Phase I Study: safety and immunogenicity of vaccination with XAGE1B long peptides combined with poly-ICLC in patients with pulmonary adenocarcinoma

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Primary objective:* To evaluate the safety of vaccination with XAGE1B peptides emulsified in Montanide ISA 51 co-mixed with the adjuvant Hiltonol® (Poly-ICLC) in patients with pulmonary adenocarcinoma.Secondary objective* To evaluate the capacity of...

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

Summary

ID

NL-OMON45223

Source
ToetsingOnline

Brief title
XAGE trial

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified
- Respiratory tract neoplasms

Synonym
lung carcinoma, non small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,1. Cancer vaccine Collaborative (CVC) / Cancer Vaccine Acceleration Fund (CVAF) 2. Cancer Research Institute/ Ludwig Institute for Cancer Research (CRI/LICR);New York ;USA

Intervention

Keyword: immunotherapy, lung cancer, vaccine, XAGE1b

Outcome measures

Primary outcome

Safety will be assessed during the whole study by collecting all adverse events according to the CTC version 3 and by monitoring vital signs, blood chemistry and hematological parameters.

Secondary outcome

Immunological assessments will be performed in all vaccinated patients using a blood sample drawn at several time points (day 1, 22 and 43) and a skin biopsy of the last vaccination site. Immunological responses will be monitored using peripheral blood lymphocytes that are tested by IFN*-ELISPOT and intracellular IFN*/IL-2 staining for directly ex-vivo detection and enumeration of antigen-specific CD4+ and/or CD8+ T-cells, as well as following one round of in vitro stimulation. In addition, proliferation (lymphocyte stimulation test: LST) and associated cytokine production (IFN*, TNF*, IL-4, IL-5, IL-10, and IL-2) will be assessed. Furthermore, biopsy samples of the last vaccination site will be used to assess the migratory capacity of vaccine-induced T-cells.

Study description

Background summary

In the Netherlands, approximately 10000 new cases of lung cancer are diagnosed each year. 80% of cases are comprised by non-small cell lung cancer (NSCLC). The majority of patients present with advanced disease (stage III/IV). Morbidity and mortality rates are high and survival rates are poor. The overall 5-year survival is 12-15%. Therefore, research efforts in the field of lung cancer should focus on finding new treatment strategies.

Immunotherapeutic treatment of cancer, aimed at enhancing the anti-tumor immunity, is a very promising new anti-cancer treatment. Progress in this field has recently led to the FDA approval of a vaccine for the treatment of prostate cancer (sipuleucel-T) as well as a therapeutic antibody for the treatment of advanced melanoma (Ipilimumab). At the LUMC, we have extensive experience and expertise in the field of immunotherapy in which we successfully use long peptide based vaccines in patients. We have demonstrated clinical results in patients with HPV-16 induced (pre)malignant lesions and showed a clear link between the kinetics and phenotype of the immune response and complete regression of lesions.

Identifying suitable target antigens is a prerequisite for immunotherapy of cancer. XAGE1B is a relevant tumor antigen for lung adenocarcinoma (a subtype accounting for 40% of NSCLC) as in these tumors it is highly expressed and able to spontaneously induce humoral and cellular immune responses, at least in Asian patients. We are currently conducting a preclinical study on the expression and immunogenicity of XAGE1B in lung adenocarcinoma to confirm these findings in a Dutch population. Our (yet unpublished) data confirm the reported XAGE1b overexpression in pulmonary adenocarcinoma. Importantly, in these patients we have found both humoral and cellular XAGE1b specific immune responses systemically (peripheral blood) as well as locally (tumor draining lymph node, tumor itself). These data will be published in a peer reviewed journal in the near future.

Using this background knowledge on the spontaneous XAGE1B specific immunity in pulmonary adenocarcinoma, we have designed a phase I clinical study in which a new XAGE1B synthetic long peptide (SLP) vaccine combined with a TLR3-agonist (polyICLC, Hiltonol®) will be investigated in adenocarcinoma patients who have finished their standard therapy schedules.

Study objective

Primary objective:

* To evaluate the safety of vaccination with XAGE1B peptides emulsified in

Montanide ISA 51 co-mixed with the adjuvant Hiltonol® (Poly-ICLC) in patients with pulmonary adenocarcinoma.

Secondary objective

* To evaluate the capacity of the vaccination strategy to induce XAGE1B-specific humoral and cellular immune responses in lung adenocarcinoma patients, including the migratory capacity of XAGE-1B vaccine-induced T-cells into the vaccine injection site

Study design

Phase I interventional study

Intervention

Patients will be given a subcutaneous injection of a vaccine consisting of 5 overlapping peptides covering the entire XAGE1B protein emulsified in Montanide ISA 51 co-mixed with the adjuvant Hiltonol® (Poly-ICLC). The first 2 groups of 5 patients (stage I&II and stage III&IV adenocarcinoma) will be vaccinated with a peptide dose of 50 *g together with the adjuvant (dose 1 mg). The groups will start simultaneously. In the next 2 groups of 5 patients (stage I&II and stage III&IV adenocarcinoma), the dose of peptides will be simultaneously increased to 150 *g together with the adjuvant (dose: 1 mg). The last 2 groups of 5 patients (stage I&II and stage III&IV adenocarcinoma) will be simultaneously vaccinated with a peptide dose of 300 *g together with the adjuvant (dose: 1 mg).

Study burden and risks

During the trial, patients will visit the Department of Pulmonology of the Leiden University Medical Center five times more compared to routine follow up in a period of 12 weeks. During the visits, patients are 4 times vaccinated in combination with Montanide and Hiltonol® , blood is drawn (total 250 ml) and a skin biopsy from the second vaccination site is taken.

To our knowledge, this is the first in-man study in which a XAGE1b based SLP® combined with Montanide and Hiltonol® vaccine is used in human subjects. Therefore, no clinical data currently exist on vaccine-induced XAGE1b specific immunity or on clinical efficacy of a XAGE1b vaccine. We expect that adverse events in this trial mainly consist of swelling and redness of the vaccination site, due to the vaccine induced immune response.

This expectation (described in detail in the Investigator's Brochure) is based on:

- a preclinical toxicology study in which the referred to vaccine scheme was tested in New Zealand rabbits. No mortality or systemic toxicity was observed. However, local injection site reactions were observed.

- A recently published phase I trial in which a comparable peptide vaccine (NY-ESO-1, like XAGE1B a member of the cancer-testis gene family) was combined with Montanide and Hiltonol® . Again, no mortality or systemic toxicity was observed. However, local injection site reactions were observed.

- our extensive experience with previous SLP (p53, HPV16) vaccines that were used in several clinical trials, in which generally no adverse events > grade 2 were observed, mainly consisting of local injection site reactions or transient fever after vaccination.

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

For stage I&II pulmonary adenocarcinoma patients:
* Histologically proven pulmonary adenocarcinoma stage I or II according to recent guidelines on TNM classification of NSCLC
* Age * 18 years
* Completion of curative resection or SBRT and adjuvant chemotherapy or radiotherapy if necessary according to guidelines.
* Good WHO performance status (0-2)
* Adequate bone marrow function: WBC * 2.0 x 109/l, platelets > 100 x 109/l, hemoglobin > 5.0 mmol/L
* Survival expectation > 3 months
* Written informed consent according to the local Ethics Committee requirements;For stage III pulmonary adenocarcinoma patients:;* Histologically proven pulmonary adenocarcinoma stage IIIb according to recent guidelines on TNM classification of NSCLC.
* Age * 18 years
* Completion of standard chemo-radiotherapy
* No intention for further chemotherapy treatment
* Good WHO performance status (0-2)
* Adequate bone marrow function: WBC * 2.0 x 109/l, platelets > 100 x 109/l, hemoglobin > 5.0 mmol/L
* Survival expectation > 3 months
* Written informed consent according to the local Ethics Committee requirements;For stage IV pulmonary adenocarcinoma patients:
* Histologically proven pulmonary adenocarcinoma stage IV according to recent guidelines on TNM classification of NSCLC 1.
* Age * 18 years
* Completion of standard (platinum-based) chemotherapy schedules with no intention for further chemotherapy treatment
* Good WHO performance status (0-2)
* Adequate bone marrow function: WBC * 2.0 x 109/l, platelets > 100 x 109/l, hemoglobin > 5.0 mmol/L
* Survival expectation > 3 months
* Written informed consent according to the local Ethics Committee requirements

Exclusion criteria

* Progressive disease after finishing standard treatment
* Inadequate bone marrow function more than 3 weeks after last chemotherapy treatment.
* Poor WHO performance status (3-5)
* Eligibility for treatment with Tyrosine Kinase Inhibitors (e.g. erlotinib)
* History of an autoimmune disease or other systemic intercurrent disease that might affect the immunocompetence of the patient, or patients receiving immunosuppressive therapy including transplant recipients

* Second primary tumor of non-pulmonary origin
* CD4 cell count < 200/m3 at baseline
* Known seropositivity for Hepatitis B Virus and/or HIV
* History of serious liver or kidney dysfunction, heart condition or thyroid disorder
* Pregnancy or Lactating
* Known hypersensitivity reaction to any of the components used during treatment
* Medical or psychological condition which in the opinion of the treating chest physician and investigator would not permit the patient to participate in or to complete the study

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):	26-10-2015
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Hiltonol®
Generic name:	poly-ICLC
Product type:	Medicine
Brand name:	XAGE1B SLP vaccine

Ethics review

Approved WMO

Date:	04-07-2013

Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-11-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-02-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-08-2017
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	EUCTR2013-001254-95-NL
CCMO	NL44189.000.13