Safety and tolerability of neoadjuvant nivolumab for locally advanced resectable oral cancer, combined with [18F]BMS-986192 / [18F]-FDG PET imaging and immunomonitoring for response prediction.

Published: 14-02-2019
Last updated: 11-04-2024

1) To assess uptake of [18F]BMS-986192 in tumor lesions before and after treatment with nivolumab, in relation to [18F]-FDG uptake as potential whole body biomarker for response. 2) To evaluate safety and tolerability of neoadjuvant nivolumab 3) To...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50077

Source
ToetsingOnline

Brief title
NeoNivo

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
Head and Neck Cancer, Head and Neck Squamous Cell Carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Bristol-Myers Squibb

Intervention

Keyword: HNSCC, immunotherapy, neoadjuvant, nivolumab

Outcome measures

Primary outcome

1. To investigate heterogeneity in tumor uptake of [18F]BMS-986192 between patients and within tumor lesions of the same patient (primary tumor and TDLN/lymph node metastases) before treatment, in relation to changes in [18F]-FDG uptake before and on treatment.

2. To investigate the feasibility and safety of neoadjuvant nivolumab immunotherapy prior to surgery for locally advanced oral cancer.

Secondary outcome

3. To investigate effects of nivolumab treatment on PD-L1 expression and availability for tracer binding in the patient and the relation to (changes in) [18F]-FDG uptake.

4. To investigate the relationship between [18F]BMS-986192 tumor uptake and tumor cell and tumor infiltrating lymphocyte (TIL) PD-1 and PD-L1 expression as well as other immune parameters.

5. To investigate changes in [18F]-FDG uptake during treatment.

6. To investigate the genomic profile of the tumor (neoantigens, mutational load, copy number changes and splice variants), in relation to [18F]BMS-986192

uptake, immune activation parameters and clinical response.

7. To investigate blood based analyses of the immuneprofile and plasma vesicle miRNAs on treatment and after treatment, in relation to immune activation parameters and clinical outcome.

Study description

Background summary

Intensive treatment regimens with surgical resection and adjuvant (chemo)radiotherapy of patients with locally advanced oral cancer still result in only 50-60% cure rate, leaving a substantial group of patients who will develop a local recurrence or distant metastases with minimal curative salvage treatment options. Treatment with anti-PD1 monoclonal antibodies (mAbs) has shown promise in patients with recurrent/metastatic head and neck squamous cell carcinoma (r/m HNSCC). This supports the hypothesis that including treatment with anti PD-1 mAb nivolumab could improve the outcome for patients with locally advanced oral cancer resulting in a higher cure rate. Response rate with nivolumab was below 20% in unselected patients with r/m HNSCC. Therefore, biomarkers for response are urgently needed. Tumor PD-L1 immunohistochemistry (IHC) was shown to be
related to nivolumab response but cannot be reliably used for patient selection. Temporal and spatial heterogeneity of tumor PD-L1 expression (within and between tumor lesions) might be responsible for its suboptimal predictive value as biomarker of response. Therefore there is a need to further evaluate tumor PD-L1 expression as predictive biomarker, as well as exploring alternatives. Serial PET imaging with [18F]BMS-986192 (anti-PD-L1 tracer) and [18F]-FDG has the potential to provide whole body information of the patient over time, at baseline as well as on treatment and represents a biomarker for toxicity and efficacy. In addition, we will investigate the immunophenotype of the patient and tumor, as well as the presence of neoantigens and other potential other biomarkers such as plasma vesicle miRNAs.

Study objective

1) To assess uptake of [18F]BMS-986192 in tumor lesions before and after treatment with nivolumab, in relation to [18F]-FDG uptake as potential whole body biomarker for response.
2) To evaluate safety and tolerability of neoadjuvant nivolumab
3) To evaluate tumor and blood immunoprofiling, presence of neoantigens, and

other potential biomarkers of response such as plasma vesicle miRNAs.

Study design

This pilot study is a single arm, open label, mono-center study. It is designed to asses the safety and feasibility of neoadjuvant nivolumab and serve as a pilot study to asses possible biomarkers for response.

Intervention

After screening, eligible subjects will undergo a standard [18F]-FDG PET scan and an experimental [18F]BMS-986192 PET scan. Patients will be treated with a single dose of 480 mg of nivolumab followed by an experimental [18F]BMS-986192 and [18F]-FDG PET scan 14 days later to monitor changes in biodistribution and early therapeutic effects. Patients are planned to undergo surgery within 30 days after diagnosis. Tissue samples will
be collected at diagnostic panendoscopy and at surgery. Blood samples will be collected at multiple time points. Up to two additional biopsies can be performed depending on the baseline imaging results and whether the location can be reached safely. Treatment and follow-up (12 months) after surgery will be according to standard procedures.

Study burden and risks

* PET scans
No toxicity is expected from PET scans with tracer microdoses. The amount of [18F]BMS986192 will be in the pico to nano molar quantity, far below the dose for a pharmacological effect. Patients do not derive benefit from the PET scan results. Since there is a lack of a well performing predictive biomarker of response, the results of this imaging biomarker study can be of high interest for HNSCC patients that are eligible for anti-PD-(L)1 treatment in the future.

* Tumor biopsy
Additional tumor biopsies obtained at panendoscopy are considered safe with a low complication rate as during this procedure already standard biopsies are taken. Besides, additional biopsies are allowed in this study (after the baseline PET scans) in case the [18F]BMS-986192 or the [18F]-FDG PET scan show heterogeneous or discrepant uptake in individual patients. Although this is demanding for patients, tumor biopsies in cancer patients are considered safe with a low and manageable complication rate. These biopsies will be used to explain heterogeneous tracer uptake and relate the imaging results to that of the tissue biomarkers PD-1 IHC (locally) and PD-L1 IHC (BMS Dako assay), as well as immune monitoring outcomes.

* Blood withdrawal
By performing immunophenotyping on PBMC*s at the indicated time points unique

insight will be gained in the kinetics of T cell activation following PD-1 blockade and pre- and ontreatment immune effector/suppressor subset profiles that may serve as biomarkers for clinical response and/or outcome, as we previously showed in a trial of combined ipilimumab and Prostate GVAX immunotherapy [Santegoets, 2012].

* Nivolumab treatment
The overall cure rate for locally advanced oral cancer is 50-60% with surgery and if indicated adjuvant (chemo)radiotherapy. Preliminary data have shown promising responses with neoadjuvant treatment with nivolumab or pembrolizumab. It is therefore not unlikely that patients derive benefit from this study. As can be found in the Investigator Brochure, the toxicity is manageable and the safety profile acceptable.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Histologically confirmed diagnosis of locally advanced oral cancer (stage III/IV) which is planned for treatment with curative intent includiing surgical resection.
- Must provide tissue from fresh tumor biopsy pretreatment and from the surgical resection material to determine actual PD-L1 status and perform immunomonitoring and DNA/RNA profiling.
- Willing to allow up to two additional biopsies when baseline [18F]BMS-986192 PET /[18F]-FDG PET scans show heterogeneous and/or discrepant uptake.
- ECOG performance scale 0-1
- Have adequate organ function (hematological, renal and hepatic) as demonstrated by screening laboratory test.
- Women of childbearing potential must use appropriate method(s) of contraception during the study and for 23 week after the last dose of nivolumab
- Men who are sexually active with women of childbearing potential must use any contraceptive method with a failure rate of less than 1% per year.

Exclusion criteria

- Is currently participating in or has participated in a study of an investigational agent within 4 weeks of the first dose of treatment or has not recovered (i.e., * Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
- Has a known current additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy or synchronous head and neck squamous cell carcinoma.
- If subject received major surgery for any other reason, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of day -5. Inhaled or topical steroids, and adrenal replacement steroid > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
- Has an active autoimmune disease requiring systemic steroid treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids.
- Has evidence of interstitial lung disease or active, non-infectious pneumonitis.
- Has an active infection requiring systemic therapy.
- Has a history or current evidence of any condition, therapy, or laboratory

abnormality that might confound the results of the trial, interfere with the subject*s participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
- Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
- Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks after the last dose of trial treatment.
- Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
-Has a known history of Human Immunodeficiency Virus infection with a detectable viral load. Patients with an undetectable load (<50 copies/ml) receiving adequate anti-retroviral therapy, are allowed to participate.
- Has known active Hepatitis B or C.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-09-2019
Enrollment:	15
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:	PD-L1 adnectin PET tracer
Generic name:	BMS-986192

Ethics review

Approved WMO Date:	14-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-02-2019
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2018-002643-28-NL
CCMO	NL66823.029.18