'DURVIT': Single low-dose DURValumab IntraTumorally injected in cervical cancer: safety, toxicity and effect on the primary tumour- and lymph node microenvironment.

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

Summary

ID

NL-OMON50047

Source
ToetsingOnline

Brief title
DURVIT

Condition

- Reproductive neoplasms female malignant and unspecified
- Cervix disorders (excl infections and inflammations)

Synonym
cervix cancer, uterine cervical cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Astra Zeneca

Intervention

Keyword: Checkpoint inhibitor, Immunotherapy, Intratumoral delivery, Uterine Cervical Neoplasms

Outcome measures

Primary outcome

This is a phase-I study and therefore we have the following primary objective:

to study clinical safety and tolerability a of locally administered single

dose of durvalumab in cervical cancer patients scheduled to undergo

lymphadenectomy or lymph node debulking in the context of radical hysterectomy

or chemo radiation. This method of administration has not been tested before in

cervical cancer patients. We expect the occurrence and severity of AEs to be

much lower as compared to intravenous administration of durvalumab. Safety will

be evaluated through the analysis of Adverse Events (AE), laboratory tests,

physical examination, vital signs and performance status. The Common

Terminology Criteria for Adverse Events (CTCAE) v4.03 will be used for the

assessment of adverse events. The primary goal of the study is to determine the

maximum tolerated dose (MTD) of local injection of durvalumab in cervical

cancer patients.

Secondary outcome

The secondary objective is to study the immunological effects of locally

administered durvalumab on the microenvironment of the primary tumour and the

draining lymph nodes as well as on the systemic antitumor immune response. As

previously stated, we have already studied the immune status of cervical tumours and their draining lymph nodes and will now study the effect of durvalumab and ascertain its possible ability to affect PD-L1 expression in macrophages and Treg rates.

Study description

Background summary

Cervical cancer is the fourth most common cancer in women worldwide and is caused by a high-risk human papilloma virus (HPV) types persistent infection. In the Netherlands, the highest cervical cancer incidence lies between 35 and 45 years. The most important prognostic factor in early-stage cervical cancer is the presence of metastatic tumor cells in the pelvic lymph nodes. After radical hysterectomy and pelvic lymphadenectomy, women with negative lymph nodes, staged as FIGO IB or IIA, have a 5-year survival rate of around 80-85%, compared to 40-75% for patients with lymph node metastasis. Additional treatments are urgently needed to improve the prognosis of these patients. In order to achieve this, novel immunotherapeutic strategies are pursued. A highly promising area of research focuses on lifting of tumor-induced immune suppression. One of the major recent breakthroughs in (clinical) oncology has been the unraveling and harnessing of the PD-1/PD-L1 checkpoint pathway for different types of cancer. However, the current systemic treatment with PD-1 and PD-L1 inhibitors often causes autoimmune-related inflammatory side-effects. As cervical cancer does not readily metastasize to distant organs but initially to regional lymph nodes we believe that local, intratumoral administration of durvalumab (PD-L1 checkpoint inhibitor) at an early stage (as tested in the DURVIT trial) will deliver these antibodies exactly where they are needed and most effective, i.e. the primary tumor and the tumor-draining lymph nodes (TDLN). Consequently, metastatic spread will be halted at an early stage, resulting in a major clinical benefit for these patients, while significantly reducing the undesirable systemic side-effects. Most promisingly, we recently demonstrated in patients with melanoma that such local immune modulation can also lead to boosting of systemic immunity and profoundly increased 10-year recurrence-free survival rates(Koster et al., submitted). This proposal will demonstrate the biological efficacy of local PD-L1 blockade in early-stage cervical cancer and will yield informative and possibly early predictive signatures that may prove useful in patient selection and the rational design of follow-up clinical trials. The ability to stop cancer in its tracks at an early stage by local treatment resulting in loco-regional and systemic tumor control (with minimal side effects), will have

a major impact on patient survival and quality of life. Moreover, it could save society the towering costs associated with systemic treatments in more advanced stages of the
disease.

Study objective

In the proposed project, we will conduct a clinical phase I trial with cervical cancer patients, scheduled to undergo radical hysterectomy and pelvic lymphadenectomy, to assess the safety and toxicity as primary endpoints and, as an explorative outcome, immunological effects of local administration of durvalumab on the primary tumour- and lymph node microenvironment. Obtained results may open new ways for pre-operative localized treatment of cervical cancer with minimal risk of unwanted side effects. The accompanying immune monitoring program will not only deepen our knowledge of mechanisms underlying clinical efficacy but may also advance patient stratification, which could aid personalized treatment.
The ability to stop cancer in its tracks at an early stage by local treatment resulting in loco-regional and systemic tumor control (with minimal side effects), will have a major impact on patient survival and quality of life. Moreover, it could save society the towering costs associated with systemic treatments in more advanced stages of the disease.

Study design

This is a non-randomized, single-arm, open-label, phase I study. Patients with cervical cancer who are scheduled for radical hysterectomy with lymph node dissection will be enrolled at the AMC/NKI-AVL (NB: study medication will only be administered at the AMC). Two weeks before the scheduled surgical treatment of the patients, durvalumab will be injected locally into the cervix. Three doses of durvalumab will be tested in a 3+3 dose escalation design: 5, 10 and 20 mg. The Common Terminology Criteria for Adverse Events (CTCAE) v4.3 will be used for the assessment of adverse events. If no DLTs or treatment related SAEs are observed in the 3 different dose cohorts (5, 10, 20 mg) and no clear (systemic) immunological responses are detected, an extra dose cohort of 3 patients treated with 50 mg durvalumab i.t. will be added. The injection procedure is identical to the i.t. injections already performed in a standardized fashion for the sentinel lymph node procedure in various centers. Blood samples will be taken once during the screening period, at day 0 (prior to durvalumab administration, i.e. baseline), at day +14 (at the time of surgery), after 4 weeks, and at 3 months after administration of durvalumab. During surgery, patent blue will be injected intratumorally (in the same manner as the durvalumab injection), for identification of the sentinel lymph nodes. Post-surgery biopsies of the removed tumour and draining lymph node samples as well as pre- and posttreatment peripheral blood samples will be collected for immunomonitoring.

The proposed correlative immunoassays will shed light on mechanisms underlying the biological effects of PD-L1 blockade and may demonstrate its biological efficacy, they will aid in the selection of optimal dose and target population for subsequent studies, and facilitate a rational approach to the design of subsequent Phase II trials of this novel immunotherapy.
Since this is a phase I clinical trial, a Data Safety Monitoring Board (DSMB) does not have to be established.

Intervention

Two weeks before the scheduled surgical treatment of the patients, durvalumab will be injected intratumorally. Three escalating dose levels will be tested, i.e. 5, 10 and 20 mg (three patients per dose level, with an additional three at the highest tolerated dose). Possibly, an extra dose cohort with 50 mg durvalumab will be added. The injection procedure is identical to the injections already performed in a standardized fashion for sentinel lymph node detection.

Study burden and risks

Since the patients present with early stage of cervical cancer, we do not expect or allow any treatment related SAEs exceeding grade 3. In accordance with this assumption, in the study CD-ON-durvalumab-1108 no treatment-related * Grade 3 AEs, and no DLTs have been reported in the dose escalation cohorts of <10 mg/kg.
Immune-related AEs (irAEs) that have been observed with (higher doses of) intravenously administered durvalumab include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis and nephritis. Other inflammatory responses with potential immune-mediated etiology reported with durvalumab and similar immune checkpoint inhibitors include, but are not limited to, myocarditis, pericarditis, and uveitis. These events are manageable by available/established treatment guidelines as described in the study protocol.
In addition to the AEs described in the IB, which only account for AEs with intravenous administration, we anticipate that the risks of local administration of durvalumab may include:
* local inflammation reaction of the vagina, vulva and/or cervix with one or more of the following symptoms:
o change in the volume, consistency, colour, or odour of vaginal fluor
o vulvar or vaginal irritation or burning sensation
o pruritis
o dysuria
o genital edema
* hemorrhage or fistula due to tumour or tissue necrosis/degeneration

Since this is a phase I study, no benefits for the patients are expected.

Still, our experimental therapy could lead to an increased activation of the immune system against the tumour and this might even lead to a higher chance of disease free survival.
Patients will be asked to come to the hospital for follow-up. These visits will entail blood drawings and clinical examinations. Besides, the patient has to undergo an extra gynaecological examination for the injection of the durvalumab.

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 at time of study entry
* Willing and able to undergo the planned study procedures
* World Health Organisation (WHO) performance status of 0 or 1

* Written informed consent
* Histologically confirmed cervical cancer of all histological types
* Scheduled to undergo radical hysterectomy and lymphadenectomy
* No indication of an active infectious disease: HIV, HCV and HBV negative
* No history of autoimmune disease or systematic underlying disease which might affect immunocompetence
* Adequate bone marrow function
* Subjects must either be of non-reproductive potential or must have a negative urine pregnancy test upon study entry
* Ability of subject to understand Dutch language

Exclusion criteria

* Prior treatment with immunotherapy, including therapeutic vaccines
* Involvement in the planning and/or conduct of the study
* Participation in a study with another investigational drug within 30 days prior to enrolment in this study
* Major surgery within 28 days before inclusion (conization or biopsy is not major surgery)
* Severe cardiac, respiratory, or metabolic disease
* Use of oral anticoagulant drugs (except ascal)
* Severe infections requiring antibiotics
* Lactation or pregnancy
* Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid
* Any prior Grade *3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
* Active or prior documented autoimmune disease within the past 2 years
* Active or prior documented inflammatory bowel disease
* History of primary immunodeficiency/allogeneic organ transplant/previous clinical diagnosis of tuberculosis/ uncontrolled intercurrent illness
* Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab
* Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results

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):	30-11-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Durvalumab
Generic name:	Durvalumab

Ethics review

Approved WMO

Date:	25-04-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	06-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	30-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	20-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO

Date:	01-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 29031
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
Other	6119
EudraCT	EUCTR2016-004243-36-NL
CCMO	NL59122.018.17
OMON	NL-OMON29031