Cemiplimab treatment in patients with locally advanced and metastatic secondary angiosarcomas

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Primary objective: 1) To evaluate the overall response rate (ORR) after 24 weeks of cemiplimab in secondary angiosarcomas, according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 or daylight photography as per WHO Offset Publication...

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

Summary

ID

NL-OMON55079

Source
ToetsingOnline

Brief title
Cemiplimab for secondary angiosarcomas

Condition

- Soft tissue neoplasms malignant and unspecified

Synonym
Secondary angiosarcomas, soft tissue sarcoma

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Genzyme Europe B.V. ,Sanofi-aventis

Intervention

Keyword: Cemiplimab, Immunotherapy, PD-L1, Secondary Angiosarcomas

Outcome measures

Primary outcome

Primary objective:

1) To evaluate the overall response rate (ORR) after 24 weeks of cemiplimab in secondary angiosarcomas, according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 or daylight photography as per WHO Offset Publication No. 48.

Secondary outcome

Secondary objectives:

1) To establish the best ORR of patients with secondary angiosarcomas receiving cemiplimab.

2) To establish the median time to response (TTR) and duration of response (DOR) in patients with secondary angiosarcomas receiving cemiplimab.

3) To assess the median progression-free survival (PFS) of patients with secondary angiosarcomas receiving cemiplimab.

4) To establish the overall survival (OS) of patients with secondary angiosarcomas receiving cemiplimab.

5) To investigate possible relations between response to cemiplimab and tumour characteristics (i.e. PD-L1 expression, tumour infiltrating lymphocytes, MYC status and tumour mutational burden).

6) To assess differences in response to cemiplimab between UV associated and radiation induced secondary angiosarcomas.

7) To assess effects of cemiplimab on tumour tissue by comparing pre- and

post-treatment biopsies.

8) To quantify toxicity during cemiplimab treatment.

Study description

Background summary

Angiosarcomas are aggressive mesenchymal tumours arising from cells with endothelial properties and belong to the group of soft tissue sarcomas (STS). Angiosarcomas are rare with an incidence of only 0.1-0.2/100.000/year. Prognosis is poor with a 5-years specific survival of 30-40% for all stages. In selected trial patients with metastatic disease the range in median overall survival was between 5.5-19.5 months. In our real life series, the median overall survival of 203 primary metastatic angiosarcoma patients diagnosed between 1989-2014, was only 5 months. For metastatic disease, only chemotherapy (mostly doxorubicin or paclitaxel) and one targeted drug (pazopanib) is available. There is need for more treatment options, and for a more effective treatment.
Angiosarcomas encompass de novo (primary) angiosarcomas and secondary angiosarcomas, which frequently are located in the skin and arise due to DNA damaging noxes, like radiotherapy or UV radiation. The clinical behaviour, genetic and molecular background and clinical outcomes of secondary angiosarcomas differ from primary angiosarcomas and have similarities to cutaneous squamous-cell carcinoma cSCC.
Cemiplimab showed impressive results in advanced cSCC. At the ASCO Annual Meeting 2019, updates were presented of a phase II study. With a median follow up of 9.3 months, 10 complete and 24 partial responses were observed in 78 patients with locally advanced disease (ORR 44%). Median time to response was 1.9 months and the median duration of response was not yet reached. For metastatic disease, 10 complete responses and 19 partial responses were observed in 59 patients (ORR 49%), which was prolonged (> 12 months) in 22 patients and again with a median time to response of 1.9 months. With a median follow up of 16.5 months, median progression free survival (PFS) was 18.4 months and median overall survival (OS) was not yet reached (ASCO abstract 9526).
At the ASCO Annual Meeting 2020 the latest updates were presented after a longer follow up of a phase II study. Of the 193 patients treated with cemiplimab for locally advanced or metastatic cSCC with a median follow up of 15.7 months, ORR was 46.1%. Median DOR was not yet reached. In responding patients, the estimated proportion of patients with ongoing response at 24 months was 69.4%. In 31 patients (16.1%) a complete response was reported with

a median time to complete response of 11.2 months. Partial response was reported in 58 patients (30.1%). Median OS was not yet reached, estimated median PFS was 18.4 months. (ASCO abstract 367) Cutaneous SCC are UV light associated cancers with subsequently a high mutational load, which explains this excellent efficacy.
There are anecdotical reports of responses to checkpoint inhibitors in UV associated secondary angiosarcomas. Moreover, there are several reasons to expect increased susceptibility of secondary angiosarcomas to immune checkpoint inhibitors. Secondary angiosarcomas have an increased mutational load, which in itself make them potentially more sensitive to immunotherapy. As in cSCC, secondary angiosarcomas have high MYC expression, which is of interest given the dependency of PD-L1 expression on MYC.
In our preliminary work (29 UV and 27 radiotherapy associated angiosarcomas), 28 (50%) were PD-L1+ (>10%) of which 11 strongly positive (>50%). In 19 samples PD-1 was also positive. Furthermore, we found 12/56 (21%) MLH1-. 14/56 (25%) MSH2-, 9/56 (16%) MSH6-, 11/56 (20%) PMS2- and 4/56 (7%) cases negative for all four markers.
Since the similarities between cSCC and secondary angiosarcomas and the need for more available and effective treatment options and we here propose a study with cemiplimab in secondary angiosarcomas.

Study objective

Primary objective:
1) To evaluate the overall response rate (ORR) after 24 weeks of cemiplimab in secondary angiosarcomas, according to Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 or daylight photography as per WHO Offset Publication No. 48.

Secondary objectives:
1) To establish the clinical benefit of patients with secondary angiosarcomas receiving cemiplimab. Clinical benefit is defined as the combined number of patients with a complete or partial response and stable disease.
2) To establish the median time to response (TTR) and duration of response (DOR) in patients with secondary angiosarcomas receiving cemiplimab.
3) To assess the median progression-free survival (PFS) of patients with secondary angiosarcomas receiving cemiplimab.
4) To establish the overall survival (OS) of patients with secondary angiosarcomas receiving cemiplimab.
5) To investigate possible relations between response to cemiplimab and tumour characteristics (i.e. PD-L1 expression, tumour infiltrating lymphocytes, MYC status and tumour mutational burden).
6) To assess differences in response to cemiplimab between UV associated and radiation induced secondary angiosarcomas.
7) To assess effects of cemiplimab on tumour tissue by comparing pre- and post-treatment biopsies.

8) To quantify toxicity during cemiplimab treatment.

Study design

This single arm phase II study will be conducted at the Radboudumc and a maximum of 3 other tertiary sarcoma centres. Patients with locally advanced or metastatic angiosarcomas, in the first line of treatment unfit for chemotherapy and patients in advanced lines of treatment can be included. All participating patients will be treated with cemiplimab every three weeks. In total, 18 patients will be included in this study. After the first 13 patients are included, a interim analysis will be conducted. If there are 1 or fewer responses in these 13 patients, the study will be stopped due to ineffectivity. Otherwise, 5 additional patients will be accrued for a total of 18 patients. The expected time to include 18 patients is two years. During treatment, patients will be frequently evaluated (as is also the case in regular treatment), and side effects and treatment effect will be monitored. Patients can continue the treatment as long as it effective in treating the disease, with a maximum of 2 years as is common practice in patients treated with immunotherapy. The maximum treatment duration is not a limiting factor of this study, but common practice in treating patients with immunotherapy. Treatment will be stopped preliminary in case of unacceptable toxicity or ift the patients decides to stop participation in the study. In case of disease progression, treatment will also be stopped.

Intervention

In this study we want to evaluate the effect cemiplimab, a known drug registered for another type of cancer, in patients with locally advanced or metastatic secondary angiosarcomas. Patients in the first line of treatment unfit for chemotherapy and patients in advanced lines of treatment will be included. Treatment will continue until disease progression, unacceptable toxicity or until withdraw of informed consent.

Patients will be treated with cemiplimab 350mg every three weeks, the registered dose and time intervall for patients with cutaneous squamous cell carcinoma.

Study burden and risks

Adverse events of cemiplimab may occur. Cemiplimab is registered as a treatment for cutaneous squamous cell carcinomas, and dosing and toxicity have been evaluated in phase I-II studies for this indication. In our study we will treat patients with the registered dose of cemiplimab. Follow up of the study during therapy will include laboratory research, regular visits to the outpatient clinic and evaluation using CT- or MRI-scan (if not possible, daylight photography will be used). Additional research blood samples will be taken

during regular visits to the outpatient clinic, together with standard safety lab. A tumour biopsy will be taken at baseline and after 12 weeks of treatment. Due to the etiology of secondary angiosarcomas, this will usually be a minimally invasive dermatological biopsy. Per biopsy, two tissue samples will be collected. The risk is considered low. A tumour biopsy will be taken at end of treatment if a patient specifically signed informed consent for this.
Follow-up after the end treatment (maximum 2 years as is common practice in treating patients with immumotherapy), in case of disease progression or discontinuation due to toxicity or after withdrawal of consent or other reason will be every 12 weeks (to check for Adverse Events and survival). Additional blood will be drawn for translational research purposes, Blood collection will be done during regular treatment visits so no additional venapunctures are required. Microbiome research requires that patients provide feces for translational research purposes. This will be asked four times during the treatment. It will be accompanied with by a questionaire asking about recent medication use, diet and stool consistency. No lifestile interventions ore other personal questons are part of this research. At several timepoints, patients will be asked to fill out a questionnaire about the quality of life. This is the QLQ-C30 validated questionnaire of the EORTC.

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. Adult patient aged >= 18 years.
2. Signed written informed consent.
3. Histologically confirmed diagnosis of progressive unresectable locally advanced or metastatic secondary angiosarcoma.
4. Patients in the first line of systemic treatment unfit for chemotherapy and patients in advanced lines of systemic treatment
5. Measurable disease per RECIST 1.1 or per physical examination / daylight photography (WHO Offset Publication No. 48) as determined by the investigator.
6. Tumour tissue material available (archival or recent tumour biopsy).
7. WHO ECOG 0-2.
8. Hepatic function:
a. Total bilirubin <= 1.5 x ULN (if liver metastases: <= 3 x ULN).
b. Transaminases <= 3 x ULN (if liver metastases: <= 5 x ULN).
c. Patients with Gilbert*s Disease and total bilirubin up to 3x ULN may be eligible after communication with and approval from the medical monitor
d. Alkaline phosphatase <= 2.5 x ULN (if liver OR bone metastases <=5 x ULN).
9. Renal function: serum creatinine <= 2 x ULN or estimated CrCl > 30 mL/min.
10. Creatine phosphokinase (CPK) (also known as CK [creatine kinase]) elevation <= grade 2
11. Bone marrow function:
a. Hemoglobulin >= 9.0 g/dL.
b. ANC >= 1.5 x 109/L.
c. Platelet count >= 75 x 109/L.
12. Expected life expectancy of at least 3 months as judged by the investigator.

Exclusion criteria

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for irAEs. The following are not exclusionary: vitiligo, childhood asthma that has resolved, type 1 Diabetes mellitus, residual hypothyroidism that required only hormone therapy, or psoriasis that does not require systematic treatment.
2. Prior treatment with immune checkpoint inhibitors.

3. Continuous immunosuppressive corticosteroid treatment (doses > 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab. Note: patients who require a brief course of steroids (e.g. as prophylaxis for imaging studies) are not excluded.
4. Active uncontrolled infection requiring therapy, including infection with HIV, active infection with HBV or HCV.
5. History of pneumonitis within the last 5 years.
6. Untreated brain metastasis(es) that may be considered active.
a. Note in clarification: Patients with previously treated brain metastases may participate provided that the lesion(s) is (are) stable (without evidence of progression for at least 6 weeks on imaging obtained in the screening period), and there is no evidence of new or enlarging brain metastases, and the patients do not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 28 days of the first dose of cemiplimab.
7. Patients with allergy or hypersensitivity to cemiplimab or to any of the excipients must be excluded. Specifically, because of the presence of trace components in cemiplimab, patients with allergy or hypersensitivity to doxycycline or tetracycline are excluded.
8. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments
9. Patients with a history of solid organ transplant (patients with prior corneal transplants may be allowed to enroll after discussion with and approval from the medical monitor).
10. Any anticancer treatment other than radiation therapy (chemotherapy, targeted systemic therapy, imiquimod, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of cemiplimab or planned to occur during the study period
11. Receipt of live vaccines (including attenuated) within 30 days of first study treatment
12. Prior use of PI3K-D inhibitors
13. Women of childbearing potential (WOCBP)*, or sexually active men, who are unwilling to practice highly effective contraception prior to the initial dose/start of the first treatment prior to the start of the first treatment, during the study, and for at least 6 months after the last dose.
14. Breastfeeding
15. Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary, upon communication with and approval from the medical monitor)
16. Any other condition that might interfere with experimental treatment and the study procedures as judged by the investigator.

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):	02-03-2022
Enrollment:	18
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Libtayo
Generic name:	cemiplimab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	05-10-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-11-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2020-005465-13-NL
ClinicalTrials.gov	NCT04873375
CCMO	NL74804.091.21