Neo-adjuvant Pembrolizumab in vulvar squamous cell carcinoma: a clinical proof-of-concept study.

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This study has been transitioned to CTIS with ID 2024-512862-32-00 check the CTIS register for the current data. The primary objectives of this trial are to study clinical efficacy and immune activation of neoadjuvant PD-1 blockade in VSCC.

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

Summary

ID

NL-OMON53949

Source
ToetsingOnline

Brief title
APOLLO study

Condition

- Skin neoplasms malignant and unspecified
- Obstetric and gynaecological therapeutic procedures

Synonym
vulvar carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Oncode Institute,Merck Sharp & Dohme

(MSD)

Intervention

Keyword: anti-PD1, Immunotherapy, Pembrolizumab, vulvar squamous cell carcinoma

Outcome measures

Primary outcome

1. To study the clinical efficacy of neoadjuvant PD-1 blockade in VSCC, as measured by an objective change in tumor size (according to RECIST 1.1) and documented by calipers using standardized digital photography with reference ruler) at the time of surgery (approximately 6 weeks after first administration Pembrolizumab).

2. To study the activation, proliferation and migration of CD4+CD39+PD-1+ effector T cell population upon PD-1 blockade.

Secondary outcome

1. To study pathological complete responses (pCR) at time of surgery

2. To study feasibility(defined as delay in planned surgery and surgical outcome), safety according to NCI-CTC version 5.0

3. To study the activation, proliferation and migration of the CD8+CD103+CD39+PD-1+ intratumoral T-cell population upon PD-1 blockade.

Study description

Background summary

Vulvar squamous cell carcinoma (VSCC) is a rare cancer with a rising incidence. Standard treatment comprises wide local excision of the primary tumour and inguinal lymph nodes and sometimes (chemo) radiotherapy. Treatment is associated with impressive and long-lasting morbidity, sexual and psychological

dysfunction and wound healing disorders. Recurrent disease develops in up to 40% of all treated patients. The unmet need, therefore, is a less radical and more effective treatment for VSCC. Based on the local immune profile in a large fraction of patients with primary VSCC we hypothesize that neoadjuvant PD-1 checkpoint inhibition may reinvigorate tumor-specific T cells resulting in a reduced tumor load, potentially leading to less radical surgery and reduces the recurrence rate.

Study objective

This study has been transitioned to CTIS with ID 2024-512862-32-00 check the CTIS register for the current data.

The primary objectives of this trial are to study clinical efficacy and immune activation of neoadjuvant PD-1 blockade in VSCC.

Study design

This is a prospective, multicenter phase II non-controlled clinical trial in 40 VSCC patients.

Intervention

Anti-PD1 antibody pembrolizumab, 200 mg IV Q3W for a total of 2 administrations per patient over a period of 6 weeks prior to surgery.

Extension phase: Responders have the option to participate in an extension cohort with adjuvant pembrolizumab (400 mg IV, Q6W, 7 times) from week 16 to week 58, to monitor long-term (safety/immune monitoring) effects.
Non-responders and responders who do not receive extended pembrolizumab will visit the hospital at weeks 13 and 16 to monitor potential long-term effects of pembrolizumab, including blood draws for safety values and for oncology follow-up in accordance with standard of care guidelines

Study burden and risks

The extra burden for the patient consists of one extra examination and biopsy at the start of study, a pregnancy test, standardized tumor measurement by caliper (clinical exam), and 6 time points in which blood samples are collected. Moreover, patients will be asked to fill out a quality of life questionnaires at baseline, and at week 13, and for objective clinical responders continuing treatment in week 61.
Furthermore, standard of care treatment is delayed for at least 4 weeks. The use of pembrolizumab requires 2 extra visits to the clinic and is associated with possible side effects as reported in the registered use of Keytruda® (pembrolizumab) for the treatment of patients across a number of indications

(https://www.ema.europa.eu/en/medicines/human/EPAR/keytruda; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125514s096lbl.pdf). See the Investigator brochure (IB) for more details on specific indications.
The most common adverse reactions are fatigue (24%), rash (19%), itchiness (pruritus) (17%), diarrhea (12%), nausea (11%) and joint pain (arthralgia) (10%). Other adverse effects occurring in between 1% and 10% of patients include anemia, decreased appetite, headache, dizziness, distortion of the sense of taste, dry eye, high blood pressure, abdominal pain, constipation, dry mouth, severe skin reactions, vitiligo, various kinds of acne, dry skin, eczema, muscle pain, pain in a limb, arthritis, weakness, edema, fever, chills, myasthenia gravis, and flu-like symptoms. This may theoretically result in postponement of surgery for 1-3 weeks. We expect that after management using corticosteroids surgical treatment can still be successfully achieved in these patients. Based on current guidelines, postponing surgery for this time-period will not negatively affect prognosis.
Neoadjuvant use of one infusion of pembrolizumab in HPV-unrelated resectable head and neck cancer and stage III/IV resectable melanoma suggest that treatment associated grade 1-2 AEs and an occasional grade 3 AE are to be expected during neoadjuvant treatment. Importantly, in both studies no unexpected delays in surgery or unexpected surgical complications were found, while about 40% of the patients showed a pathological response or a complete/major pathological response. Similar observations were made with 2 infusions of neoadjuvant anti-PD1 antibody nivolumab in stage I-IIIa resectable lung cancer.
Based on the response rate to ICB in the abovementioned clinical trials women included in this trial can potentially benefit from ICB prior to standards-of-care therapy. The potential benefit of study participation is that neo-adjuvant treatment with pembrolizumab might result in a complete or partial decrease of tumor size. In addition, the risk of recurrence may be reduced in these responders.
Participation of responders in the extension phase is optional. Participation in the extension phase may increase the risk of side effects and may reduce the risk of disease recurrence.
All patients contribute to our knowledge and understanding how to further develop new strategies for anti-cancer therapies. In our opinion, the benefits outweighs the risks of the study. *

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. Signed written informed consent prior to performance of study- specific procedures or
assessments, and must be willing to comply with treatment and follow- up assessments.
2. Age >= 18 years old at the day of signing informed consent
3. Histologically confirmed primary vulvar squamous cell carcinoma, with all of the following characteristics:
- At least 1 lesion that can be measured in at least 1 dimension with >= 10 mm in largest diameter.
- Clinically stage FIGO I-III.
- Documentation confirming the absence of distant metastasis (M0) as determined by institutional practice. Routine exams to discard metastases will be performed according to Investigator judgement but are mandatory in case of suspicion of metastatic disease.
- Vulvar cancer eligible for primary surgery
- In the case of a multifocal tumor (defined as the presence of two or more foci of cancer on the vulva), the largest lesion must be >= 10 mm and all lesions >= 10 mm are designated as "target" lesion(s) for all subsequent tumor evaluations and biopsies.

Exclusion criteria

1. Locally advanced tumor not amenable to surgical therapy.
2. A woman of child bearing potential who has a positive urine pregnancy test within 72 hours prior to allocation. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
3. Prior therapy with an anti-PD-1, anti-PD-L1, or anti PD L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (eg, CTLA-4, OX 40, CD37)
4. Prior systemic anti-cancer therapy including investigational agents within 4 weeks [prior to allocation.
Note: Participants must have recovered from all AEs due to previous therapies to <=Grade 1 or baseline. Participants with <=Grade 2 neuropathy may be eligible.
Note: If participant received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting study treatment.
5. Prior radiotherapy within 2 weeks of start of study treatment. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis.
6. Major surgery within 2 weeks of starting study treatment and patients must have recovered from any effects of any major surgery.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-02-2024
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Keytruda
Generic name:	Pembrolizumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	27-02-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	11-04-2023
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
EU-CTR	CTIS2024-512862-32-00
EudraCT	EUCTR2022-002500-21-NL
CCMO	NL82378.058.22