A Phase II Trial of Personalized Tumor Neoantigen Based Vaccine FRAME-001 for Advanced Non-Small Cell Lung Cancer

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To determine FRAME-001-specific immune responses in peripheral blood after administration of FRAME-001 to patients with advanced NSCLC.Secondary objectives- To assess safety and tolerability of FRAME-001.- To evaluate clinical anti-tumor response to...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Respiratory and mediastinal neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON49932

Source
ToetsingOnline

Brief title
FRAME-001 personalized vaccine in NSCLC

Condition

- Respiratory and mediastinal neoplasms malignant and unspecified

Synonym
non-small cell lung carcinoma, NSCLC

Research involving
Human

Sponsors and support

Primary sponsor: Frame Pharmaceuticals B.V.
Source(s) of monetary or material Support: Frame Pharmaceuticals B.V. (particuliere investeerders)

Intervention

Keyword: Cancer, Non small cell lung carcinoma, NSCLC, Vaccine

Outcome measures

Primary outcome

Primary objective:

- To determine FRAME-001-specific immune responses in peripheral blood after administration of FRAME-001 to patients with advanced NSCLC.

Primary endpoint:

- Antigen-specific immune responses in peripheral blood to one or more Frame peptides following application of a personalized FRAME-001 vaccine, based on a positive outcome in one or more of the following assays:
4-Day interferon gamma (IFNg) enzyme-linked immunospot (ELISpot) assay
IFNg, tumor necrosis factor alpha (TNFa), and/or interleukin-2 (IL-2) producing CD4+ and/or CD8+ T cells determined in intracellular cytokine staining assay
Specific cytokine production as measured by Th1/Th2 cytokine bead array in culture supernatants.

Secondary outcome

Secondary endpoints

- Incidence, type, grade, and number of adverse events (AEs) according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

- Tumor response and tumor response duration according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 criteria.

- Progression-free survival (PFS) and overall survival (OS).

Exploratory endpoints

- Phenotypic composition of and functional changes in immune cells in peripheral blood and changes in plasma cytokine levels after vaccination with FRAME-001 determined by immunomonitoring assays, including but not limited to multiparametric flow cytometry, enzyme-linked immunoadsorbent assay (ELISA), functional T cell assays (T cell proliferation, cytokine production), T cell receptor repertoire, and other relevant immunological assays.
- Relative change in immune cell infiltration and expression of PD-1 on tumor infiltrating lymphocytes and PD-L1 on tumor and immune cells in tumor biopsy (if available) after vaccination with FRAME-001.
- Analysis of ctDNA in plasma.
- Correlation of immune responses to PD-L1 expression of the tumor, and to Framome status.

Study description

Background summary

Despite encouraging results of programmed cell death protein -1 (PD-1) immune checkpoint inhibitor treatment combined with chemotherapy in advanced non-small cell lung cancer (NSCLC), only the minority of approximately 20% of patients derive durable clinical benefit from such treatment. Patients with stable disease (SD) after four cycles of treatment with PD-1 inhibitor pembrolizumab monotherapy or in combination with chemotherapy (standard of care in advanced NSCLC in the Netherlands) have a low probability of still acquiring a complete response (CR) or durable disease control to such treatment and no other curative standard treatment options are available, emphasizing the need for novel therapeutic approaches. Tumor-specific neopeptides resulting from

frameshift mutations in tumor cells, so-called Frames, present potentially potent targets for the immune system and can be utilized in therapeutic anti-cancer vaccination with the intention to synergize in their effect with immune chckpoint inhibitors. Frames are prevalent in NSCLC patients, with 95% of lung tumors harboring one or more Frames. The entire collection of Frames expressed by a tumor is referred to as the*Framome. Vaccination against strongly antigenic neopeptides present in a patient*s tumor furnishes a perspective of enhancing the therapeutic effect of the immune checkpoint inhibition in NSCLC with expected limited additional toxicities. The current clinical trial is designed to determine immune response, safety, and clinical response of personalized vaccine FRAME-001 based on a patient*s Framome and selection of Frame peptides in advanced NSCLC cancer patients after standard first line treatment consisting of immune checkpoint inhibitor pembrolizumab as monotherapy or combined with chemotherapy (carboplatin/cisplatin and pemetrexed/paclitaxel), and who attained SD after four cycles of such therapy. The personalized FRAME-001 vaccine will be administered during maintenance phase of treatment with pembrolizumab monotherapy.

Study objective

To determine FRAME-001-specific immune responses in peripheral blood after administration of FRAME-001 to patients with advanced NSCLC.

Secondary objectives
- To assess safety and tolerability of FRAME-001.
- To evaluate clinical anti-tumor response to FRAME-001.
- To assess survival after treatment with FRAME-001.

Exploratory objectives
- To determine changes in the peripheral blood immune profile following FRAME-001 vaccination.
- To assess molecular responses based on circulating tumor DNA (ctDNA) in plasma.
- To assess immune responses in the tumor tissue before and after administration of FRAME-001.
- Correlate FRAME-001-specific immune response to PD-L1 expression of the tumor and to Framome status.

Study design

Prospective, single arm, multi center, open-label, phase II clinical trial

Intervention

Patients will receive personalized peptide vaccine FRAME-001 based on frame-shift mutations (Frames) detected by Whole Genome Sequencing

(WGS)/Ribonucleic Acid sequencing (RNAseq) in a tumor biopsy. FRAME-001 vaccine will contain up to 24 peptides divided over four vials (each up to six peptides) admixed with immune adjuvant Montanide ISA 51 VG and will be administered in four sequential cycles at 3-week interval (Q3W), along standard maintenance monotherapy of pembrolizumab (administration Q3W or Q6W). Each cycle will be consisting of up to four subcutaneous injections at up to four different sites in the upper and lower limbs.

Study burden and risks

Please see the Investigator's Brochure (IB) for a detailed background and data on FRAME-001

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

- Age *18 years.
- Eastern Cooperative Oncology Group (ECOG) performance status * 1
- -Pathologically and radiologically confirmed advanced squamous or non-squamous NSCLC with SD after four cycles of treatment with pembrolizumab as monotherapy or in combination with chemotherapy (carboplatin/cisplatin and pemetrexed/paclitaxel) and suitable for maintenance treatment with pembrolizumab monotherapy.
- Patient Framome identification with demonstrated frameshift mutations (Frames) completed as part of molecular pre-screening:
o Presence of at least 3 expressed frameshift mutations;
o A combined length of *100 amino acids for the neopeptides resulting from the frameshifts, with preferably more than 100 amino acids.
o No mutations/genetic aberrations in genes relevant for MHC presentation (e.g., beta-2-microglobulin, human leukocyte antigen [HLA] genes).
- An expected survival of at least 3 months.
- Presence of tumor lesion(s) suitable for biopsy and radiological assessment as per RECIST v1.1 criteria.
- 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.
- For all women of childbearing potential (defined as < 2 years after last menstruation or not surgically sterile) must have a negative highly sensitive pregnancy test at screening (serum/urine) and agree to use highly effective method of contraconception according to European Union (EU) Clinical Trial Facilitation Group guidance from time of signing informed consent form until at least 120 days after the last administration of FRAME-001. The partners of participants of childbearing potential must also apply contraceptive methods and are recommended not to donate sperm.
- Written informed consent according to International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP).

Exclusion criteria

- Any active infection that according to investigator might interfere with FRAME-001 vaccination.

- Patients planned or foreseen to receive systemic immunosuppressive treatment including corticosteroids during the trial are not eligible.
- Use of systemic corticosteroids (or other immunosuppressive agents; >10mg daily prednisone equivalent). Inhaled, intranasal or topical and physiological replacement doses of up to 10 mg daily prednisone equivalent are permitted.
- Live vaccine within 30 days prior to first dose of FRAME-001.
- 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 (i.e., synthetic long peptides, Montanide ISA 51 VG).
- 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:
o Basal or squamous cell carcinoma of the skin;
o Carcinoma in situ of the cervix;
o Carcinoma in situ of the breast;
o Incidental histologic finding of prostate cancer.

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	15
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	FRAME-001

Ethics review

Approved WMO Date:	23-12-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-03-2022
Application type:	First submission
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	EUCTR2021-003166-12-NL
ClinicalTrials.gov	NCT04998474
CCMO	NL78379.000.21