Multicenter Phase 1b trial testing the Neoadjuvant Combination of Domatinostat, Nivolumab, and Ipilimumab, in IFN-gamma signature-low and IFN-gamma signature-high RECIST 1.1-measurable Stage III Cutaneous or Unknown Primary Melanoma -DONIMI.

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Primary objectives: - To assess safety and feasibility of neoadjuvant nivolumab +/- domatinostat +/- ipilimumab- To identify pathologic response rates of nivolumab +/- domatinostat +/- ipilimumabSecondary objectives: - To describe all grade...

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

Summary

ID

NL-OMON54971

Source
ToetsingOnline

Brief title
DONIMI

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: 4SC

Intervention

Keyword: domatinostat, ipilimumab, melanoma, nivolumab

Outcome measures

Primary outcome

- Safety and feasibility of patients as measured by the adherence to the timelines in the study protocol. A treatment arm will be declared as not feasible if 2/5 or 4/10 patients cannot adhere to the planned time of surgery (week 6 +/- 1 week) due to treatment related adverse events.

- Pathologic response rates (pPR, near-pCR, and pCR).

Secondary outcome

- Frequency of treatment-related toxicities as measured according to CTCAE 5.0.

- RFS, as determined according to RECIST 1.1 criteria.

- Identification of RNA signatures associated with pathologic response and RFS for each arm (by RNAseq and NanoString gene expression analysis).

- Characterization of changes in immune infiltrates/markers at week 3 and/or 6 compared to baseline by NanoString DSP technology.

- Inter-arm comparison of the expansion of tumor-resident T cell clones, as measured by TCR sequencing of the baseline tumor-biopsy and PBMC samples from baseline week 3 and week 6.

- Feces microbiome diversity analyses and its correlation with pathologic

response and toxicities.

- Quality of life as measured by EORTC QLQ C30, the melanoma and the surgery subscale of FACT-M, the Cancer Worry Scale, HADS questionnaire and assessment of work performance.

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. In earlier stage melanoma ipilimumab + nivolumab is currently tested in the adjuvant setting (Checkmate 915, NCT03068455) in stage III melanoma, after ipilimumab, nivolumab, and pembrolizumab monotherapies have all shown to improve relapse free survival (RFS), and overall survival (OS, to date only for ipilimumab) in phase 3 trials. In addition, adjuvant targeted therapy using the BRAF+MEK inhibitor combination of dabrafenib + trametinib in BRAFV600E/K mutation positive patients has been shown to improve RFS and OS (only RFS significantly).
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 - MHC 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 (neoadjuvant treatment).
In melanoma, this concept was pioneered by the Netherlands Cancer Institute testing in a phase 1 trial neo-adjuvant and adjuvant application of 4 courses of ipilimumab + nivolumab in stage III melanoma (OpACIN, CA209-278, NCT02437279), showing that neo-adjuvant immunotherapy was feasible, but with

the current standard regimen (4 courses ipilimumab 3mg/kg + nivolumab 1mg/kg) too toxic for (neo)adjuvant application. Pathologic responses (pRR) 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 32 months. The expansion of tumor-resident T cell clones was more frequent after neoadjuvant application and a baseline interferon (IFN)-gamma signature was associated with outcome (IFN-gamma low patients had a very high chance for relapse after neoadjuvant ipilimumab + nivolumab).
The observed feasibility and pathologic responses, combined with the observed toxicity, formed the rationale for the design of the subsequent phase 2 trial, OpACIN-neo (NCT02977052), that compared safety and efficacy of three different dosing schemes of neo-adjuvant ipilimumab + nivolumab. With only two neoadjuvant courses of ipilimumab + nivolumab, this trial confirmed the high efficacy of targeting CTLA-4 and PD-1 in the neoadjuvant setting and identified a combination scheme (ipilimumab 1mg/kg + nivolumab 3mg/kg) that was tolerated (20% grade 3/4 toxicity rate with no specific grade 3/4 toxicity >5%), while efficacy was preserved (77% pRR). Again, the baseline IFN-gamma signature discriminated patients with a high chance for relapse (IFN-gamma signature low) and no relapse (IFN-gamma signature high) after neoadjuvant ipilimumab + nivolumab. The signature was insufficient discriminative in this larger cohort for intermediate IFN-gamma signature patients.
The identified winner combination is currently tested in the PRADO extension cohort to confirm the pRR and toxicity rate in a larger cohort of patients. The other aim of the PRADO extension cohort is to test whether a subsequent lymph node dissection can be omitted in patients achieving a major pathologic response (pCR or near pCR).
However, as only 77-78% of patients have pathologic response upon neoadjuvant ipilimumab + nivolumab, and patients with no pathologic response are at very high risk for relapse (currently 57%), there is a need for identification of new treatment combinations that can induce responses in patients that do not respond to neoadjuvant ipilimumab + nivolumab.
Patients that do relapse after neoadjuvant ipilimumab + nivolumab are characterized, in addition to the negative IFN-gamma signature, by low PD-L1 expression, low tumor T cell infiltration, and lower b2m expression.
Domatinostat tosilate (domatinostat) is an orally available HDACi that specifically inhibits the class I HDAC isotypes 1, 2 and 3. In preclinical studies, domatinostat inhibits Wnt and Hedgehog (HH) signaling pathways, which are relevant for proliferation, differentiation and metastasis of tumor cells.
In addition, in preclinical models it has been shown that domatinostat increases tumor T cell infiltration, MHC and CD86 expression and presentation of tumor-associated antigens. Furthermore, the combination of domatinostat with checkpoint inhibitors (PD-1 or PD-L1) resulted in reduced tumor growth and prolongued survival in syngeneic mouse models. This makes domatinostat an attractive combination partner for checkpoint inhibitors and other immunotherapies.
Since the combination of domatinostat with anti-PD-(L)1 did not increase the frequency or intensity of immune-related AEs, domatinostat could be a

well-tolerated combination partner for checkpoint inhibiting antibodies in stage III disease.
These hypotheses form the rationale for DONIMI, a phase 1b trial testing the combination of domatinostat + nivolumab or nivolumab monotherapy in IFN-gamma signature high patients and of domatinostat + nivolumab or domatinostat + nivolumab + ipilimumab in IFN-gamma signature low patients with de-novo or recurrent macroscopic stage III cutaneous or unknown primary melanoma.

Study objective

Primary objectives:
- To assess safety and feasibility of neoadjuvant nivolumab +/- domatinostat +/- ipilimumab
- To identify pathologic response rates of nivolumab +/- domatinostat +/- ipilimumab

Secondary objectives:
- To describe all grade toxicities of the regimens
- To describe relapse free survival (RFS)
- To identify subgroups of patients benefiting from the individual schemes
- To compare the immune activating activity of the combination schemes
- To identify baseline biomarkers predictive for pathologic complete response (pCR)/pathologic near complete response (pnCR)
- To evaluate health related quality of life

Study design

This is an open-label phase 1b trial consisting of 45 stage III cutaneous or unknown primary melanoma patients with RECIST 1.1 measurable de-novo or recurrent disease (short axis lymph node metastasis >=1.5cm).
NanoString IFN-gamma signature high patients will be randomized to:
- 6 weeks neo-adjuvant treatment with nivolumab (10 patients).
- 6 weeks neo-adjuvant treatment domatinostat + nivolumab (10 patients).

NanoString IFN-gamma signature low patients will be randomized to :
- 6 weeks neo-adjuvant treatment with domatinostat + nivolumab (10 patients)
- 6 weeks neo-adjuvant treatment with domatinostat + nivolumab + ipilimumab (20 patients). Based on the safety data of this dosing scheme, the domatinostat dose can be increased (200mg BID, d1-14, q3wks), decreased (100mg OD, d1-14, q3wks) or kept at the same dosing scheme 200mg OD, d1-14, q3wks). The trial was initially designed to decide on the dose increase/decrease after 5 patients were treated in arm D. However, based on the safety data of the first 5 patients in arm D, the DSMB advised to continue with the same dosing scheme of 200mg OD, d1-14, q3wks and to re-evaluate a potential dose increase after 10 patients. After 10 patients were treated, the DSMB decided that is was safe to increase the domatinostat dose to the 200mg BID dosing scheme, d1-14 q3wks. We

therefore expanded this arm with 10 extra patients to be treated with the 200mg BID scheme (20 patients in total) for the evaluation of feasibility and safety.

Post-surgery (starting at week 12), the patients will start with adjuvant nivolumab or pembrolizumab for 52 weeks according to institute*s standard. In case of no pathologic response after neoadjuvant immunotherapy, the alternative application of adjuvant dabrafenib + trametinib should be considered in BRAFV600E/K mutation positive patients.
Follow-up after the adjuvant therapy will be for 2 years, according to the institutes* standard.
Screening will require approximately 80-100 patients (NanoString IFN-gamma signature) to identify the 20 IFN-gamma signature low and 20 IFN-gamma signature high patients.
Toxicity and pathologic response rates will be descriptive.
In case of 2/5 or 4/10 patients not undergoing their lymph node dissection at week 6 +/- 1 week due to treatment related toxicity, this arm will be declared unfeasible.

Intervention

In DONIMI patients will be treated pre-surgically for 6 weeks with the combination of nivolumab +/- domatinostat +/- ipilimumab. For ipilimumab and nivolumab flat-dose equivalents of the winner scheme identified in OpACIN-neo will be applied.
Medicine tested: 2 courses nivolumab 240mg q3wks +/- domatinostat 200mg QD, d1-14, q3wks +/- ipilimumab 80mg q3wks.
Lab testing (incl. collection of PBMC, plasma, serum, feces) will be performed during screening, at week 3, and at week 6 pre-surgery.
Tumor biopsies for material preservation is required at baseline, week 3, and from the surgery specimen.
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*s/institutional*s standards for high-risk melanoma (3 monthly most common standard).
Collection of additional PBMC, plasma, serum, feces, and tumor biopsies will be performed in case of relapse.

Study burden and risks

Standard adjuvant therapy for patients with high-risk stage III melanoma is currently either nivolumab, pembrolizumab or adjuvant dabrafenib + trametinib (for BRAF V600 mutant patients only). These standard options are based on phase 3 trials showing improved RFS without showing significant OS benefit so far. Adjuvant nivolumab and pembrolizumab improved significantly RFS (as compare to ipilimumab and placebo respectively). Treatment-related grade 3/4 toxicity

rates were low with 14.4% and 14.7%. The 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 comparing adjuvant and neoadjuvant trials (latter representing more intention-to-treat populations) hard to compare due to the high patient selection in the adjuvant trials.
Adjuvant dabrafenib + trametinib also improved significantly the RFS in BRAF V600 mutation-positive patients. Grade 3/4 toxicity rate was 41% as compared to 14% in the placebo arm, and thus clearly higher than for adjuvant anti-PD-1.
The participants in this trial will be exposed to one or two immunotherapeutic agents (ipilimumab, nivolumab) known to induce immune related adverse events, resulting in expected higher grade 3/4 toxicities rate of at least 20% (as based on the OpACIN-neo trial data). Therefore, the rate of grade 3/4 toxicity is expected to be higher than for anti-PD-1 adjuvant therapies, but lower than for the standard adjuvant BRAF + MEK inhibition. While such immune-related adverse event could hamper on-time surgery, we have not observed this within our OpACIN and OpACIN-neo trials.
Domatinostat is currently under evaluation in two phase 1b/2 trials in combination with pembrolizumab and in combination with avelumab (SENSITIZE and EMERGE). The pattern of AEs in the combination trials were mild to moderate and similar to the one in the TOPAS monotherapy trial. No increase in frequency or intensity of immune-related AEs could be observed in combination with anti-PD-(L)1 antibodies so far (cut-off-date: 15-July-2019). In a third trial (KN0142) the HDAC inhibitor entinostat was combined at standard dosing of 5mg qw with pembrolizumab 200mg q3w (Sullivan et al., AACR 2019). Similarly, in this trial the addition of the HACDi did not increase the frequency of grade 3/4 immune related toxicities beyond the expected percentages known for prembrolizumab monotherapy (9.4% grade 3/4 toxicities with rash, colitis, pneumonitis and ir hepatitis being most frequent ranging fom 1.9 to 3.8%). We expect that the same will be the fact for the triple combination of ipilimumab, nivolumab and domatinostat in stage III patients. However, since the triple combination has not been tested in humans before, the first 5 patients in this arm will be treated with a lower dose of domatinostat (200mg OD, d1-14) followed by the 200mg BID, d1-14 dosing scheme.
Additional burden evolving from participation in this trial are extra blood draws, two additional CT scans, feces collection, and two (three in case of relapse) additional tumor biopsies. Also, patients are asked to fill in a diet questionnaire and several questionnaires about their quality of life.
On the benefit side, patients treated in this trial with neoadjuvant checkpoint inhibition and HDACi can be judged concerning their pathologic response, and if needed, the therapy can be adjusted for the adjuvant therapy if other adjuvant therapies are approved and available. This might lead to a benefit for the individual patient concerning their outcome as compared to applying standard adjuvant therapy only.
To ensure the safety of these patients, a data safety monitoring board will be installed, and a strict safety rule will be implemented, closing any treatment cohort if 2/5 or 3/10 patients are unable to undergo their lymph node

dissection due to treatment related adverse events from the neoadjuvant immunotherapy combination.
For arm D, the DSMB will be consulted after 5 patients are treated with the lower domatinostat dose (200mg OD, d1-14). Based on the amount of grade 3-4 AEs, completion of two neoadjuvant treatment cycles and timely performance of surgery, the decision will be made about proceeding into the higher domatinostat dosing schedule (200mg BID, d1-14).

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 or histologically confirmed resectable stage III cutaneous

melanoma (unknown primary also allowed) 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.
- IFN-gamma signature low or high according to the NanoString test (IFN-gamma signature intermediate not allowed).
- No other malignancies, except adequately treated and a cancer-related life-expectancy of more than 5 years.
- Patient willing to undergo quadruple tumor biopsies and extra blood withdrawal during screening, week 3 and in case of relapse.
- No immunosuppressive medications within 6 months prior trial registration.
- 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.
- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of ipilimumab + nivolumab.
- Patient is capable of understanding and complying with the protocol requirements and has signed the Informed Consent document.

Exclusion criteria

- Distantly metastasized melanoma.
- Uveal or mucosal melanoma.
- History of in-transit metastases within the last 6 months.
- No measurable lymph node 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.
- Patients with any active gastrointestinal disorder that could interfere with the absorption of domatinostat (as per judgement of the investigator), such as ulcerative colitis, Crohn*s disease, diabetic gastroparesis, or other syndromes characterized by malabsorption.
- Prior CTLA-4 or PD-1/PD-L1 targeting immunotherapy.
- Prior radiotherapy.
- Patients will be excluded if they test positive for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody), indicating acute or chronic infection; if treated and being at least one year free from HCV patients are allowed to participate.
- Patients will be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
- Allergies and Adverse Drug Reaction:

- History of allergy to study drug components;
- History of severe hypersensitivity reaction to any monoclonal antibody.
- Underlying medical conditions that, in the Investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity or adverse events.
- Patients with a marked baseline prolongation of QT/QTc interval, e.g., repeated demonstration of a QTc interval >450 msec (Grade 1 NCI-CTCAE); Long-QT-Syndrome) and patients receiving agents known to prolong the QT interval and known risk of Torsades de Pointes.
- Patients with significant current cardiovascular disease including:
- Unstable angina pectoris within 6 months prior to screening
- Uncontrolled hypertension
- Congestive heart failure (New York Heart Association (NYHA) Class III or IV) related to primary cardiac disease
- Conditions requiring anti-arrhythmic therapy (patients with status post pace maker implantation can be included)
- Symptomatic ischemic or severe valvular heart disease, or a myocardial infarction within 6 months prior to the trial entry
- Women who are pregnant or lactating
- Use of other investigational drugs before study drug administration 30 -days and 5 half-times before trial registration.

Study design

Design

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:	Completed
Start date (anticipated):	07-01-2020
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Domatinostat
Generic name:	Domatinostat
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:	20-11-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	29-11-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	12-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-10-2020
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	30-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-07-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-07-2021
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	EUCTR2019-002878-30-NL
ClinicalTrials.gov	NCT04133948
CCMO	NL70859.031.19