Ovarian cancer treatment with a liposome formulated mRNA Vaccine in combination with (neo-)adjuvant chemotherapy

Published: 07-08-2018
Last updated: 10-01-2025

Systemic induction / expansion of vaccine antigen-specific T cells.

Ethical review	Approved WMO
Status	Completed
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON49404

Source
ToetsingOnline

Brief title
OLIVIA

Condition

- Reproductive neoplasms female malignant and unspecified
- Ovarian and fallopian tube disorders

Synonym
Ovarian cancer, ovarian carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: BioNTech RNA Pharmaceuticals GmbH,KWF-

subsidie en BioNtech RNA Pharmaceuticals GmbH

Intervention

Keyword: Chemotherapy, Ovarian cancer, Phase I, Therapeutic immunization

Outcome measures

Primary outcome

Systemic induction / expansion of vaccine antigen-specific T cells

Secondary outcome

1) Intratumoral induction / expansion of vaccine antigen-specific T cells

2) Progression-free survival of primary OC patients treated with the vaccines

in combination with carboplatin/paclitaxel

3) Assessing the safety and tolerability of repetitive doses of the vaccine in

combination with carboplatin/paclitaxel

Study description

Background summary

Advanced stage serous ovarian cancer (OC) is the leading cause of death from gynaecological malignancies with a 5-year survival of no more than 40%. Current treatment (surgery and chemotherapy) is initially effective, but almost all patients suffer from chemotherapy-resistant relapse. Moreover, despite adjustment of chemotherapeutic schedules and the introduction of innovative targeted drugs, survival and quality of life have barely improved. A promising new approach that may improve outcome for these patients is immunotherapy. In particular, immune checkpoint inhibition (CPI) therapy targeting e.g. PD-L1 or PD-1 have improved patient survival rates across malignancies, with some responses also observed in ovarian cancer patients. Nevertheless, response to CPIs is almost always dependent on a pre-existing anti-cancer immune response, frequently absent in ovarian cancer patients. In order to increase/ induce an anti-tumor response an optimized liposomal formulated RNA vaccine targeting tumor-associated antigens (TAA) is developed. This vaccine protects RNA from degradation by plasma RNAses and shows an almost 100% targeted accumulation of RNA in the spleen suggesting a direct delivery to dendritic cells. Here, we

therefore propose to increase/induce an anti-tumor immune response in patients with ovarian cancer while receiving neoadjuvant chemotherapy by use of the BNT115 vaccine. The simultaneous treatment with vaccinations and neoadjuvant chemotherapy provides a tumor immune environment where immune defences are decreased. Thereby enhancing the effectiveness of a vaccine induced immune response. Making it a perfect setting for the induction of a tumor specific immune response, with the ultimate aim of moving towards combination therapy of chemotherapy/vaccination with checkpoint inhibition for these patients.

Study objective

Systemic induction / expansion of vaccine antigen-specific T cells.

Study design

A GMP-grade RNA vaccine targeting serous OC antigens will be used to induce a systemic immune response and more importantly tumor accumulation of vaccine-induced T cells.

Patients with primary epithelial ovarian carcinoma will receive eight vaccinations, in the same period they will receive three cycles of neoadjuvant chemotherapy, an operation and adjuvant chemotherapy (standard treatment). We will need to include 10 evaluable patients to determine the primary outcome.

Data collected for analyzing vaccine-specific systmic immune response is obtained before and after vaccinations by collection of PBMCs by leukapheresis and/or venous blood collections.

Data collected for analyzing vaccine-specific intra-tumoral immune response is obtained by collection of tumor material by biopsy before vaccination and surgery after 5th vaccination (standard care).

To determine the safety and tolerability of the vaccine, adverse events will be recorded during the study, also ECOG-status is measured and bloodchemistry and heamatology is monitored.

To assess the exploratory endpoint, results from the intratumoral visualization of CD25+ T cells by the [18F]FB-IL2 PET-CT imaging (expressed as standardized uptake values (SUV)) is compared to CD25+ T-cell infiltration in matching tumor material (evaluated by immunohistochemistry).

Intervention

Intravenous administration of the vaccine (8 times)

Study burden and risks

Patients in this phase I pilot trial have an active disease and might experience benefit from this study. The intended goal of the study is to induce a specific anti-cancer immune response which may ultimately lead to eradication of the malignant lesions. When long-lasting immunity is induced, the immunotherapy may also sensitize patients for further treatment with ICB or even prevent recurrence of the disease.
For each patients study procedures will take approximately 9 months. The study includes 16 hospital visits, we expect to combine at least 6 visits with SOC visits.

Eight vaccinations by intravenous (i.v.) injection are performed with additional vena punctures for bio / immune monitoring. Visits and study related blood collections are aligned to and combined with SoC procedures as much as possible.

Initial clinical data from RNA(LIP) studies demonstrated that a dosage of 100 µg total RNA is safe and sufficient for induction of a potent immune response. We will monitor the safety and toxicity of this cancer vaccine in the current trial, using GCP guidelines. Toxicity will be graded according to the NCI CTCAE Version 5.0. Earlier clinical studies indicate that liposome delivery of RNA further augments this immunogenicity in the absence of any toxicity.

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

- Primary epithelial OC patients with measurable tumor lesions (determined by CT or MRI), who are intended to be treated with neo-adjuvant chemotherapy, carboplatin/paclitaxel, subsequent surgery and adjuvant chemotherapy
- Age >= 18 years
- Signed informed consent in accordance with institutional and regulatory guidelines
- Adequate access of the tumor for image-guided biopsy
- Adequate (according to the institutional standards) hematology, liver and kidney function to undergo chemotherapy with carboplatin and paclitaxel
- ECOG-performance status of 0 or 1 at screening
- Current BMI > 18.5 and no weight loss of >5% over the past month. Notably, weight loss due to drainage of ascites is not applicable.

Exclusion criteria

- History of a second malignancy except for curatively treated low-stage tumors with a histology that can be differentiated from the epithelial OC type

-Patients must have no ongoing or recent evidence (within the last 5 years) of significant autoimmune disease that required treatment with systemic immunosuppressive treatments which may suggest risk for immune-related adverse events (irAEs).
Note: Patients with autoimmune-related hyperthyroidism, autoimmune-related hypothyroidism who are in remission, or on a stable dose of thyroid-replacement hormone, vitiligo, or psoriasis may be included.

- Patients must have no uncontrolled infection with human immunodeficiency virus, hepatitis B or hepatitis C infection; or diagnosis of immunodeficiency that is related to, or results in chronic infection. Mild cancer-related immunodeficiency (such as immunodeficiency treated with gamma globulin and without chronic or recurrent infection) is allowed.
o Patients with known HIV who have controlled infection (undetectable viral load and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards.

o Patients with known hepatitis B (HepBsAg+) who have controlled infection (serum hepatitis B virus DNA PCR that is below the limit of detection AND receiving antiviral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA per local standards. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of trial treatment.
o Patients who are known hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by PCR either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.

- Use of systemic continuous corticosteroid therapy (e.g. prednisone i.v. or p.o. >7.5 mg / day).
- Pregnancy or breast feeding
- Participation in a trial with another investigational drug within 30 days prior to the enrolment in this trial
- Any condition that in the opinion of the investigator could interfere with the conduct of the trial.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	09-12-2019
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	BNT115 vaccine

Ethics review

Approved WMO Date:	07-08-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-11-2018
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-04-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-11-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-10-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	17-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-02-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	16-05-2022
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	EUCTR2017-004585-10-NL
ClinicalTrials.gov	NCT04163094
CCMO	NL66895.000.18

Study results

Date completed:	27-06-2023

Results posted:	01-07-2024
Actual enrolment:	8

Summary results
Trial ended prematurely

First publication
26-06-2024