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

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON29031

Source
Nationaal Trial Register

Brief title
DURVIT

Health condition

Cervical cancer. Cervix carcinoma. PD-L1 checkpoint inhibition. Checkpoint inhibitor. Immunotherapy. Intratumoral. Human Papillomavirus.
Cervixcarcinoom. Baarmoederhalskanker. Durvalumab. Immuuntherapie. Intratumoraal. Humaan Papilloma Virus.

Sponsors and support

Primary sponsor: Academic Medical Center (AMC)
Source(s) of monetary or material Support: Stichting VUmc-CCA, Astra Zeneca

Intervention

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 (radical) hysterectomy with lymph node dissection. 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

To study the effects of locally administered durvalumab on the microenvironment and immune status of the primary tumour and the draining lymph nodes as well as on systemic immunity in these patients by:

• characterizing the primary tumour and lymph node microenvironment in pre- and post-treatment biopsies by seven colour fluorescent immunohistochemistry.

• analyzing viable tumour- and lymph node material (single-cell suspensions) as well as peripheral blood by 8-10 multi-colour FACS panels before and after durvalumab treatment.

• Assessment of frequencies of HPV-specific T cells (HPV-16 E6/E7) by IFNγ elispot assay using an established in vitro stimulation culture protocol or by MHC-I multimer staining.

• Monitoring functional Th1/2/17 activity by ex vivo polyclonal stimulation.

Study description

Background summary

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.
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. 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 Common Terminology Criteria for Adverse Events (CTCAE) v4.3 will be used for the assessment of adverse events. 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.

Study objective

The current systemic treatment with PD-1 and PD-L1 inhibitors can cause autoimmune side effects. As cervical cancer does not readily metastasize to distant organs but initially to regional lymph nodes we believe that local administration of PD-1/PD-L1 checkpoint inhibitors at an early stage will deliver these antibodies exactly where they are needed resulting in a major clinical benefit for these patients while reducing undesirable systemic side effect: this is the central hypothesis of our study. Additional interest in local administration of checkpoint inhibitors is raised by the fact that the locally administered doses are expected to be much lower, leading to a critical and highly desirable decline in the expenses involved, which threaten to cripple the health care system.

For this Phase-I study, we hypothesize that it is safe to locally administer durvalumab in patients with cervical cancer, scheduled to undergo surgery ((radical) hysterectomy with lymphadenectomy). The primary endpoint of this study is safety on the basis of assessment of AEs and serious AEs. This will be measured according to the standard procedures. Common Terminology Criteria for Adverse Events (CTCAE) v4.03 will be used for this.

Study design

Day -60 day 0: screening procedures.

Day 0: administration durvalumab

Day 14 (+- 3 days): (radical) hysterectomy with lymph node dissection

week 4 (+- 3 days): follow-up

month 3 (+- 1 week): follow-up

The Common Terminology Criteria for Adverse Events (CTCAE) v4.03 will be used for the assessment of adverse events at timepoints: day 0 (injection durvalumab), day 14 (surgery), week 4 and month 3. Also, blood samples will be taken on these time points.

Intervention

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. 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: 5, 10 and 20 mg (three patients per dose level, with an additional three at the highest tolerated dose). 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. The Common Terminology Criteria for Adverse Events (CTCAE) v4.3 will be used for the assessment of adverse events. 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.

Contacts

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Eligibility criteria

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 al histological types

• Scheduled to undergo (radical) hysterectomy with lymph node dissection

• 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
Intervention model:	Other
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-11-2017
Enrollment:	24
Type:	Actual

IPD sharing statement

Plan to share IPD: Undecided

Ethics review

Positive opinion

Date:	01-11-2016
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 50047
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL5938
NTR-old	NTR6119
CCMO	NL59122.018.17
OMON	NL-OMON50047

Study results