ImmunoModulation by the Combination of Ipilimumab and nivolumab neoadjuvant to Surgery In advanced Or recurrent Head and Neck Carcinoma, (IMCISION), a phase-Ib/II trial. Subtitle: Hypoxia as a determinant for the effect of nivolumab with or without ipilimumab on intra-tumoral T cell capacity

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Herewith, we present a research protocol that allows us to examine feasibility and safety of checkpoint blockade neoadjuvant to standard of care (SOC) in a patient population in need for improved clinical outcome and in tumors likely to respond to...

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

Summary

ID

NL-OMON42832

Source
ToetsingOnline

Brief title
Immunotherapy neoadjuvant to surgery in head and neck carcinoma (IMCISION)

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
head and neck 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,Private funder en aanvullend budget Bristol Myers Squibb.

Intervention

Keyword: carcinoma, Head and Neck, Immunotherapy, Neoadjuvant

Outcome measures

Primary outcome

Primary endpoints:

- Phase Ib: Primary endpoint is measured as the number of patients that will not endure a delay in surgery (surgery should be performed in week 5-6) due to neoadjuvant immunotherapy (nivolumab, ipilimumab) related toxicity (measured in terms of SAEs and CTCAE v4.0) OR toxicity due to the treatment of immunotherapy related toxicity (ie high dose corticosteroids)**.

** To meet this endpoint, all patients will be discussed in our immunotherapy team meeting (consisting of at least medical oncologist and head and neck surgeon) the week before surgery, to evaluate whether immunotherapy-related toxicity or treatment of immunotherapy-related toxicity will lead to delay in surgery or not.

** Delay in surgery due to logistical problems (i.e. no IC bed after surgery) or other co-morbidity (i.e. bacterial pneumonia) will not be considered

dose-limiting toxicity.

- Phase II: Tumor response to neoadjuvant IT in terms of tumor tissue pathological response5 at time of surgery compared to RECIST 1.1 (FDG-PET and perfusion and diffusion weighted MRI).
- Phase Ib/II: Primary read-out will also be to explore the potential impact of local tumor hypoxia on tumor T-cell abundance and capacity before and after neo-adjuvant immunotherapy, through HX4-PET-guided tumor biopsies1,2 from hypoxic and normoxic tumor3 regions and subsequent immunological analyses4.

NB:

1: Tumor biopsies will be taken -before and after neoadjuvant immunotherapy- guided by hypoxia(HX4)-PET images. All scans will be made in irradiation-mask to ensure spatial correlation between HX4-PET, MRI and FDG-PET. Prior to the biopsy procedure a 3D-model of the tumor and surrounding structures will be generated based on MRI. Within the tumor model the HX4-PET will be visualized as hypoxic and normoxic subregions. The 3D model will be available in the OR, and can be used as a visual guidance to determine biopsy locations (collaboration with Jasper Nijkamp). If possible, for spatiotemporal validation between imaging and research tissue samples, an XperCT scan will be made in operating room, directly after the biopsy is taken (collaboration with Bas Pouw). The biopsy holes will be filled with contrast enhanced material to make them visible on the scan.

2 An MRI scan is needed to ensure vital tumor tissue in case of hypoxic tumor areas defined by the HX4-PET.

3Tumor sample hypoxia or normoxia will be further assessed by comparison of RNAseq data on obtained biopsies with validated bulk RNA hypoxia signatures, and by tumor HIF1alpha IHC

4 Tumor T-cell abundance by IHC, tumor T-cell transcriptome / RNA sequencing after T cell sorting, bulk Tumor IHC and Luminex and RNA sequencing.

5 Defined as percentage residual tumor cells after neoadjuvant immunotherapy by comparing the tumor tissue biopsies before and after nivolumab w/wo ipilimumab, according to existing guidelines to assess pathological tumor response to neoadjuvant therapy. Also, the tumor immune infiltrate will be scored.

Secondary outcome

Secondary endpoints:

- We will monitor immune cell subsets and cytokines in the peripheral blood compartment.
- Rate and type of late AEs (NCI CTCAE v 4.0) up to 2 years FU after SOC (see Figure 1).
- Relapse free survival (RECIST 1.1) and overall survival at 2 years follow-up.

Study description

Background summary

Head and neck squamous cell carcinoma (HNSCC) is the 7th most common cancer in men and the 9th most common cancer in women. In 2011, 3000 patients were diagnosed with head and neck cancer in the Netherlands. In advanced stage oral cavity carcinoma and salvage surgery after failed (chemo)radiation, patients generally suffer extensive mutilating surgery, and nevertheless have a very poor prognosis of 37% 5-year overall survival in stage IV oral HNSCC and 20-40% 2-year overall survival after salvage surgery. Although multiple (neo)adjuvant chemotherapeutic regimens have been evaluated, clinical benefit fails to appear.

T cell checkpoint blockade by anti-CTLA and/or anti-PD1 is currently the most promising in immunomodulation anticancer therapies. In HNSCC, pembrolizumab (anti-PD1 monoclonal antibody) given at a fixed dose of 200 mg every 3 weeks was well tolerated and demonstrated a clinically meaningful overall response rate of 24.8% in patients with recurrent/metastatic disease, irrespective of HPV status. In addition, biweekly Nivolumab 3 mg/kg in recurrent or metastatic setting of HNSCC has doubled the 1 year survival rate from 16% to 36%.

The rationale behind combining aPD1 and aCTLA4 is that nivolumab and ipilimumab enhance T-cell antitumor activity through distinct but complementary mechanisms resulting in both enhanced T-cell priming and enhanced local T-cell-mediated tumor destruction. The complementary effect of both checkpoint inhibitors was first proven in a phase III trial treating metastatic melanoma with response rates of 58%. Shortly after, a study involving thirty-nine stage IIIB/IV Non-Small Cell Lung Carcinoma patients treated with nivolumab 3 mg/kg and ipilimumab 1 mg/kg, 8 and 2 infusions respectively, and an overall treatment period of 15-18 weeks, resulted in 31% durable response rates.

Moreover, very recently, it was postulated that offering the combination of nivolumab and ipilimumab in neo-adjuvant setting would exert even stronger immunomodulation and increased tumor responses to treatment, when compared to adjuvant immunotherapy. One hypothesis is that the presence of tumor load before surgery offers increased neo-antigen presentation with consequently more efficient T-cell receptor triggering. In addition, reduced tumor heterogeneity, as compared to treatment in the metastatic setting, and improved immune status during earlier disease status are factors that are likely to positively influence the efficacy of immunomodulation in this setting. Indeed, recent, early clinical data evaluating the activity of neo-adjuvant nivolumab and ipilimumab in stage III melanoma provide support for this hypothesis.

Although immunotherapy has proven to be effective in various tumor types, a reliable predictive biomarker for treatment response does not exist. Hypoxia is a well-known biomarker for treatment response (RT, chemotherapy and surgery) in various solid tumors (e.g. lung, kidney, HNSCC) and a vast amount of preclinical data indicates a key role for hypoxia on T cell (both CD4 and CD8)

metabolism, fate and function. Therefore, hypoxia may be a clinical biomarker for tumor response to immunotherapy in solid cancers in general.

Reported by others, repeated hypoxia PET scans with [18F]HX4 provide reproducible and spatially stable results in patients with head and neck cancer and patients with lung cancer. [18F]HX4 PET imaging can be used to assess the hypoxic status of tumors and has the potential to aid hypoxia-targeted treatments. Furthermore, robust RNA expression hypoxia signatures have been developed over the years. Such signatures are used to identify patients for selective treatment to overcome hypoxia. Recently, a 15-gene hypoxia classifier was validated in 323 patients with HNSCC randomized for hypoxic modification or placebo in combination with radiotherapy. Tumors categorized as hypoxic on the basis of the classifier were associated with a significantly poorer clinical outcome than non-hypoxic tumors. In addition, technical validation of the 15-gene hypoxia classifier demonstrated that it is suitable for implementation in prospective clinical trials as well.

Study objective

Herewith, we present a research protocol that allows us to examine feasibility and safety of checkpoint blockade neoadjuvant to standard of care (SOC) in a patient population in need for improved clinical outcome and in tumors likely to respond to neoadjuvant aPD1 and aCTLA4. Participation in this trial, may offer our patients the chance for a significant improved clinical outcome in terms of loco-regional control and survival.

In addition, with this research protocol we can assess the potential impact of intratumoral hypoxia on tumor infiltrating lymphocyte (TIL) abundance, differentiation and effector function, and the potentially divergent effects of T cell checkpoint blockade in areas of hypoxia and normoxia. As such, the results of our study may have large implications for the development of combination treatments that aim to further enhance tumor-specific T cell activity in solid tumors characterized by intra-tumoral hypoxia (as ao HNSCC and lung cancer) during checkpoint blockade therapy.

Study design

This is a Phase 1b/II trial. For the design see figure 1.

The phase Ib is designed as 3 + 3, with primary objective feasibility and toxicity.
The phase II is designed as a single arm design with primary endpoint efficacy.
Of Note: we wish to see endpoints reached in all 6 patients of cohort 1 and 2, before we will continue to the next cohort.

In phase Ib, two cohorts will be used (cohort 1: nivolumab only and cohort 2:

nivolumab and ipilimumab neoadjuvant to surgery) to define which neoadjuvant immunotherapy regimen will be taken towards the expansion cohort 3. Of Note: we wish to see endpoints reached in all 6 patients of cohort 1 and 2, before we will continue to the next cohort.

Thirty-two patients will be treated with : nivolumab (240 mg flat dose, week 1 and week 3, twice in total) as a single agent or: the combination of ipilimumab (1 mg/kg) + nivolumab (240 mg flat dose) in week 1, and nivolumab 240 mg flat dose in week 3, neoadjuvant to SOC (surgery with or without adjuvant (C)RT).

Intervention

Patients will be treated with
- 2x nivolumab 240 mg flat dose, weeks 1 and 3, OR
- the combination of 1x ipilimumab 1 mg/kg + nivolumab 240 mg flat dose in week 1 and nivolumab mono-therapy 240 mg flat dose in week 3.

Immunotherapy (IT) is given neoadjuvant to standard of care (SOC: surgery with or without adjuvant (C)RT). Surgery will be planned in week 5. Adjuvant (C)RT will start 4-6 weeks after surgery.

Study burden and risks

Benefit
Advanced primary or recurrent HNSCC is treated with major surgery (commando-procedure) with or without (C)RT. Despite the use of surgical free vascular reconstruction flaps *allowing for the reconstruction of large defects and proper resection margins- and despite adding high-dose cisplatin concurrently to adjuvant RT, the overall survival of these patients remained 20-40% 5-year. In addition, no improvement of clinical outcome was established by applying neo-adjuvant chemotherapy regimens.

In 2015, with Pembrolizumab a new and promising treatment modality for this type of patients was introduced, as Seiwert found 25% tumor response rate in metastatic HNSCC, in both HPV- and non-HPV related disease. In addition, in recurrent and metastatic disease, Nivolumab has shown to double the one-year survival rates of HNSCC form 17% to 39%.
Meanwhile, it was shown that combining aPD1 and aCTLA4 checkpoint inhibitors leads to superior immunomodulation, resulting in increased durable tumor response rates of 58% and 31% in other carcinomas with a high-mutational load as melanoma and lung carcinoma, respectively.

Therefore, participation in this trial may offer these patients the chance for significant improved clinical outcome in terms of loco-regional control and survival, based on the above observations.

Risk
In palliative HNSCC setting, Nivolumab monotherapy 3 mg/kg every 2 weeks for a treatment time of 1.9 months has resulted in 13% grade 3-4 side effects. In a previous trial involving lung carcinoma and the combination treatment of (neoadjuvant) nivolumab 3 mg/kg (median 8 doses, every 2 weeks) and ipilimumab 1 mg/kg (median 2 doses, every 6 weeks) was accompanied by 28% grade 3-4 AEs. As lung carcinoma patients may be relatively comparable to head and neck SCC patients concerning age and smoking status, it could be that the toxicity data of this lung carcinoma trial may reflect the toxicity to be expected in our patient population. Of Note: Our IMCISION trial involves less infusions (two dosages) of immunotherapy and consequently a shorter immunotherapy treatment time (3 weeks), when compared to the above described trial.

Preliminary data of our institute show that our hospital has gained the expertise to manage a nivo/ipi combination scheme in a neoadjuvant setting without delaying the time of surgery. Nevertheless, of caution, the proposed IMCISION treatment cohort 2 will offer the combination of nivo/ipi (nivo 240 mg flat dose and ipi 1mg/kg) once in the first week, and it will offer nivo monotherapy (240 mg flat dose) in week 3, whereas the OPACIN trial offered combined nivo/ipi (3 and 3 mg/kg) in both weeks 1 and 4. As in our proposed study the combination of nivolumab and ipilimumab (cohort 2) will be given 4 weeks prior to surgery, and as the last infusion of nivolumab will be given two weeks prior to surgery, patients will be enabled to recover from acute side effects.

In summary, we believe that the expected grade 3-4 toxicity in the proposed IMCISION trial will be manageable and will not delay the time of surgery.

For this trial, patients will undergo 2-3 extra tumor biopsies for research purposes twice: the first time during routine investigation under general anesthesia, and the second time during routine surgery. The first time, it is our experience that patients may endure slight temporarily discomfort due taking extra biopsies and a very small enlarged risk (< 1%) for bleeding and infection afterwards. The second time, patients will obviously not experience any side-effects from harvesting these biopsies, as the whole tumor will be dissected during surgery.

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. No immunosuppressive medications prior study inclusion, adults age > 18 years, and
2. Histologically confirmed T3-4N0-3M0 HNSCC (with soft tissue infiltration depth of * 1 cm) of the oral cavity, oropharynx, hypopharynx or supraglottic larynx, eligible for curative surgery as primary treatment or salvage surgery after failed (chemo)radiation.
3. WHO 0-1

Exclusion criteria

- Distant metastasis
- Autoimmune disease
- A condition requiring systemic treatment with either corticosteroids or other immunosuppressive medications within 14 days of study drug administration.
- Prior systemic treatment with immunotherapy targeting T-cell costimulation or immune checkpoint pathways;
- Hepatitis B / C, HIV or (AIDS);
- Pregnant or nursing.

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):	27-02-2017
Enrollment:	32
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:	10-11-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	14-11-2016
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	30-06-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-02-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2019
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	EUCTR2016_002366_31-NL
CCMO	NL57794.031.16