A multicenter, open label Phase I/II study to determine the safety and immune modulating effects of the therapeutic Human Papilloma Virus Type 16 (HPV16) E6/E7 Synthetic Long Peptides Vaccine (ISA101/ISA101b) immunotherapy in combination with standard of care therapy (carboplatin and paclitaxel with or without bevacizumab) in women with HPV16 positive advanced or recurrent cervical cancer who have no curative treatment options.

Published: 04-07-2013
Last updated: 22-04-2024

Primary objectives: • To assess the safety and tolerability of different doses of the ISA101 vaccine with or without pegylated IFNα as combination therapy with carboplatin and paclitaxel.• To qualitatively assess the safety profile of ISA101b...

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

Summary

ID

NL-OMON45132

Source
ToetsingOnline

Brief title
CervISA: ISA-HPV-01-12

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
advanced or recurrent cervical cancer, cervical cancer

Research involving
Human

Sponsors and support

Primary sponsor: ISA Therapeutics B.V.
Source(s) of monetary or material Support: ISA Therapeutics B.V.

Intervention

Keyword: Cervical cancer, HPV16 vaccin, ISA101(b), Phase I/II study

Outcome measures

Primary outcome

The primary endpoints of the study are:

• Safety:

o Safety will be determined by the incidence rate at each dose level based on the following safety parameters: adverse events (AEs) and serious adverse events (SAEs), 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 4.0 will be used.

The safety profile of ISA101b in the bridging cohort(s) will be qualitatively compared to the safety profile observed at the same dose level(s)

of ISA101.

• HPV-specific immune responses:

o HPV-specific immune responses to the ISA101 vaccine with or without pegylated IFNα in combination with carboplatin and paclitaxel will be determined by the quality, breadth and magnitude of the HPV16 E6/E7-specific T-cell responses as measured by a validated assay (IFNγ-ELISPOT) following injection of the different doses of the ISA101 vaccine.

o The HPV-specific immune responses to ISA101b in the bridging cohort(s) will be qualitatively compared to the responses observed at the same dose level(s) of ISA101.

Secondary outcome

Secondary endpoint:

• Antitumor efficacy according to RECIST 1.1:

o Objective Response Rate (ORR) will be calculated as the proportion of patients with a best overall response of confirmed Complete Response (CR) or Partial Response (PR).

o Disease Control Rate (DCR) will be calculated as the proportion of patients with a best overall response of confirmed CR, PR or Stable Disease (SD).

o Progression Free Survival (PFS) is defined as the time from start of carboplatin and paclitaxel (with or without bevacizumab) treatment to the documented progression or death from any cause.

Exploratory endpoint:

• General responsiveness of the immune system as measured by exploratory assays

, in particular 1) lymphocyte proliferation as measured by 3H-thymidine

incorporation in PBMCs in response to HPV E6/E7 peptides in vitro, 2)

antigen-presenting cell (APC) function tests, 3) assay of myeloid and lymphoid

cell composition as assessed by flow cytometry and 4) recall proliferative

responses of PBMC in response to common microbial antigens as measured by

3H-thymidine incorporation.

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Study description

Background summary

Cervical cancer is the second most frequent cancer in women worldwide. Cervical cancer is divided into early-stage cervical cancer (FIGO stages IA1-IIA) with a low risk of recurrence (15%) after treatment and advanced cervical cancer (FIGO stages IIB/III/IV) with a high risk of recurrence (up to 70%) and a poor prognosis.
The causal role of HPV infections in the development of cervical intraepithelial neoplasia and subsequent cervical carcinoma has been unambiguously established. Genital infections with high-risk HPV are mainly acquired through sexual activity and are highly prevalent in young sexually active individuals. In the majority of infected subjects the infection is cleared within one year. However, infection with the high-risk HPV type 16 (HPV16) is associated with a greater risk for progression and is most common in patients with invasive cervical cancer. HPV16 encodes the two tumour-specific oncoproteins E6 and E7 that can elicit a favourable immune response in which specific T-cells play a critical role in the control and elimination of the HPV infection. The virus-specific interferon-γ (IFNγ)-producing CD4+ cells (Th1 cells) and CD8+ cytotoxic T-lymphocytes (CTL) are able to recognise peptides processed from the oncoproteins E6 and E7 and contribute to the virus elimination.
However, in case of an uncontrolled persistent infection with a high-risk HPV type, the expression of the viral oncoproteins E6 and E7 contributes to the development of cervical (pre)malignancies. Apparently, the spontaneous HPV-specific T-cell response fails in these patients and there is no or a negligible activation and expansion of the proper HPV16-specific CD4+ and CD8+

T cells.
The standard treatment for advanced cervical cancer consists of platinum-based chemotherapy, often in combination with a taxane such as paclitaxel. However, with a response rate of 20% to 50%, this therapy is rarely curative and should be considered as palliative treatment. . The simultaneous use of several chemotherapeutic agents has been shown to marginally increase survival times, and was sporadically associated with higher response rates. Treatment with chemotherapy combinations in the setting of stage IVB, recurrent, or persistent cervical carcinoma leads to median overall survival (OS) of approximately 1 year (range 10-14 months). Importantly, if women with these disease stages are offered the option to receive combination chemotherapy it also seems as if a proportion of them, approximately 10-20%, can survive 3 years and beyond. Recently, a phase III trial of four cisplatin-containing doublet combinations was performed in patients with stage IVB, recurrent or persistent cervical carcinoma. The median OS varied between 10 and 13 months. There was a trend towards a slightly improved response rate, progression-free survival (PFS) and OS with the combination of paclitaxel plus cisplatin. In a retrospective evaluation, carboplatin/paclitaxel compared favourably with cisplatin/paclitaxel and demonstrated a superior overall response rate (53% vs. 29%) and similar survival (median survival of 14 and 11 months, respectively). In addition, the authors considered the ease of administration and improved toxicity profile of carboplatin/paclitaxel as important factors using this treatment for advanced, recurrent or progressive cervical cancer18. The utilization of chemotherapy, including the specific combination of carboplatin and paclitaxel for women with metastatic, persistent and recurrent cervical cancer is included in global and local guidelines. A recent study showed that addition of bevacizumab to standard of care chemotherapy of patients with recurrent or metastatic cervical cancer further improves the therapeutic results, improving overall survival with 3.7 months (17 months versus 13.3 months with chemotherapy alone
Combining current treatment strategies such as radiotherapy, chemotherapy, in addition to bevacizumab and combinations thereof with immunotherapy could offer a novel approach in which traditional chemotherapy and radiation treatment are expected to synergize with immunotherapy. The rationale for exploring this is that several chemotherapeutic agents have shown a positive influence on the immune system, in particular on the immunosuppressive micro-environment, both in preclinical animal models and in clinical trials. In addition, pre-clinical data have shown promising results of the combination of traditional chemotherapy with therapeutic vaccines. Indeed, application of therapeutic vaccines for malignancies has been generally disappointing in the clinic when applied as monotherapy, sometimes due to suboptimal vaccine design, but more importantly as a result of the tumour-associated immunosuppressive micro-environment discussed above. However, combination treatment of powerful therapeutic cancer vaccines, such as synthetic long peptides (SLPs), in combination with chemotherapy that alleviates the cancer-associated immunosuppression, creates a novel treatment paradigm of considerable promise.

Study objective

Primary objectives:
• To assess the safety and tolerability of different doses of the ISA101 vaccine with or without pegylated IFNα as combination therapy with carboplatin and paclitaxel.
• To qualitatively assess the safety profile of ISA101b vaccine compared to ISA101 at the same dose level(s).
• To assess the safety of ISA101b vaccine with carboplatin, paclitaxel with or without bevacizumab.
• To assess the HPV-specific immune responses to different doses of the ISA101 vaccine with or without pegylated IFNα as combination therapy with carboplatin and paclitaxel.
• To qualitatively assess the HPV-specific immune responses of ISA101b vaccine relative to the same dose level(s) of ISA101.
• To qualitatively assess the HPV-specific immune responses of ISA101b vaccine with carboplatin, paclitaxel with or without bevacizumab.

Secondary objective:
• To evaluate the clinical efficacy of immunotherapy with ISA101/ISA101b in combination with standard therapy i.e. carboplatin and paclitaxel with or without bevacizumab.

Exploratory objective:
• To evaluate the general responsiveness of the immune system of the patient in correlation with the HPV-specific immune responses and/or clinical efficacy.

Study design

This is a multicenter, open label, non-randomized Phase I/II study. Patients with advanced or recurrent HPV16 positive cervical cancer for whom no curative treatment options exist will be enrolled in eight cohorts of six patients each to include in total 48 patients. The maximum total treatment duration for a patient is six cycles (1 cycle is 21 days) of carboplatin and paclitaxel (18 weeks, if there are no dose interruptions/delays). On Day 15 (±3 days) of Cycle 2 the vaccination scheme of ISA101 with or without pegylated IFNα will start.

The patients will be vaccinated with a fixed dose of ISA101 every three weeks for a total of three rounds of vaccination. Four dose levels of ISA101 will be tested. The first 6 patients will be enrolled in cohort 1, the next 6 patients in cohort 2, and so on until completion of all 8 cohorts (i.e. there are 2 cohorts at each ISA101 dose-level, an initial cohort at a given dose level in which patients do not receive IFNα (cohorts 1, 3, 5, and 7) followed by an additional cohort at the same dose of ISA101 that does receive IFNα [cohorts 2, 4, 6 and 8]). The decision to start enrollment at the next dose level (i.e cohort 3, 5 or 7) will be made by assessing the safety after at least 3 out of

6 patients at the previous dose level (i.e. cohort 1, 3 or 5) have completed chemotherapy Cycle 1 to 3 and received at least 2 of the possible 3 vaccinations with ISA101. The Data Monitoring Committee (DMC) will receive listings of individual patient data from the Sponsor related to baseline characteristics, safety, and study medication administration for the patients necessary to assess per above before enrolment is started at the next dose level. Based on review of the available data, the DMC will make a recommendation to the Sponsor whether or not to start of enrolment at the next dose level.

Frequent dose limiting toxicities are not anticipated based on previous clinical experience in approximately 180 women with premalignant vulvar, cervical intraepithelial neoplasia or cervical cancer who received vaccination HPV-16-SLP in Montanide. Patients will be evaluable for immunogenicity if they have received at least two vaccinations with ISA101 and have pre-vaccination blood sample and two post-second vaccination blood samples (all with sufficient peripheral blood mononuclear cells (PBMCs)). Patients who are not evaluable for the HPV16 E6/E7-specific T-cell response assays (Interferon gamma-Enzyme-linked immunosorbent spot (IFNγ-ELISPOT)) and will be replaced unless treatment was stopped prematurely due to toxicity of ISA101.

In the extension study a total of approximately 12 evaluable patients will be enrolled, 6 subjects in each of two cohorts (03B and 05B) with an ISA101 dose regimen previously determined to have an acceptable safety profile.

After completion of enrolment of the extension cohorts at 40 and 100 µg per peptide, the study will continue to enroll additional patients in bridging cohort(s) using the modified ISA101b vaccine at a dose of 100 µg per peptide plus carboplatin and paclitaxel to determine if the safety profile of the new drug product is qualitatively similar to those induced by the original ISA101 used in previous cohorts. In addition, data on the immune response to ISA101b will be collected. These data on the safety and immune response to ISA101b will inform the dose selection for further clinical studies of ISA101b. After evaluation of the initial safety data of 3 patients who have received at least two ISA101b doses of 100 µg per peptide, the safety data will be reviewed by the sponsor and the DMC to determine if 3 additional patients will be treated at the 100 µg/peptide dose level. Based on review of the data and recommendations of the DMC, another cohort is planned to assess patients who would otherwise receive standard first line therapy (paclitaxel, carboplatin and bevacizumab) for recurrent cervical cancer. This cohort will include 6 additional patients to be treated with carboplatin, paclitaxel, and bevacizumab with ISA101b (100 µg per peptide pending DMC safety review). If deemed appropriate, based on recommendation of the DMC, an additional 12 patients may receive a dose of ISA101b at <=100 µg per peptide without or with bevacizumab.

In the bridging cohorts a total of 24 patients will be enrolled, 6 subjects in each of four cohorts:

- Cohort 9 (ISA101b 100µg per peptide)
- Cohort 10 (ISA101b µg per peptide, with bevacizumab 15mg/kg)
- Cohort 11 (ISA101b <= 100µg per peptide)
- Cohort 12 (ISA101b <= 100µg per peptide, with bevacizumab 15mg/kg)

Intervention

Subjects eligible for the study will be assigned to a dose level cohort. All patients will be treated with AUC 6 Carboplatin and 175 mg/m2 paclitaxel. Patients will be treated at one of 4 different dose levels of ISA101 vaccine (namely 20, 40, 100 or 300 µg per peptide). Half of the patients will additionally receive 1 µg/kg pegylated IFNα during dose escalation. In the extension cohorts, patients will not receive IFNα.

In the bridging cohorts, patients will be treated with AUC 6 Carboplatin and 175 mg/m2 paclitaxel and ISA101b (maximum dose 100 µg per peptide), with or without bevacizumab 15mg/kg.

Study burden and risks

In summary, the patient population to be included in the current study constitutes a population of women with cervical cancer who according to global and local consensus should be offered standard chemotherapy as used in this study. These women may benefit by tumor load reduction leading to symptom improvement and prolonged time to disease progression. In addition to the standard chemotherapy, the women participating in the trial will receive well-timed (in relation to the chemotherapy , see Section 1.5) vaccinations with ISA101/ISA101b formulated in Montanide for the induction of a strong and broad cytotoxic T cell response against HPV16 E6 and E7, which in turn might lead to a prolonged control of the tumor compared with chemotherapy only (as has been documented in preclinical models, see above). Half of the women will also receive concurrent injections with Pegintron at the time points of vaccinations to further potentiate the HPV16 immunity which may further enhance the possibility of achieving a strong enough immune response to synergize with chemotherapy and improve outcomes.

The toxicity burden and risks associated with delivering the standard of care carboplatin and paclitaxel and bevacizumab chemotherapy combination far outweigh the burden and risks associated with vaccination against HPV16. Based on the already available data from the CervISA trial, the combination treatment with chemotherapy and ISA101/ISA101b including Montanide (with or without Pegintron) does not appear to be associated with substantially greater toxicity than the individual components by themselves. In contrast, the immunological and therefore potential clinical benefits might be considerable as judged from the preclinical and clinical experiments data outlined above. Thus, it is judged that the possible benefits outweigh the risks and thereby the

benefit/risk assessment performing the study is favorable.

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

1) Women >= 18 years of age.
2) Cervical cancer confirmed by histology.
3) Advanced (Stage IIIb/IVa with para-aortic lymph nodes involvement beyond the renal vein) or, metastatic (Stage IVb) or recurrent cervical cancer confirmed by clinical and/or radiological proof with no curative treatment options.
4) For cohort 10 (and 12) patients should be eligible to receive bevacizumab at each site per standard of care, patients may be primary stage IVB (including persistent) or first recurrent carcinoma of the uterine cervix (squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma). Prior treatment with chemotherapy for recurrent disease is not

permitted. However, one prior line of chemotherapy with platinum during primary radio-chemotherapy or platinum-base chemotherapy as neoadjuvant chemotherapy prior to surgery is permitted.
5) Tumour must be HPV16 positive (to be determined on archival tumour tissue (<=10 years old); if that is not available a pre-treatment biopsy will be required).
6) Patients should be eligible for chemotherapy with carboplatin and paclitaxel, and have consented with chemotherapy with carboplatin and paclitaxel, before the start of the informed consent procedure for the study.
7) Performance status (WHO scale/ECOG) <= 1.
8) Written informed consent according to local guidelines.
9) Written approval by the treating physician / investigator of his/her clinical judgment that the patient has a reasonable life expectancy and is sufficiently fit and motivated to complete the study treatment and comply to all study procedures specified by the protocol.

Exclusion criteria

1) Prior treatment with anti-HPV agents.
2) Chronic systemic steroid use. Local application (i.e. stable doses of topical or inhaled corticosteroids) is allowed.
3) Less than 4 weeks since the last treatment with other cancer therapies less than 8 weeks for cranial radiotherapy, and less than 6 weeks for nitrosoureas and mitomycin C.
4) Toxicities resulting from previous anti-cancer therapy
5) Recent treatment (within 30 days of first study treatment) with another investigational drug.
6) Patients with known hypersensitivity to any component of the Investigational Medicinal Product (e.g. ISA101/ISA101b,, Montanide, dimethylsulfoxide pegylated, cremophor also known as Macrogolglycerol Ricinoleate, or IFNα for those subjects assigned to pegylated IFNα cohorts).
7) Any contraindication to the use of authorized applied products (i.e. paclitaxel, carboplatin or bevacizumab).
8) Inadequate bone marrow function
9) Inadequate liver function
10) Clinical suspicion or radiological evidence of brain or leptomeningeal metastases.
11) Previous or current malignancies at other sites
12) Active HIV, chronic hepatitis B or C infection.
13) Patients of childbearing potential (defined as < 2 years after last menstruation and having an intact reproductive system), not willing to consistently and correctly use a contraceptive method according to ICH (M3) resulting in low failure rate, i.e. less than 1% per year such as oral contraceptives or use of effective means of contraception.
14) Pregnancy or lactation.
15) Major surgical procedure within 28 days prior to the first study treatment.
16) Uncontrolled sustained hypertension
17) Clinically significant (i.e. active) cardiovascular disease
18) History of severe bronchial asthma and/or severe allergy.
19) Evidence of any other medical conditions (such as psychiatric illness, infectious diseases,

auto-immune diseases) that may interfere with the planned treatment (i.e. the possibility to receive all six cycles of planned chemotherapy including the concomitant vaccinations), affect patient compliance or place the patient at high risk from treatment-related complications

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):	11-09-2013
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bevacizumab
Generic name:	Bevacizumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Carboplatin
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paclitaxel
Generic name:	Paclitaxel
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	PegIntron
Generic name:	Peginterferon alfa-2b
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	04-07-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-02-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	01-07-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-08-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-02-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	11-02-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-07-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	11-08-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-11-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-11-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-07-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-09-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	23-01-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-02-2017
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	EUCTR2013-001804-12-NL
ClinicalTrials.gov	NCT02128126
CCMO	NL44981.000.13

Study results

Results posted: 28-08-2019

First publication
09-08-2019