A multicenter, open label non-randomized phase I/II dose escalation study with extension cohort to determine the safety, tolerability and immune modulating effects of the therapeutic LRPAP1 synthetic long peptide (LRPAP7-30V-SLP) vaccine (TEIPP24) at different doses in HLA-A*0201-positive patients with non-small cell lung cancer (NSCLC).

Published: 20-05-2021
Last updated: 06-06-2025

Primary objectives- A multicenter, open label non-randomized phase I/II dose escalation study with extension cohort to determine the safety, tolerability and immunogenicity of the therapeutic LRPAP1 synthetic long peptide (LRPAP7-30V-SLP) vaccine (...

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

Summary

ID

NL-OMON51164

Source
ToetsingOnline

Brief title
TEIPP24

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
lung cancer, non-small cell lung cancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Oncode instituut

Intervention

Keyword: HLA-A*0201-positive, LRPAP1, non-small cell lung cancer, synthetic long peptide vaccin

Outcome measures

Primary outcome

Safety will be determined by the incidence rate at each dose level based on the following safety parameters: adverse drug reactions and serious ADRs, changes in haematology and chemistry values, including those associated with hepatic and renal function, and assessment of physical examinations, vital signs and performance status. NCI-CTCAE version 5.0 will be used.

TEIPP-specific immunity: HLA-A*0201-restricted LRPAP21-30 -specific CD8+ T-cell reactivity will be determined by measuring the magnitude and function of HLA-A*0201-restricted LRPAP21-30 -specific CD8+ T-cell present in the blood and/or tumor samples before and after TEIPP24 vaccination.

Secondary outcome

Secondary enpoints:

- The specificity and immune modulatory effects of the vaccine.

- The antigen and immune status of the patients.

- The progression free survival (PFS) and overall survival (OS) up to one year

after first vaccination.

- The radiological tumor response and tumor response duration up to one year

after first vaccination according to RECIST v.1.1 criteria.

Study description

Background summary

Immunogenic tumors can be controlled by tumor-reactive T-cells either directly or after checkpoint blockade. In the end, most tumors will develop mechanisms to escape immune control. One of such a mechanism is formed by the functional impairment of the intracellular peptide transporter TAP1/TAP2 by mutation of downregulated expression. As a result the presentation of conventional T-cell epitopes in HLA class I is lost, and hence tumor-reactive CD8+ T-cells fail to recognize and kill tumor cells. This type of immune escape can occur in up to 50% of primary tumors and is increased in the metastatic lesions of such tumors. The presence of these TAP defects correlate with worse clinicopathological parameters and has been associated with loss of durable benefit to checkpoint inhibition. The unmet need, therefore, is the development of a therapy that can reinforce effective tumor-immunity to cancers displaying TAP-defects for which conventional therapeutic cancer vaccines and/or checkpoint blockade do not work. TEIPP therapy may fill this position by reinstalling an effective antitumor response to TAP-defective tumors thereby increasing the overall survival of patients failing first line therapy. While TAP defects result in a failure to present the conventional tumor antigens in HLA class I, a novel set of shared neoantigens - referred to as T-cell epitopes associated with impaired peptide processing or *TEIPP* - becomes available for recognition by CD8+ T-cells. We have identified a human TEIPP in the ubiquitously expressed protein LRPAP1. This LRPAP1-TEIPP is able to activate HLA-A*0201-restricted CD8+ T-cells that preferentially recognize a series of TAP-negative/low tumor cells while remaining unresponsive to healthy cells of the same tissue type. In addition, we identified the LRPAP7-30 synthetic long peptide (LRPAP7-30V-SLP) sequence to stimulate HLA-A*0201-restricted LRPAP21-30 -specific CD8+ T cells and showed that in vitro vaccination resulted in a rapid expansion of T-cells able to specifically recognize

HLA-A*0201-positive, LRPAP1-positive and TAP-defective tumor cells.

Study objective

Primary objectives
- A multicenter, open label non-randomized phase I/II dose escalation study with extension cohort to determine the safety, tolerability and immunogenicity of the therapeutic LRPAP1 synthetic long peptide (LRPAP7-30V-SLP) vaccine (TEIPP24) at different doses in HLA-A*0201-positive patients with non-small cell lung cancer (NSCLC) failing first line therapy of checkpoint blockade with/without chemotherapy and who can*t endure or are not willing to receive 2nd line treatment with docetaxel chemotherapy.

Secondary objectives
- To assess the specificity and immune modulatory effects of the vaccine.
- To assess the antigen and immune status of the patients.
- To determine progression free survival (PFS) and overall survival (OS) after vaccination.
- To determine the radiological tumor response and tumor response duration after vaccination according to RECIST v.1.1 criteria.

Study design

Study design: This is a prospective, single arm, multicenter, open-label, phase I-II clinical study. HLA-A*0201-positive patients with NSCLC failing first line of treatment will be enrolled in 3 cohorts and one extension cohort of 6 patients each to include 24 patients in total. The maximal total treatment duration is 9 weeks. The first 6 patients will be enrolled in cohort 1, the next 6 patients in cohort 2, the next 6 patients in cohort 3. In the extension cohort, patients will receive the highest safe dose in combination with pembrolizumab. The decision to start enrollment at the next dose level will be made by assessing the safety after 3 out of 6 patients at the previous dose level have completed vaccine therapy. The Principal Investigator (PI) will study individual patient data related to baseline characteristics, safety, and study medication administration for the patients necessary to assess per above before decision to start enrollment at the next dose level. The PI will assess information per above for relevant patients, summarize findings, and give a recommendation whether or not he/she endorses the start of enrolment at the next dose level. The summary and recommendation from the PI, including all necessary individual patient background material, should be reviewed and commented on by the DSMB members. After having received the opinion of the DSMB, the PI can issue a written approval (or disapproval) regarding the start of enrollment at the next dose level. No dose limiting toxicities are anticipated based on previous clinical studies with synthetic long peptide vaccines. Patients who have not received at least two vaccinations with TEIPP24 and for whom no pre-vaccination blood sample and two post-second vaccination

blood samples have been collected (all with sufficient peripheral blood mononuclear cells (PBMCs)) are not evaluable for the HLA-A*0201-restricted LRPAP21-30 -specific CD8+ T cells assays and will be replaced unless treatment was stopped prematurely due to toxicity.

Intervention

Patients will receive an off the shelf TEIPP24 vaccine mixed with Montanide ISA-51 adjuvant, which will be admistered every three weeks for a period of three rounds of vaccination. The TEIPP24 vaccine is dissolved in dimethylsulfoxide, dilute with water for injection (WFI) and emulsified with Montanide ISA-51 (Seppic). Patient cohort 1 will be treated with TEIPP24 at a dose of 20ug of peptide, patients in cohort 2 with TEIPP24 at a dose of 40ug of peptide and patients in cohort 3 with TEIPP24 at a dose of 100ug of peptide. Patients will receive three rounds of vaccination three weeks apart via one subcutaneous (SC) injection in a limb. Subsequently patients will be followed until 1 year after the first vaccination. Patients in the extension cohort will receive the highest safe dose in combination with pembrolizumab. Patients will receive up to 3 cycles of pembrolizumab concurrently with the 3 TEIPP24 vaccinations (3 cycles every 3 weeks).

Study burden and risks

First line treatment of NSCLC (SCC & AC) consists of anti-PD-L1 checkpoint inhibition (CPI) in combination with chemotherapy. Median progression free survival ranges from 8-13 months (refs) after which no other treatment option exists other than chemotherapy with docetaxel as 2nd line treatment. Docetaxel is associated with treatment related adverse events, grade 3 or 4 in 55% of the treated patients, whereas this is <15% in patients treated with PD-1 or PD-L1 CPI (refs) and not likely to be increased in combination with vaccination (ref) . These adverse events caused by docetaxel mainly comprised neutropenia, fatigue and nausea and especially life-threatening infections (refs). Due to the side effects, most patients don*t want or can*t endure docetaxel, causing a very low percentage of patients treated with second line treatment (below 25%) but when treated, an estimated 24% of SCC and 39% of AC NSCLC patients survive 1 year only.

The TEIPP24 (LRPAP7-30V-SLP) vaccine comprises an amino acid sequence derived from LRPAP1, which is an ubiquitously expressed protein in human cells. Therefore, the use of a peptide vaccine aiming to induce T-cell reactivity to part of the LRPAP1 sequence carries two potential major risks: a) cross-reactivity to proteins containing similar amino acid sequences, and b) off-tumor/on-target reactivity, thus inflicting an immune response against healthy tissues. Off tumor//on-target healthy tissue recognition has never been observed in our extensive experience with the murine TEIPP model (ref). Furthermore, the pre-clinical toxicity testing of human LRPAP1-specific CD8+

T-cell clones showed reactivity only against TAP-downregulated targets and only to target cells that express LRPAP1. In addition, the targeted peptide sequence has not been found in the healthy tissue database of HLA class I-presented peptides (ref). Peptide vaccination has a very good safety profile in general. Also SLP in Montanide ISA-51 vaccines are safe, based on our own large series of trials (refs), specifically at the dose range of 20-100 *g per peptide per injection with treatment emergent injection site reactions/systemic allergic reactions NCI-CTC<2 (ref). Thus, based on the adata above, serious AEs (SAEs) or suspected unexpected adverse reactions (SUSARs) related to the vaccine are not expected. As with all vaccines, systemic allergic reaction may occasionally occur, which can easily be treated with anti-histamine.

Patients will have adequate and appropriate checkups during this study to monitor for potential (S)AEs and to minimize risk. The potential risks identified from earlier peptide vaccination studies are judged to be acceptable. Patients will undergo tumour biopsies as part of standard clinical care. Furthermore, additional tumour biopsies will be obtained throughout the course of the trial, only if an extra biopsy is safe and feasible. Peripheral blood sampling will take place prior to each and after last vaccine administration. The risk of blood withdrawals is negligible.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

Dr. Molewaterplein 40
Rotterdam 3015 GD
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Age >18 years
- Pathologically and radiologically confirmed advanced NSCLC.
- Progression after minimally 4 cycles of combination platinum containing chemotherapy and immunotherapy (PD1), or after 4 cycles of platinum containing chemotherapy and immunotherapy (PD-1) followed by maintenance chemo immunotherapy
- HLA-A*0201 positive
- An expected survival of at least 3 months
- WHO/ECOG performance status <= 2 (Appendix 3)
- Adequate renal function as defined by creatinine clearance > 40 mL/min based on the Cockroft-Gault glomerular filtration rate (GFR)
- Adequate hepatic function as evidenced by
o Serum total bilirubin <= 2.5 × upper limit of normal (ULN) unless considered due to hepatic metastases
o Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) <= 3.0 × ULN, unless considered due to hepatic metastases
- Ability to return to the hospital for adequate follow-up as required by this protocol.
- Written informed consent according to International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) .

Exclusion criteria

- Active infection, including hepatitis B or C or HIV infection that is uncontrolled at inclusion. An infection controlled with an approved or closely monitored antibiotic/antiviral/antifungal treatment is allowed.
- Current use of steroids (or other immunosuppressive agents). Patients must have had
6 weeks of discontinuation and must stop any such treatment during the time of the
study. Prophylactic usage of dexamethasone during chemotherapy is excluded from this 6 weeks interval.
- Concomitant participation in another clinical intervention trial (except participation in a
biobank study).

- Pregnant or lactating women.
- Known allergy to any of the ingredients of the vaccine (peptide, Montanide ISA-51, trifluoroacetic acid, acetonitrile, dichloromethane, dimethylsulfoxide).
- Any medical or psychological condition deemed by the Investigator to be likely to interfere with a patient*s ability to give informed consent or participate in the study
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
- Patients with a currently active second malignancy. However, patients with the following history/concurrent conditions are allowed: Basal or squamous cell carcinoma of the skin; Carcinoma in situ of the cervix; Carcinoma in situ of the breast; Incidental histologic finding of prostate cancer.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	29-09-2021
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	therapeutic LRPAP1 synthetic long peptide (LRPAP7-30V-SLP) vaccine (TEIPP24)

Ethics review

Approved WMO

Date:	20-05-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-05-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	10-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-11-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-02-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-02-2023
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	EUCTR2020-005427-36-NL
CCMO	NL75654.000.20