Neo-adjuvant T-VEC + Nivolumab combination therapy for resectable early metastatic (stage IIIB/C/D-IV M1a) melanoma with injectable disease.

Published: 04-06-2020
Last updated: 10-04-2024

Primary objective:- To investigate if neo-adjuvant combination of talimogene laherparepvec and nivolumab will achieve a pathologic response rate of 45% complete responses (either *pathological complete response (pCR)* or *pathological near complete...

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

Summary

ID

NL-OMON49074

Source
ToetsingOnline

Brief title
NIVEC

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: Amgen,farnaceutisch bedrijf

Intervention

Keyword: melanoma, Nivolumab, T-VEC

Outcome measures

Primary outcome

- Pathologic response according to central revision by pathology of NKI

(com-plete response, near complete response (<10% vital tumor remaining)).

Secondary outcome

- Rate of delay of surgery >14 days and rate of failure to perform surgery

de-fined as no surgery at all (due to PD or AE).

- Relapse free survival (RFS) as defined from date of surgery until date of

first replase (regardless of site).

- Safety of neo-adjuvant combination of talimogene laherparepvec and nivolumab

according to CTCAE v5.0.

- Description of possible prognostic and predictive biomarkers.

Study description

Background summary

Currently, standard treatment options available for Stage III disease include locoregional management (i.e. surgery) or systemic treatment (adjuvant to surgery or primarily in the case of unresectable disease).
Adjuvant treatment options have shown major improvements in OS and relapse free survival (RFS) in resected stage III or IV melanoma.
In our daily practice, T-VEC monotherapy is used for unresectable Stage IIIB-IVM1a (injecta-ble) disease, whereas Nivolumab is used for stage IV melanoma (among other systemic therapies).
The next major developments are in neo-adjuvant treatment options for resectable stage III disease, where 3 small studies reported high response

rates with systemic immunotherapy.

This study evaluates the combination treatment of T-VEC + Nivolumab in the neo-adjuvant setting. The concept is that T-VEC can turn an immune desolate *cold* tumor into an immu-nogenic *hot* tumor. The hypothesis is that this will upregulate the expression of PD-L1 and make it more susceptible for treatment with an anti-PD-1 agent. We believe neo-adjuvant Nivolumab + T-VEC will thus change the tumor microenvironment in patients with stage IIIB/C/D/IVM1a (AJCC 8) melanoma with resectable cutaneous or subcutaneous satellite or in-transit metastases (ITM) and/or tumor positive lymph nodes. With this trial we aim to de-termine safety and feasibility of combination neo-adjuvant Nivolumab + T-VEC in patients with stage III melanoma with resectable ITM and/or tumor positive lymph nodes. The treat-ment schedule is based on 4 courses of intralesional T-VEC and 3 courses of intravenous Nivolumab. T-VEC first, in order to achieve the best synergistic effect with influx of CD8+ T cells prior to the first Nivolumab dose. T-VEC monotherapy with the dose 108 PFU/mL is given every 2 weeks (± 3) days after 3 weeks of the first T-VEC dose (with the first dose of T-VEC 106 PFU/mL to allow for seroconversion) , and Nivolumab can be given either every 2 weeks or every 4 weeks. Therefore we suggest the same dosing schedule for T-VEC and Nivolumab every 2 weeks for the purpose of this trial.

Recent data of neo-adjuvant T-VEC monotherapy in patients with resectable stage IIIB-IVM1a melanoma has shown pathologic complete response rates (pCR) in 17.1 - 22.8%, with 13.2% clinical ORR. Recent data for neo-adjuvant pembrolizumab therapy showed pCR and near pCR rates of 30% and neo-adjuvant nivolumab showed pCR rates of 25%.With these data and the hypothesis of the additive effect of T-VEC in combination with nivolumab, we aim to show improved pathological complete responses (pCR) or pathological near-pCR up to 45% (either pCR or near-pCR defined as no viable tumor present or <=10% viable tumor present, resepectively defined by the International Neo-adjuvant Melanoma Consortium (INMC) as described by Tetzlaff et al.) in patients with stage IIIB/C/D/IV M1a (AJCC 8) melanoma when treated with combination T-VEC and nivolumab in the neo-adjuvant setting.

Study objective

Primary objective:
- To investigate if neo-adjuvant combination of talimogene laherparepvec and nivolumab will achieve a pathologic response rate of 45% complete responses (either *pathological complete response (pCR)* or *pathological near complete response (near-pCR)*, in patients with stage IIIB/C/D/IV M1a (AJCC 8) melanoma.

Secondary objectives:
- To investigate the rate of delays or failures (delays >=14 days) to perform surgery.
- To investigate the effect of neo-adjuvant comabination of talimogene

laherparepvec and nivolumab on relapse free survival (RFS).
- To determine the safety of neo-adjuvant combination of talimogene laherparepvec and nivolumab.
- To acquire tumor tissue for prognostic and predictive biomarker research.

Study design

Phase 2 open-label single arm single site study.

Intervention

Products: Nivolumab + talimogene laherparepvec (T-VEC)
Route of administration: Intravenous (Nivolumab) + intralesional (T-VEC)
Dosing:
- Nivolumab: Flatdose of 240mg Nivolumab intravenously every 2 weeks after the first intralesional T-VEC injections (starting at 2nd T-VEC dose at week 3, followed by the next doses at week 5 and 7).
- T-VEC: Up to 4ml T-VEC (first dose 10^6 PFU per mL, subsequent doses at 10^8 PFU per mL) in week 0, 3, 5 and 7.
Treatment duration: 7 weeks (week 0, week 3, week 5 and week 7, resection at week 9).
(Thus 4 doses of T-VEC (1 x 10^6, 3 x 10^8) and 3 courses of Nivolumab (240mg))

Study burden and risks

Currently patients with resectable cutaneous, subcutaneous satellite or in-transit metastases and/or lymph node metastases (stage IIIB/C/D/IVM1a (AJCC 8)) are primarily operated. Thus, any neo-adjuvant approach in this patient category has the associated burden of participation in terms of neo-adjuvant treatment, which would otherwise not have been given. In this case, 4 doses of T-VEC intralesionally, which has a 100% rate of any adverse event, but usually only grade 1/2 and grade 3 or higher in a small proportion of patients (4-11% of patients). At the same time, 3 courses of Nivolumab is known to have grade 3/4 adverse events in approximately 14% of patients. Furthermore, there is the associated blood draws to determine adverse events of the drugs and to see if a next course is safe. Finally, participation in the study will require additional tumor biopsies. Considering the very high chance of relapse in this patient category (approximately 70-80% risk of relapse), any neo-adjuvant approach might reduce this risk of relapse and be of benefit to the patients, comparable to the observed results from the OpACIN and OpACIN-neo studies. However, prior to the study, we cannot be sure of this potential benefit.

Contacts

Public
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
NL
Scientific
Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121
Amsterdam 1066 CX
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.
- WHO performance score of 0 or 1.
- Cytologically or histologically confirmed diagnosis of stage IIIB/C/D/IVM1a (AJCC 8th edition) melanoma, eligible for surgical resection.
- Subjects must have measurable disease according to RECIST 1.1 and must be a candidate for intralesional therapy with at least one injectable cutaneous, subcutaneous or nodal melanoma lesion (>= 10 mm in longest diameter) or with multiple injectable lesions that in aggregate have a longest diameter of >= 10 mm.
- Prior isolated limb perfusion (ILP) is allowed (>= 12 weeks prior to enrollment).
- Screening laboratory values must meet the following criteria: - WBC >=

2.0x10^9/L, Neutrophils >=1.5x10^9/L, Platelets >=100 x10^9/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.
- LDH < 2 x ULN.
- Women of childbearing potential (WOCBP) must use highly effective method(s) of contraception during T-VEC and nivolumab treatement and for a period of 5 months after the last dose of nivolumab.
- Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 72 hours prior to en-rollment and within 24 hours prior to the start of Nivolumab.
- Men receiving nivolumab and who are sexually active with WOCBP should use contraception during treatment and for a period of 7 months after the last dose of nivolumab.
- Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year.
- Women who are not of childbearing potential (i.e., who are postmenopausal), or sur-gically sterile as well as azoospermic men do not require contraception.
- Patient is capable of understanding and complying with the protocol requirements and has signed the Informed Consent document.
- Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- International normalization ratio (INR) or prothrombin time (PT) <=1.5 x ULN, unless the subject is receiving anticoagulant therapy, in which case PT and partial thromboplastin time (PTT)/ activated PTT (aPTT) must be within therapeutic range of intended use of anticoagulants.

Exclusion criteria

- Liver, Bone, Lung, Brain or other Visceral Metastases
- No measurable lesion according to RECIST 1.1.
- Prior radiotherapy for melanoma.
- Prior systemic cancer therapies, including, but not limited to anti-CTLA-4, anti-PD-1, anti-PD-L1.
- No other malignancies, except adequately treated and a cancer-related life-expectancy of more than 5 years.
- 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.
- Patients will be excluded if they have known history of testing positive for human im-munodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
- History or evidence of active autoimmune disease that requires systemic treatment (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or

physiologic corticosteroid re-placement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Evidence of clinically significant immunosuppression such as the following:
- Primary immunodeficiency state such as Severe Combined Immunodeficiency Disease.
- Cconcurrent opportunistic infection.
- Receiving systemic immunosuppressive therapy (> 2 weeks) including oral steroid doses > 10 mg/day of prednisone or equivalent within 7 days prior to enrollment.
- Active herpetic skin lesions or prior complications of HSV-1 infection (e.g., herpetic keratitis or encephalitis).
- Requirement of intermittent or chronic systemic (intravenous or oral) treatment with an antiherpetic drug (e.g., acyclovir), other than intermittent topical use.
- Previous treatment with talimogene laherparepvec or any other oncolytic virus.
- Received live vaccine within 30 days prior to enrollment.
- Subject has known sensitivity to talimogene laherparepvec or nivolumab or any of its components to be administered during dosing.
- Female subject of childbearing potential who is unwilling to use highly effective method(s) of effective contraception during study treatment and through 5 months after the last dose of study medication (per protocol through 3 months after the last dose of talimogene laherparepvec and through 5 months after the last dose of nivolumab).
- Sexually active subjects and their partners unwilling to use male or female latex con-dom to avoid potential viral transmission during sexual contact while on treatment and within 30 days after treatment with talimogene laherparepvec.
- Subjects who are unwilling to minimize exposure with his/her blood or other body fluids to individuals who are at higher risks for HSV-1 induced complications such as immunosuppressed individuals, individuals known to have HIV infection, pregnant women, or infants under the age of 3 months, during talimogene laherparepvec treatment and through 30 days after the last dose of talimogene laherparepvec.
- No Allergies and Adverse Drug Reaction.
- History of allergy to study drug components.
- History of severe hypersensitivity reaction to any monoclonal antibody.
- No underlying medical conditions that, in the Investigator's opinion, will make the ad-ministration of study drug hazardous or obscure the interpretation of toxicity determination or adverse events.
- No use of other investigational drugs before study drug administration 30 days and 5 half-times before study inclusion.*

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):	01-10-2020
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism
Product type:	Medicine
Brand name:	Imlygic
Generic name:	T-VEC (Talimogene laherparepvec)
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	04-06-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	21-12-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-01-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2019-001911-22-NL
ClinicalTrials.gov	NCT04330430
CCMO	NL71866.000.19