Feasibility Study to Identify the Optimal Adjuvant Combination Scheme of Ipilimumab and Nivolumab in resectable stage III melanoma patients (OpACIN)

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Primary objective: To determine safety, feasibility, and the immune-activating capacity of short-term combined neo-adjuvant and adjuvant ipilimumab + nivolumab.Secondary objectives: To determine relapse free survival (RFS), any late adverse events,...

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

Summary

ID

NL-OMON42085

Source
ToetsingOnline

Brief title
Study to identify the Optimal Adjuvant Scheme in melanoma patients (OpACIN)

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: Bristol-Myers Squibb,zie G2.

Intervention

Keyword: adjuvant, ipilimumab, melanoma, nivolumab

Outcome measures

Primary outcome

Primary readout will be the alteration in magnitude or breadth of the neo-antigen specific T cell response in the time interval pre- to post-adjuvant therapy in peripheral blood. To this purpose the immunogenic mutational load of each patient*s melanoma will be determined by DNA and RNA sequencing from baseline biopsies (3x14g, 5ug tumor DNA). Proteasomal degradation and peptide presentation in HLA will be predicted in silico. MHC-tetramer staining containing the predicted peptides will be done as described before.
In addition, we will analyze the effect of therapy on intratumoral T cell responses to obtain better insight into the mode of action of therapy.
Identified neo-antigen specific T cells will be analyzed with respect to their phenotype and immunologic function (intracellular cytokine staining, lytic function as determined by CD107 staining, and coculture with APC presenting the cognate antigen).
Safety and feasibility as measured by SUSARs and adherence to the timelines in the study protocol.

Secondary outcome

RFS, as determined according to RECIST 1.1 criteria.
Rate and type of adverse events and late adverse events
Correlation between RFS and the delta of magnitude and/or breadth of

neo-antigen T cell population

Pharmacokinetics and pharmacodynamics of nivolumab and ipilimumab comparing the

two different treatment arms

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 has been tested with promising results in stage III melanoma, however due to short follow-up time (median 3 years) up-to now, no melanoma specific survival (MSS) data could be analyzed or reported. These results are expected by 2016.
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, we postulate, that adjuvant immunotherapy will work most efficiently, when adjuvant treatment is initiated prior to surgery.

Study objective

Primary objective: To determine safety, feasibility, and the immune-activating capacity of short-term combined neo-adjuvant and adjuvant ipilimumab + nivolumab.
Secondary objectives: To determine relapse free survival (RFS), any late adverse events, pharmacokinetics/pharmacodynamics, and the correlation between

RFS and changes in neo-antigen specific T cell response

Study design

This is a two-arm phase 1b feasibility trial consisting of 20 patients receiving the combination of ipilimumab+nivolumab, either adjuvant, or split neo-adjuvant and adjuvant.

Intervention

Resectable stage III melanoma patients with palpable lymph nodes, naïve for CTLA-4/PD-1/PD-L1 immunotherapy, will be treated either post-surgery for 12 weeks with the combination of ipilimumab+nivolumab or in a split design for 6 weeks upfront surgery and for 6 weeks post-surgery (10 patients per arm).
Medicine tested: Ipilimumab 3 mg/kg q3wks, Nivolumab 1 mg/kg q3wks
Lab testing (incl. PBMC, serum collection) will be performed during screening, at baseline, direct post-surgery, at the indicated time points until week 18, and subsequently every three months.
Tumor biopsies/material preservation is required at baseline and during surgery.
CT scans will be required at baseline, week 6 (only neo-adjuvant arm), week 18, and subsequently every 3 months up to 3 years.
Another PBMC, serum collection and tumor biopsies will be performed at the timepoint of relapse.

Study burden and risks

Currently there is no standard adjuvant therapy for stage III melanomas. 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. 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) and serious toxicity has led to the fact that interferon is not a generally accepted adjuvant treatment in Europe. Adjuvant systemic immunotherapy with ipilimumab is the only treatment so far to improve RFS in stage III melanoma. However, OS benefit has not been shown thus far (possible due to short follow-up period) and toxicity was high, mainly when applied longer than four courses of ipilimumab (12 weeks).
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. However, this exposure will be restricted to 4 courses (12 weeks) in total.
In addition patients within this trial cannot 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, 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 this benefit in a prospective randomized controlled phase 3 trial in stage III patients and the combination of ipilimumab with nivolumab induces superior response rates as compared to ipilimumab alone in stage IV melanoma.

Contacts

Public
Nederlands Kanker Instituut

Plesmanlaan 121
Amsterdam 1066CX
NL
Scientific
Nederlands Kanker Instituut

Plesmanlaan 121
Amsterdam 1066CX
NL

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
• Histologically confirmed resectable stage III melanoma with palpable lymph node

metastases and no history or active in-transit metastases within the last 6 months
• Patient willing to undergo triple tumor biopsies during screening and in case of disease progression
• No prior immunotherapy targeting CTLA-4, PD-1 or PD-L1
• No immunosuppressive medications within 6 months prior study inclusion
• Presence of at least two of the defined HLA alleles
• 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 (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug
• 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
• Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year Men who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product
• Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception

Exclusion criteria

• Distantly metastasized 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, 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 within this trial
• Patients will be excluded if they are positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection
• 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 determination or adverse events;
• Concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids;
• Use of other investigational drugs before study drug administration 30 days and 5 half-times before study inclusion

• Pregnant or nursing

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-08-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nivolumab
Generic name:	nivolumab
Product type:	Medicine
Brand name:	Yervoy
Generic name:	ipilimumab
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	19-12-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	20-03-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	17-06-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2014-004764-38-NL
CCMO	NL51280.031.14