First-in-human Phase I dose escalation study assessing safety, tolerability and preliminary efficacy of immunomodulatory nanoparticles

Published: 27-07-2020
Last updated: 08-04-2024

The primary objectives of this trial are:- To determine the safety and tolerability of increasing doses of PRECIOUS-01 after intravenous (i.v.) administration in subjects with solid tumors;- To assess the effect of increasing doses of PRECIOUS-01 on...

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

Summary

ID

NL-OMON52685

Source
ToetsingOnline

Brief title
PRECIOUS-01

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
solid tumors

Research involving
Human

Sponsors and support

Primary sponsor: Tumor Immunology
Source(s) of monetary or material Support: Europese Unie

Intervention

Keyword: Immunomodulatory nanomedicines, NY-ESO-1, Phase I

Outcome measures

Primary outcome

The primary endpoints of the trial are:

- Safety profiles: incidence of treatment-emerging Adverse Events (AEs) and Serious Adverse Events (SAE), and laboratory abnormalities graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0 reporting severity and relatedness (see Appendix I); occurrence of DLTs; incidence of treatment discontinuations and treatment modifications due to AEs and laboratory abnormalities; changes in vital signs, electrocardiogram (ECG) and Eastern Cooperative Oncology Group performance status (ECOG PS); deaths;
- The immune modulating effect directly in the tumor is planned to be assessed at baseline and after Cycle 3 specifically to analyze the immunological composition in tumor biopsies using an established immunohistochemistry (IHC) assay for the detection of CD3, CD8, FoxP3, CD45RO and CD20 positive cells; these results will support the decision on the RP2D as part of the planned trial.

Secondary outcome

The secondary endpoints of the trial are:

- The RP2D, which will be evaluated using all data on safety and the immune modulating effect per dose level tested (if MTD is reached at one of the tested dose levels, then this dose will be used)

- Evaluation of the immune modulating activity at each dose level (focused on the presence of NY-ESO-1-specific T cells, iNKT cell activation, DC activation, cytokine responses, and anti-NY-ESO-1-specific antibody responses) using peripheral blood.

Study description

Background summary

In the rapidly evolving treatment landscape of advanced solid tumors, immunotherapeutic approaches have revolutionized cancer care for patients. Despite these advances, there is an undiminished need for the development of novel immunotherapeutic treatment modalities that can orchestrate an effective anti-tumor immune response in a highly targeted way, while circumventing immunosuppressive characteristics of the tumor microenvironment.
In this trial, we investigate a new class of immunomodulatory nanomedicines: PLGA-nanoparticles loaded with tumor antigen NY- ESO-1 peptides in combination with the invariant Natural Killer T (iNKT) cell activator IMM60.
PLGA-nanoparticles
Biodegradable PLGA-nanoparticles function as a delivery platform for immunomodulators and tumor antigens to induce a specific anti-tumor immune response. PLGA has minimal (systemic) toxicity and is used in various drug-carrying platforms as encapsulating agent. Uptake of the nanoparticle by Dendritic Cells (DC) and subsequent prolonged presentation of PLGA-encapsulated peptides on Major Histocompatibility Complex (MHC) class I and II molecules are able to generate functional and tumor-antigen-specific CD8+ and cluster of differentiation (CD)4+ T cell responses in preclinical studies.
NY-ESO-1
NY-ESO-1 is a cancer-testis antigen expressed during embryogenesis and in the testis, an immune privileged site. Furthermore, NY-ESO-1 expression is observed in several advanced cancers: lung (2-32%), melanoma (40%), bladder (32-35%), prostate (38%), ovarian (30%), esophageal (24-33%), and gastric cancers (8-12%). Clinical trials have shown the safety and tolerability of Good Manufacturing Practices (GMP)-grade NY-ESO-1 peptides in patients with cancer. By studying published NY-ESO-1 epitopes and their respective Human Leukocyte

Antigen (HLA) alleles using a cancer antigenic peptide database, we defined two long peptides of 27 amino acids and one short peptide of 9 amino acids for nanoparticle encapsulation (85-111, 117-143, and 157- 165). In combination, all three peptides are able to cover more than 80% of the European population for both class I and class II HLA alleles. Administration of NY-ESO-1-specific peptides leads to antigen-specific T-cell responses against NY-ESO-1-positive tumors. The peptides planned to be investigated in the current trial were selected based on their previously published immunogenicity (i.e., the capacity to induce T cell responses).

iNKT cell activator ThrCer6

iNKT cells recognize glycolipid molecules presented with CD1d molecules on DCs via their invariant T cell receptor (TCR). DCs are considered the most potent Antigen-Presenting Cells (APCs) of the immune system and induce antigen-specific cytotoxic (CD8+) T cell responses to tumor antigens. Upon CD1d-dependent interaction with DCs, iNKT cells will be stimulated to secrete pro-inflammatory cytokines (e.g., interferon [IFN]-* and interleukin [IL]-12). Moreover, CD40-CD40 ligand (CD40L) mediated interaction between DCs and iNKT cells during glycolipid presentation leads to DC maturation demonstrated by the upregulation of co-stimulatory molecules.

αGalCer consists of a galactose connected via an α-linkage to a ceramide-group. Once presented with CD1d on antigen presenting cells, it functions as a potent activator of iNKT cells. ThrCer6 is an alpha-Galactosylceramide (αGalCer)-derived iNKT cell activator that possesses a superior iNKT cell activation profile compared to αGalCer in vitro as well as in vivo. Unlike αGalCer, it does not subject to glycosidase-mediated degradation. Induction of antigen-specific CD8+ T cell responses at lower concentrations of ThrCer6 than αGalCer were observed in mice due to a prolonged bioavailability. ThrCer6 maintained the capacity to induce DC maturation in vivo to a similar extent as αGalCer. Furthermore, iNKT cell-mediated anti-tumor effects include IFN-*-dependent Natural Killer (NK) cell responses, maturation of DCs, expansion of antigen-specific CD8+ T cell responses, inhibition of metastatic behavior and improved survival in cancer mouse models.

Co-encapsulation in nanoparticles: iNKT cell activator and tumor antigen

Preclinical studies in murine cancer models showed αGalCer/CD1d-dependent superiority of nanoparticles that co-encapsulated αGalCer+Ovalbumin (OVA) in terms of CD8+-specific T cell induction compared with nanoparticles with OVA combined with either nanoparticles with αGalCer or soluble αGalCer. These findings appear independent of CD4+ T cell help. Co-encapsulation of a potent iNKT cell activator such as αGalCer or ThrCer6, with a tumor antigen, such as NY-ESO-1, can result in detectable cytotoxic T lymphocyte (CTL) responses against the respective antigen. With this in mind, in vitro experiments with peripheral blood mononuclear cells were performed to first assess feasibility of co-encapsulation. These experiments demonstrated the feasibility of encapsulating three NY-ESO-1 peptides (the same peptides to be used in this trial) together with IMM60 in the same particle. Peptides were processed and presented by multiple HLA types. In mice expressing the human HLA-A2 molecule, activity of nanoparticle-encapsulated IMM60 was evident by DC maturation and

IFN-γ secretion. Also, CD4+ and CD8+ T cell responses against NY-ESO-1 peptides were observed with the same nanoparticles co-encapsulating NY-ESO-1 peptides.

Study objective

The primary objectives of this trial are:
- To determine the safety and tolerability of increasing doses of PRECIOUS-01 after intravenous (i.v.) administration in subjects with solid tumors;
- To assess the effect of increasing doses of PRECIOUS-01 on the composition and spatial heterogeneity of immune cells directly in the tumor
The secondary objectives of this trial are:
- To determine the Recommended Phase 2 Dose (RP2D) of PRECIOUS-01 for a subsequent Phase II trial. - To assess immunological responses during and after therapy with PRECIOUS-01 in blood.
The exploratory objective of this trial is:
- To evaluate the clinical outcome of PRECIOUS-01 using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
Further exploratory objectives will be determined based on results of ongoing preclinical studies.

Study design

This is an open-label, first-in-human Phase I dose escalation trial to investigate the safety and tolerability of increasing doses of PRECIOUS-01 administered i.v. in subjects with solid tumors.
Eligible subjects will receive three i.v. infusions of PRECIOUS-01 at a 3-weekly interval in three dose-finding cohorts (low: 0.4 mg/kg, intermediate: 0.8 mg/kg, and high: 1.6 mg/kg fixed doses). Subjects will be monitored for safety and the occurrence of Dose-Limiting Toxicities (DLTs). It is planned to follow a 3+3 design for the dose escalation steps. Three subjects will be enrolled sequentially per cohort. If the maximum tolerated dose (MTD) is not reached in the planned dose escalation cohorts, the RP2D will be based on the observed safety and immune-modulatory activity as pharmacodynamic parameter supporting the RP2D. The sample size is based on the determination of the MTD/RP2D. In order to collect sufficient information regarding changes in immune-related parameters as readout for pharmacodynamics of the particles (e.g., NY-ESO-1-specific CD8+ T cells, iNKT cell activation, and NY-ESO-1 antibody responses in serum) it is planned to extend the two highest dosing cohorts to a total of six subjects.
Based on accumulating data during the trial and no observed toxicity in cohort 2 after three subjects for DLT observation, no further subjects may be enrolled at that dose level. Instead, cohort 3 would start. If no toxicity is observed in the six planned subjects in cohort 3 and based on the recommendation of the Dose Steering Board (DSB), three additional subjects may be enrolled at the high dose level for a total of nine subjects. If a toxicity is observed in the first six subjects of cohort 3, three subjects will be enrolled in cohort 2

(for a total of six subjects at that dose level). The total number of subjects will not change.
The starting dose is 10% of the No Observed Adverse Effect Level (NOAEL) in the toxicology study. Doses will be escalated after a review of the safety data from the previous cohort by a DSB upon completion of the DLT observation period. Pre-defined DLT criteria will be used.

Intervention

PRECIOUS-01 will be administered i.v. three times at 3-weekly intervals (Day 1, Day 22 and Day 43).
Doses are specified as follows: low (0.4 mg/kg PRECIOUS-01), intermediate (0.8 mg/kg PRECIOUS-01) and high (1.6 mg/kg PRECIOUS-01). PRECIOUS-01 will be administered as fixed doses (based on a 70-kg average body weight).

Study burden and risks

Risks
PRECIOUS-01 has not yet been given to patients, therefore side effects to PRECIOUS-01 are unknown. The particle has a low potential risk of inducing allergic reactions. Possible AEs associated with an allergic reaction can include fever, chills, headache, weakness, nausea, vomiting, diarrhea, low blood pressure, respiratory symptoms, and rashes. Additionally, since the mode of action of PRECIOUS-01 includes potential stimulation of the immune response, there is a likelihood of immune-related AEs. Generally, such AEs have been observed after specific blocking of inhibitory receptors expressed on T cells (e.g. Programmed Cell Death Protein 1 [PD-1]) rather than after induction of tumor-specific immune responses. If PRECIOUS-01 elicits a particularly strong T-cell immune response in a few subjects predisposed to develop autoimmunity, immune-related AEs may nonetheless be observed.
Toxicology findings recorded in preclinical studies include hepatocellular necrosis, vascular/perivascular mononuclear cell infiltration and thrombosis, all partially recovered. The hepatocellular necrosis correlated with an increase in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. To mitigate the thromboembolic risks observed in preclinical studies with PRECIOUS-01, subjects who have active thromboembolic events that require anti-coagulation were excluded from the trial. Additionally, all subjects will be closely monitored for these associated laboratory parameters on Days 1, 7, and 14 of Cycle 1 and on Days 1 and 7 during Cycle 2 and 3. If needed, the frequency of monitoring for these changes will be appropriately adapted during the trail per subject.
The toxicology results also suggest an increase in IFN-γ and TNF-α production, which can potentially be associated with fever, chills, dizziness and bone marrow toxicity. The levels of IFN-γ and TNF-α will be carefully monitored as detailed in the Schedule of Assessments.
Administration of PRECIOUS-01 was associated with lower white blood cell and

platelet count, increased red blood cell mass, reticulocytes and circulating enzyme levels. These were fully recoverable.
Additional to potential risks related to administration of PRECIOUS-01, there are also procedural risks related to blood sampling, other possible subcutaneous injections and diagnostic procedures. Blood sampling and subcutaneous injections may cause pain, bleeding, bruising, and/or infections at the site of cannula insertion. Rare complications due to blood sampling are syncope, thrombophlebitis, as well as accidental punctures of an artery or nerve.

Benefits
This is the first clinical trial with PRECIOUS-01. The primary aim of this trial is to obtain safety, and tolerability data when PRECIOUS-01 is administered to subjects with NY-ESO-1-positive solid tumors. In addition to the minimal risk using PRECIOUS- 01 (please see IB), preclinical experience with the compound indicates a potential benefit that might be expected in terms of an immune response against the tumor that might lead to a beneficial clinical outcome.
The safety and efficacy data, together with the immunological data obtained from this trial, will help establish the treatment regimen and a Recommended Phase II Dose (RP2D) that can form the basis for a recommended dose suitable for subsequent clinical trials.
Benefit/risk ratio
The anticipated risks, based on the non-clinical experience with PRECIOUS-01, are expected to be manageable. The importance of the objective of this trial is considered to outweigh the risks and burdens to the subjects. Measures are implemented to minimize burdens and risks for subjects. Subjects will be monitored closely for the occurrence of any significant clinical events and treatment will only continue if it is considered safe and appropriate to do so. The benefit/risk assessment is favorable and justifies the planned trial.

Contacts

Public
Selecteer

Geert Grooteplein 26
Nijmegen 6525GA
NL
Scientific
Selecteer

Geert Grooteplein 26
Nijmegen 6525GA

NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Age >=18 years at time of signing informed consent.
2. Performance status (ECOG <= 1) (Appendix II).
3. Estimated life expectancy of at least 6 months.
4. Histologically or cytologically confirmed advanced and /or metastatic solid tumor with progressive disease at baseline, for whom no standard treatment is available. Suitable solid tumor indications include non-small cell lung cancer (NSCLC), melanoma, epithelial ovarian cancer, bladder cancer, breast cancer, and synovial sarcoma, adenoid cystic carcinoma, cervical cancer, endometrial cancer, lung cancer, pancreatic cancer, prostate cancer, myxoid and round cell liposarcoma, neuroblastoma, vulvar cancer, esophageal cancer, hepatocellular cancer, and head and neck cancer.
5. Subject with evaluable disease per RECIST v1.1.
6. Adequate hematologic, renal and liver function as defined by laboratory values performed within 14 days of start of treatment:
a. Hemoglobin (Hb) >= 6 mmol/L;
b. Absolute Lymphocyte Count (ALC) > 0.8 x 109/L;
c. Absolute Neutrophil Count (ANC) >= 1.5 × 109/L;
d. Platelet count > 100 x 109/L;
e. Serum creatinine <= 1.5 x ULN or calculated creatinine clearance >= 60 mL/min (as determined by MDRD [Modification of Diet in Renal Disease]) for patients with serum creatinine levels > 1.5 x ULN;
f. Serum bilirubin < 25 µmol/L;
g. Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT) <= ULN unless related to liver metastasis (in which case levels should be < 3 x ULN).
h. Alkaline Phosphatase (ALP) <= ULN unless related to liver or bone marrow metastases (in which case levels should be <= 3 x ULN).

7. Previous therapy-derived toxicities should be resolved to Grade < 2 according to CTCAE v5.0 (Appendix I), with exceptions for alopecia.
8. All subjects of childbearing potential (defined as < 2 years after last menstruation or not surgically sterile) must have a negative highly sensitive pregnancy test at screening (urine/serum) and agree to use a highly effective method for contraception according to the EU Clinical Trial Facilitation Group guidance from time of signing the informed consent form (ICF) until at least 120 days after the last administration of PRECIOUS-01. The partners of subjects with childbearing potential must also apply contraceptive methods, and are recommended not to donate sperm.
9. Before registration, ability of subject to give written informed consent according to International Council for Harmonisation (ICH) Good Clinical Practice (GCP), and national rules/local regulations.
10. Expected adequacy of follow-up.

Exclusion criteria

1. Second malignancy in the previous 2 years, with the exception of adequately treated in situ carcinoma of the cervix uteri and basal or squamous cell carcinoma of the skin,
2. Clinical suspicion or radiological evidence of active brain metastases. Patients with brain metastases that have been treated previously and are proven stable (computed tomography [CT] or magnetic resonance imaging [MRI] < 30 days) and without steroids for > 3 months are allowed.
3. Subjects with thromboembolic events within the past year.
4. Subjects suffering from melanoma, non-Hodgkin lymphoma, or renal cell carcinoma who have a serum Lactic Acid Dehydrogenase (LDH) > ULN.
5. Subjects on any other anticancer therapy (cytotoxic, biologic or investigational agents), unless at least 4 weeks (or 5 half-lives, whichever is shorter, 6 weeks for mitomycin-C or nitrosoureas), have elapsed since the last dose before the first administration of PRECIOUS-01. At least 4 weeks should have elapsed since receiving palliative radiotherapy. Chronic treatment with non-investigational gonadotropin-releasing hormone analogs or other hormonal or supportive care is permitted.
6. Subjects with major surgery within 4 weeks before initiating treatment or with minor surgical procedure within 7 days before initiating treatment (except for port-a-cath or central line i.v. placement, or biopsy), or anticipation of the need for major surgery during the course of the trial treatment.
7. Concomitant use of oral or i.v. immunosuppressive drugs. Inhaled, topical or intranasal steroids and adrenal replacement steroids < 10 mg/day (prednisone equivalent) are permitted in the absence of auto-immune disease.
8. Uncontrolled infectious disease, i.e., negative testing for human immunodeficiency virus (HIV), Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) and syphilis (Treponema Pallidum Hemagglutination Assay [TPHA]).
9. (Systemic) autoimmune disease such as, but not limited to, inflammatory

bowel disease, multiple sclerosis and lupus. Subjects with type 1 diabetes mellitus, hypothyroidism after autoimmune thyroiditis and skin disorders (eczema and psoriasis) are not excluded.
10. History of clinically significant cardiovascular disease (<= 6 months prior to Day 1 on trial) such as stroke, Transient Ischemic Attack (TIA), unstable angina, New York Heart Association (NYHA) Grade II or greater congestive heart failure, myocardial infarction, uncontrolled hypertension, cardiac arrhythmia requiring medication, relevant pathological ECG findings or uncontrolled hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg).
11. Serious (bleeding and clotting) condition(s) that may interfere with safe administration of PRECIOUS-01.
12. Abnormal or clinically significant coagulation parameters at the discretion of the Clinical Investigator, i.e.:
a. Prothrombin Time - International Normalized Ratio (PT-INR)
b. Activated Partial Thromboplastin Time (APTT)
c. Subjects being treated with anticoagulants are excluded if the coagulation parameters are outside the therapeutic intervals as described in the Summary of Product Characteristics (SmPC) for the administered treatment.
13. Evidence of any other conditions (such as psychological/familial sociological/geographical issues, psychiatric illness, infectious diseases, physical examination or laboratory findings) that may interfere with the planned treatment, affect subject compliance or place the subject at high risk from treatment-related complications. These conditions must be discussed with the subject before registration in the trial.
14. History of severe allergic episodes and/or Quincke*s edema.
15. Prior allogeneic tissue/solid organ transplant, stem cell or bone marrow transplant.
16. Known hypersensitivity to any component of PRECIOUS-01.
17. Pregnant or lactating women. A highly sensitive pregnancy test (urine/serum) must be performed within 7 days prior to start of trial treatment for confirmation in case of childbearing potential.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	07-04-2021
Enrollment:	15
Type:	Actual

Ethics review

Approved WMO Date:	27-07-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-09-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-11-2020
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	18-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-08-2021

Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-08-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-01-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	26-03-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-08-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2017-002567-41-NL
CCMO	NL72876.091.20