Neo-adjuvant nivolumab or nivolumab with ipilimumab in advanced cutaneous squamous cell carcinoma patients prior to standard of care surgery; the MATISSE trial

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Herewith, we present a research protocol for a phase II trial that allows us to examine the efficacy (histopathological response rate) of ICI in the form of nivolumab or nivolumab plus ipilimumab prior to SOC in patients with resectable stage III-...

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

Summary

ID

NL-OMON52693

Source
ToetsingOnline

Brief title
Neo-adjuvant IT in patients with advanced CSCC prior to SOC (MATISSE)

Condition

- Skin neoplasms malignant and unspecified
- Skin neoplasms malignant and unspecified

Synonym
cutaneous squamous cell carcinoma

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cutaneous, Immunotherapy, Neoadjuvant, Squamous cell carcinoma

Outcome measures

Primary outcome

The primary endpoint will be histopathological tumor response after neo-adjuvant ICI, defined as the proportion of viable tumor cells left in the resected specimen. Responses will be divided into histopathological complete response (pCR, no viable tumor cells), histopathological near complete response (near-pCR, <=10% viable tumor cells) and histopathological partial response (pPR, <=50% viable tumor cells).

Secondary outcome

Secondary endpoints:

- Histopathological tumor response to neo-adjuvant immunotherapy as measured in the tumor resection specimen (primary endpoint) will be compared to the tumor response as measured via serial tumor biopsies, the tumor biopsy at time of surgery and imaging (clinical photography, FDG-PET and (f)MRI).
Histopathologic response in the tumor biopsies will be defined similarly as histopathologic response in the resected specimen. Response at imaging studies will be measured as follows: Clinical photography via specific clinical observation criteria (paragraph 8.3), FDG-PET via EORTC criteria and % change in TLG or MTV (paragraph 8.3), and (f)MRI via RECIST 1.1. and experimental

measures (paragraph 8.3).

- Rate and type of AE (NCI CTCAE v 5.0) prior to standard of care, and no significant delay (>1 week) or cancelation of SOC surgery due to immune-related toxicity.

- RFS at 2 years FU of responders versus non-responders to neo-adjuvant ICI

- OS at 2 years FU of responders versus non-responders to neo-adjuvant ICI

- Rate and type of AE (NCI CTCAE v 5.0) up to 2 years FU after SOC

- Clinical and histopathalogical response of potentially additional AK surface areas after ICI identified by digital clini-cal photography on day 0, day 28 and during FU. In order to investigate TME of AK's biopsies will be taken at day 0 and day 28.

- Quality of life as measured by EORTC QLQ-C30, H&N 35, EQ5D, CWS, IT questionnaire and the sexuality questionnaire

- Cost-effectiveness of nivolumab and nivolumab plus ipilimumab at time of SOC, with a health-technology assessment.

Exploratory endpoints:

The MATISSE trial will offer exploratory translational research by collecting clinical data, tumor specimens, and blood samples at multiple time-points* short and longer term after start of immunotherapy. The translational research we aim for will provide insights in the (very) early kinetics of the tumor microenvironment (TME) and the systemic immune system. Consequently, it may identify novel parameters for antitumor immunity and/or novel immune evasion mechanisms present in CSCC patients with early stage disease, and it may

provide a rationale for the optimized timing of neo-adjuvant ICI with respect to surgery to be tested in future treatment regimens.

Exploring the TME (early) upon ICI:

- IHC and Bulk DNA & RNA sequencing of local tumor (when feasible also lymph node metas-tases) specimens at the aforementioned time points before and after start of ICI*, and its corre-lation to clinical outcome.
- The development of an ex vivo functional assay for CSCC (Daniela Thommen platform) to predict individual ICI response.
- The development of an ex vivo functional assay to challenge tumor specimens (and when feasible lymph node specimens) with ICI drugs at aforementioned time-points before and after start of neoadjuvant ICI*.
- Single cell sequencing of tumor specimens before and after start of ICI*.
- Hyperion Mass Cytometry of tumor specimens (and when feasible lymph node specimens) before and after start of ICI*.
- Residual tumor-digest supernatant and blood plasma or serum will be taken to third parties for metabolomics and lipid omics, and for cytokine and chemokines assays

Endpoints for exploring systemic immunotherapy-related alterations:

- Fresh blood flow cytometry (with a focus on suppressive cells as monocytes, neutrophils) will be performed pre-, on and post-treatment* on all blood samples.
- Heparin peripheral blood mononuclear cells (PBMCs) will be analysed pre-, on

and post-treatment* on all blood samples for a quantitative and qualitative assessment of circulating adaptive immune cells.

- Serum blood will be analysed for chemokines and cytokines, pre-, on and post-treatment* on all blood samples.

- EDTA blood will be analysed complement factors, pre-, on and post-treatment* on all blood samples.

- T-cell receptor sequencing of baseline TILs and their potential expansion in the peripheral blood compartment on-treatment (*immunoSeq*.).

- EDTA blood will be analysed for ctDNA (kinetics) before treatment, on treatment, and long-term after neo-adjuvant ICI*.

- Residual tumor digest supernatant and blood plasma or serum will be taken to third parties for metabolomics: Semi-targeted biochemical profiling assay (LUMC depart-ment of Prof Martin Giera and Jacques Neefjes) HydroRP:TripleTOF6600 uses liquid chromatographic separation able to operate on one hundred percent water condition, allowing separation of small polar metabolites in a reproducible fashion, overcoming problem of mass resolution and ionization suppression. Using a unique In-house li-brary, including accurate precursor mass, accurate retention time and fragmentation spectra, we are able to fully identify over four hundred small polar molecules (amino acids, nucleotides, sugars, alpha-cheto acids, etc).

- Residual tumor digest supernatant and blood plasma or serum will be taken to third parties for lipid omics. DMS shotgun Lipidomics assay (LUMC department of Prof Martin Giera and Jacques Neefjes) Lipidyzer:SelexIon uses differential mobility spec-trometry (DMS) which is a gas phase separation technique based on

ion mobility. We use it to separate lipid classes, thereby overcome isobar overlap, which renders the accurate MS/MS based quantification of many lipid species impossible. In addition, us-ing the Shotgun Lipidomics Assistant (SLA) software the platform is able to quantita-tively measure over 1450 lipid species across 17 lipid (sub)classes.

- Residual tumor digest supernatant and blood plasma or serum will be taken to third parties for cytokine and chemokines assays.

*= before treatment, and one week (either day 2-3, or day 4-6 or day 7-9, at least 6 people per treatment arm), two weeks (right before 2nd infusion of immunotherapy), 4 weeks (at time of surgery) and long-term after start of ICI, see figure 1 and 2, and table 1, pages (23, 24 and 47).

Study description

Background summary

Cutaneous squamous cell carcinoma (CSCC) is the most common skin cancer after basal cell carcinoma and has an increasing incidence of currently 15,000 patients per year in the Netherlands. Although most patients with CSCC present with localized disease, about 4% of the patients develops metastases. 87% of these metastases are lymph nodal. CSCC-related mortality is in 85% a consequence of uncontrolled loco-regional disease. Lymph nodal positive patients (stage III-IV) have a poor prognosis with a 3-year overall survival of 29-46%. Standard of care (SOC) in patients with stage III-IV CSCC currently comprises (major) surgery, sometimes followed by adjuvant radiotherapy (RT). Systemic chemotherapy, such as cisplatin, has been administered to patients with locally incurable or metastatic CSCC, though its efficacy is limited and not well-established. In a recent randomized trial the addition of carboplatin to postoperative RT in high-risk CSCC did not improve loco-regional control, disease-free or overall survival. Therefore, there is a need to improve SOC and

increase cure rates in patients with resectable stage III-IV disease.

T cell checkpoint blockade by anti-cytotoxic T-lymphocyte associated protein 4 (CTLA4) and/or anti-programmed cell death protein 1 (PD1) is currently a promising treatment modality for patients with broad diversity of cancers. Most patients with CSCC have a history of excessive sun exposure and CSCCs are thus characterized by ultraviolet radiation (UVR) associated DNA damage with corresponding high mutational load, rendering them potentially highly immunogenic and responsive to immunotherapy. In 2018 a phase I and II study supported this hypothesis, demonstrating the effect of immune checkpoint inhibition (ICI) with anti-PD1 monoclonal antibody cemiplimab in patients with locally incurable or metastatic CSCC, leading to its FDA approval. Cemiplimab, given at a dose of 3 mg per kg every two weeks, was generally well tolerated (42% of the patients had CTCAE grade >=3 adverse events (AE), which led to discontinuation of treatment in 5% of the patients) and induced an objective response (RECIST version 1.1) in approximately 50% and controlled disease in approximately 70% of patients with distant metastases and/or locally incurable CSCC .

To date, the efficacy of anti-PD1 ICI with nivolumab in CSCC has not been systematically investigated. More importantly, it is unclear whether CSCC patients benefit from adding anti-CTLA4 to anti-PD1 ICI.

Study objective

Herewith, we present a research protocol for a phase II trial that allows us to examine the efficacy (histopathological response rate) of ICI in the form of nivolumab or nivolumab plus ipilimumab prior to SOC in patients with resectable stage III-IVa CSCC. In addition, we aim to investigate the (ex vivo) kinetics of immune cell activity early upon nivolumab or nivolumab plus ipilimumab and to correlate our findings with clinical outcome.

Study design

An investigator-initiated randomized non-comparative phase II trial consisting of 40 patients with resectable stage III-IVa CSCC randomized 1:1 to ARM A: 2 courses of nivolumab 3 mg/kg in week 0 and 2, or ARM B: 2 courses of nivolumab 3 mg/kg in week 0 and 2 plus 1 course of ipilimumab 1mg/kg in week 0. Both treatment arms are neo-adjuvant and applied prior to SOC at week 4.

Intervention

In this trial patients will be treated neo-adjuvantly with 2 courses of nivolumab 3 mg/kg in week 0 and 2 or with the combination of ipilimumab 1 mg/kg plus nivolumab 3 mg/kg in week 0 and nivolumab 3 mg/kg in week 2. Surgery will be planned in week 4. If necessary, adjuvant RT will start 4-6 week after

surgery.

Study burden and risks

In our proposed trial all stadium III-IVa CSCC patients will receive neo-adjuvant ICI prior to SOC. Based upon the most recent literature, as described above, participation in this trial may lead to improved clinical outcome in terms of loco regional control, recurrence free survival (RFS) and OS.

Participants of this study will be exposed to one or two immunotherapeutic agents (nivolumab with or without ipilimumab) known to induce immune related adverse events. In the trial of Midgen et al, grade >=3 AE occurred in 42% of the patients with metastatic CSCC after administration of Cemiplimab monotherapy (3 mg/kg) every two weeks during the median follow up of 7.9 months. The most common AE were diarrhea (occurring in 27% of the patients), fatigue (24%), nausea (17%), constipation (15%), and rash (15%). In another previous trial containing patients with lung carcinoma receiving the combination treatment of nivolumab 3 mg/kg (every 2 weeks, median of 8.5 doses received) and ipilimumab 1 mg/kg (every 6 weeks, median of 3 doses received), 29% of the patients experienced grade >=3 treatment related AE.

The patient characteristics (concerning age, risk factors, comorbidities) of the two studies described above will be relatively comparable with the future patients of our study. So it could be, that these two trials reflect the expected toxicity in our patient population. However, the total treatment time in the MATISSE trial will be considerably shorter compared to the above-described trials. The number of infusions and total treatment time in our proposed trial will be more similar to the trial of Gross et al, of which the first results have recently been presented. In this trial, wherein 20 patients with stage III-IVa CSCC received neo-adjuvant anti-PD1 ICI (cemiplimab) prior to surgery, no surgical delays occurred and only 7 (35%) patients experienced grade 1 and 2 AE.

In the past years our hospital has gained the expertise to manage the administration of neo-adjuvant ICI (consisting of the combination nivolumab + ipilimumab) without delaying time of surgery, in almost all cases. In the IMCISION trial all 32 patients with advanced head and neck SCC (26 patients received nivolumab combined with ipilimumab) received surgery as planned with no unexpected wound healing problems (clinical data analysis done, manuscript not yet published).In the OPACIN-neo trial surgery was delayed in only 3 out of 86 patients due to immune related AE and in the OPACIN trial all patients in the neo-adjuvant arm (n=10) underwent surgery at the pre-planned time. Of note, out of precaution in this elderly CSCC population, our proposed study will offer the combination of nivolumab (3 mg/kg) with or without ipilimumab (1 mg/kg) only in the first week and nivolumab (3 mg/kg) monotherapy in the third week, whereas the OPACIN and the OPACIN-neo trial (2 of the 3 treatment arms)

offered the combination of nivolumab and ipilimumab every three weeks (so week 1 and 4). The infusion of ICI in our study will be given 4 (nivolumab with or without ipilimumab) and 2 (nivolumab) weeks prior to surgery, so patients will be enabled to recover from possible acute side effects. To conclude, we believe that in our proposed trial the expected AE will be manageable and will not delay the planned time of surgery.

For this trial patients will undergo 2 extra primary tumor biopsies and 2 extra lymph node biopsies under local anaesthesia. It is our experience that patients may endure slight temporarily discomfort due to taking the extra biopsies with a very small enlarged risk (< 1%) for bleeding and infection afterwards. Of note, the lymph node biopsies under local anaesthesia are not mandatory for inclusion in the trial. In total, 6 extra blood samples will be collected in 2 years* time. The blood samples, tumor biopsies and lymph node biopsies will be taken at the same days. The radiation burden for an extra FDG PET/CT is estimated at 5 mSv for 200 MBq FDG + 3 mSv for low dose CT = 8 mSv. These doses are in the range of normal diagnostic procedures and are in risk category IIIa (justified research in normal heathy adults for prevention or cure of diseases in the future) of the Nederlandse commissie voor stralingsdosimetrie.In addition to the baseline MRI-scan, two extra (f)MRI-scans will be made in week 2 (before ICI and the tumor biopsy) and week 3-4. The (f)MRI in week 2 is optional and not mandatory for inclusion in the trial. The duration of a (f)MRI is slightly longer than usual. Quality of life questionnaires will be taken at baseline, in week 4 (before surgery) and during FU visits. Completing the questionnaires will take a maximum of 30 minutes. Overall, this is a low risk trial whereby for participation, two extra visits to the hospital are warranted plus the 2 extra days at which patients will receive immunotherapy.

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

1. Age 18 years or older.
2. Patient is able to understand and comply with the protocol requirements and has signed the informed consent form.
3. World Health Organization (WHO) Performance Status 0 or 1 (Appendix B).
4. Patients with histologically or cytologically confirmed, de novo/primary or recurrent stage III-IVA CSCC (T3-4 N0-3 M0 or T0-2/x N1-3 M0) of all body sites.
• Primary tumor sites Head and Neck:
o Vermillion border lip: C00.0, C00.1, C00.2
o Skin of lip NOS: C44.0
o External ear: C44.2
o Skin face unspecified (ao: external lip and nasal vestibulum): C44.3
o Skin scalp and neck: C44.4
o Overlapping lesion of skin: C44.8
o Primary site eyelid: C44.1
• CSCC outside head and neck area, but not vulva, anus and penis
OR
Patients with histologically or cytologically proven stage I-II CSCC (T1-2 N0 M0), only in the case of:
• Presence of multifocal disease for which extensive and/or mutilating surgery is necessary (e.g. near-total scalp resection).
• Situated in an anatomical localization that necessitates extensive and/or mutilating surgery (e.g. orbital exenteration, (partial) nose amputation or (partial) ear amputation).
5. Eligible for standard-of-care, curatively intended surgery with or without adjuvant radiotherapy.
6. 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 (except subjects with Gilbert Syndrome, who are eligible when total bilirubin < 3.0 mg/dL).
7. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. They 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 the investigational drug.
8. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25IU/L or equivalent units of HCG) prior to the start of nivolumab or nivolumab + ipilimumab.
9. Men who are sexually active with WOCBP must use a contraceptive method with a failure rate of less than 1% per year and will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. Surgically sterile or azoospermic men do not require aforementioned contraception.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
1. Distantly metastasized (stadium IVb) CSCC.
2. SCC localized in a mucosal surface (i.e. anus, vulva, penis or mucosal portion of lip).
3. Patients for whom SOC consists of definitive (brachy)radiotherapy.
4. Primary or recurrent CSCC appearing in an area that has been previously irradiated.
5. Prior anti-CTLA4 or anti-PD1 immunotherapy.
6. Active human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS).
7. A positive test for hepatitis B virus surface antigen (HBsAg) or hepatitis C antibody (HCV Ab).
8. Subjects with any active autoimmune disease or a documented history of autoimmune disease, except for:
• Subjects with vitiligo
• Resolved childhood asthma/atopy
• Residual hypothyroidism due to an autoimmune condition requiring only hormone replacement
• Psoriasis not requiring systemic treatment
• Any condition not expected to recur in the absence of an external trigger.
9. Underlying medical conditions that, in the investigator's opinion, will make the administration of study drug hazardous or obscure the interpretation of toxicity or AE.
10. A concurrent medical condition requiring the use of immunosuppressive medications, or immunosuppressive doses of systemic or absorbable topical corticosteroids;

11. Pregnant or nursing.
12. A history of allergy to study drug components and/or a history of severe hypersensitivity to any monoclonal antibody.
13. Use of other investigational drugs 30 days before study drug administration and 5 half times before study inclusion.
14. Use of prohibited medication at start of study period (see paragraph 5.2).

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-08-2020
Enrollment:	40
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:	12-05-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	26-06-2020
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	17-03-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-10-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-07-2022
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	EUCTR2020-001074-30-NL
CCMO	NL73483.031.20