adjuvant therapy for patients with high-risk stage III melanoma. Post-surgery adjuvant radiotherapy is commonly applied, because it has been shown to marginally improve local disease control, but neither benefit in RFS, nor overall survival (OS), can be achieved in this high-risk patient population [1, 2]. High-dose interferon is currently the only systemic therapy for the adjuvant treatment of melanoma that is approved in some countries. However, questionable survival benefit (two out of three meta-analyses found no OS benefit [3-5]) and serious toxicity has led to the fact that interferon is not a generally accepted adjuvant treatment.
Recently, adjuvant systemic targeted therapy with dabrafenib and trametinib in BRAFV600E/K mutation positive patients has been shown to improve significant RFS and OS (not significant) [6]. Grade 3/4 toxicities were reported to be 41%.
Adjuvant systemic immunotherapy with ipilimumab is the only treatment so far to improve RFS and OS in stage III melanoma [7]. Immune-related grade 3 or 4 adverse events occurred in 41.6% of patients treated with ipilimumab 10 mg/kg adjuvant. Due to the high grade of toxicity and due to the upcoming trial with anti-PD-1adjuvant ipilimumab was not filed for approval as adjuvant therapy.
Recently, two phase 3 trials showed RFS benefit from anti-PD-1 adjuvant. Both, nivolumab and pembrolizumab improved significantly RFS (as compare to ipilimumab and placebo respectively), however OS benefit data are pending. Treatment-related grade 3/4 toxicity rates were clearly lower with 14.4% and 14.7% [8, 9]. Screen failure rate was high in the adjuvant pembrolizumab E1325 trial, with a total of 30% screen failures, and 14% due to early relapse within 12 weeks post-surgery, making RFS judgement on adjuvant and neoadjuvant trials (latter representing more intention to treat populations) hard to compare due to the high patient selection in the adjuvant trials. Due to the lack of OS data, adjuvant PD-1 blockade might be delayed in approval and availability for stage III melanoma patients.
Participants of this study will be exposed to two immunotherapeutic agents (ipilimumab and nivolumab) known to induce immune related adverse events at a high percentage when combined together [10]. This has been also observed in the precursor phase 1 trial (OpACIN) in which 90% of the patients developed grade 3/4 toxicities (Blank et al., in revision). 4 patients developed severe irAE: one patient developed life-threatening Steven-Johnson syndrome (after 3 courses ipilimumab + nivolumab) that recovered upon mycophenolate, one patient developed severe long-term colitis that has been stabilized with tacrolimus and recovered after months, one patient developed insulin dependent diabetes mellitus, and one patient developed polyradiculitis recovering after 1 year of revalidation. Due to these toxicities all, except 2 patients, had to stop earlier resulting in a maximum application of 2-3 courses of ipilimumab + nivolumab, independent of neo-adjuvant versus adjuvant treatment.

While such immune-related adverse event could hamper on-time surgery, we have not observed this within our OpACIN phase 1 trial, as all neo-adjuvant patients have undergone lymph node dissection on time at week 6.
On the benefit side, of the 10 patients treated in the neo-adjuvant arm of OpACIN, 5/10 patients had a PR, 2/10 SD, and 1/10 PD on CT-scan according to RECIST 1.1after the first 2 courses (in 2 patients there was no CT-scan performed before surgery). Moreover, 7/9 patients in the neoadjuvant arm achieved a pathologic response, and none of the responders has relapsed. This results currently in a 80% RFS rate and 90% OS rate at 25 months median follow-up (minimum follow-up 15 months).
These observations have led to the design of this phase 2 trial that will test only 2 courses of neo-adjuvant ipilimumab + nivolumab with tighter discontinuation rules (Chapters 6.7 - 6.9), and in 3 different combination schemes with the aim to reduce toxicity while preserving efficacy.
The design of the additional combination schemes to be tested (arm B and C) in this study are based on several observations from other early phase trials in stage 4 melanoma: a) in the phase 1 study testing ipilimumab + nivolumab in late stage melanoma also 4 courses of a lower dose of ipilimumab (1 mg/kg) were tested in combination with nivolumab 3 mg/kg indicating equally efficacy (CA209-004) [11], b) data from the Keynote 029 study testing low dose ipilimumab (1 mg/kg) with the standard dose of pembrolizumab (2 mg/kg) in 153 patients indicate that frequency of grade 3/4 toxicity is lower (to 42%), while disease control is preserved (G. Long, ASCO 2016 meeting), and c) data from a retrospective analysis of late stage melanoma patients treated at the NKI with 2 courses ipilimumab 3 mg/kg q3wks, directly followed the next day by pembrolizumab or nivolumab at standard dosing (2 mg/kg q3wks or 3 mg/kg q2wks respectively). This sequential scheme also induced a similar disease control rate, as compared to the phase 3 trial testing the standard scheme ipilimumab + nivolumab [12], but was less toxic. We observed in only 38% of the patients grade 3/4 treatment-related toxicity [13]. Subsequently, we regularly treated stage 4 melanoma patients with ipilimumab 3mg/kg for 1 or 2 courses, directly followed by nivolumab or pembrolizumab, starting on the same day after the ipilimumab infusion (2 hours observation interval), observing no additional toxicities (manuscript in preparation).
Thus, the risk of neo-adjuvant immune related toxicity in OPACIN-neo was considered to be lower (mainly in arm B or C) than that of patients within the phase I OpACIN trial. In the planned interim analysis after 39 patients of OpACIN-neo this was indeed the case observing 38%, 16%, and 46% grade 3/4 toxicities, respectively for the three arms. Unplanned additional interim analyses in April and May 2018 (performed upon request of the DSMB and due to report of a severe colitis in Arm C), reveled similar toxicity rates with 40%, 25%, and 50% for arm A, B, and C respectively. Arm C was closed earlier after 26 patients had been included upon the advice of the DSMB.
In addition, in OpACIN-neo patients are not allowed to be treated with local radiotherapy, which bears the risk of reduced local tumor control. Considering the fact that local irradiation only improves local tumor control, but does not improve RFS or OS [1], participation in this trial might offer the chance for

improved recurrence free survival. This is based on the observation that adjuvant ipilimumab has already shown RFS benefit in a prospective randomized controlled phase 3 trial in stage III patients, the combination of ipilimumab with nivolumab induces superior response rates as compared to ipilimumab alone in stage IV melanoma [7, 11, 12, 14], and the high response rates observed in the neo-adjuvant arm of the OpACIN trial.
In the PRADO extension cohort, patients will undergo resection of the marked lymph node and pathologic response will be assessed. Only patients responding on immunotherapy will not receive adjuvant radiotherapy. Non-responders may receive adjuvant radiotherapy and adjuvant systemic therapy (nivolumab or dabrafenib + trametinib). Patients achieving pCR or pnCR will not undergo subsequent CLND. Patients without CLND might bear a higher risk of relapse, which is the scope of this part of the trial to show that it is not the case.
At the same time, they can benefit from reduced surgery-related adverse event. An additional burden as compared to standard therapy is, that the patients possibly need to undergo an additional anesthesia if the location of the marked lymph node is too deep for removal under local anesthesia.
To ensure the safety of these patients, a strict safety rule will be implement

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

• Adults at least 18 years of age
• World Health Organization (WHO) Performance Status 0 or 1
• Cytologically and histologically confirmed resectable stage III melanoma with one or more macroscopic lymph node metastases (measurable according to RECIST 1.1), that can be biopsied, and no history of in-transit metastases within the last 6 months
• No other malignancies, except adequately treated and a cancer-related life-expectancy of more than 5 years
• Patient willing to undergo triple tumor biopsies and extra blood withdrawal during screening and in case of relapse
• No prior immunotherapy targeting CTLA-4, PD-1 or PD-L1
• No immunosuppressive medications within 6 months prior study inclusion
• Screening laboratory values must meet the following criteria: WBC >= 2.0x109/L, Neutrophils >=1.5x109/L, Platelets >=100 x109/L, Hemoglobin >=5.5 mmol/L, Creatinine <=1.5x ULN, AST <= 1.5 x ULN, ALT <= 1.5 x ULN, Bilirubin <=1.5 X ULN
• Normal LDH

Exclusion criteria

• Distantly metastasized melanoma
• Brain metastases
• History of in-transit metastases within the last 6 months
• No measurable lesion according to RECIST 1.1
• Subjects with any active autoimmune disease or a documented history of autoimmune disease, or history of syndrome that required systemic steroids or immunosuppressive medications, except for subjects with vitiligo or resolved childhood asthma/atopy
• Prior CTLA-4 or PD-1/PD-L1 targeting immunotherapy
• Radiotherapy prior or post-surgery (except for non-responders in PRADO extension cohort; in this group is adjuvant radiotherapy allowed)
• Patients who test positive for hepatitis B or C or HIV.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-11-2016
Enrollment:	80
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:	08-11-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-11-2016

Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-12-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-07-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-11-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-12-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-04-2019

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-04-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-08-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	07-01-2025
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-01-2025
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
EudraCT	EUCTR2016-001984-35-NL
CCMO	NL58906.031.16