A phase 1/2 trial of EO2401, a novel microbial-derived peptide therapeutic vaccine, in combination with PD-1 check point blockade, for treatment of patients with locally advanced or metastatic adrenocortical carcinoma, or malignant pheochromocytoma/paraganglioma

Published: 08-01-2020
Last updated: 16-11-2024

The objective of this trial is to evaluate safety and tolerability of an experimental drug, EO2401, in combination with another immunological treatment, nivolumab, in patients with advanced or metastatic ACC and progressive MPP.

Ethical review	Approved WMO
Status	Completed
Health condition type	Adrenal gland disorders
Study type	Interventional

Summary

ID

NL-OMON52906

Source
ToetsingOnline

Brief title
EOADR1-19

Condition

- Adrenal gland disorders

Synonym
adrenal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Enterome
Source(s) of monetary or material Support: Enterome

Intervention

Keyword: Adrenocortical Carcinoma, Paraganglioma, Pheochromocytoma, Vaccine

Outcome measures

Primary outcome

The primary objective of the phase 1 of this trial is to evaluate safety and tolerability of EO2401 in combination with nivolumab in patients with unresectable, previously treated, and previously untreated, locally advanced or metastatic ACC, and progressive MPP.

The primary objective of the phase 2 part of this trial is to determine the effect of EO2401/nivolumab on the progression-free survival rate at 6 months, per investigator/local site assessments, for patients treated in the randomized extension of Cohort 2A* (patients treated with EO2401 monotherapy and nivolumab monotherapy, respectively, will constitute internal concurrent controls in the randomized extension).

* Cohort 2A = patients with ACC who had prior systemic therapy for established locally advanced or metastatic disease

Secondary outcome

The key secondary endpoints of the trial are:

• Percentage of patients with shown immunogenicity in relation to EO2316,

EO2317, EO2318, and UCP2 that compose EO2401

The other secondary endpoints of the trial are:

• Objective response rate, time to response and Duration of response as described by RECIST 1.1 and iRECIST criteria.

• Progression-free survival as described by RECIST 1.1 and iRECIST criteria, defined as the time interval from the date of first study treatment administration to the date of progression (by RECIST 1.1 or iRECIST criteria) or death due to any cause, whichever is earlier. Patients without progression or death are to be censored at the time of the last tumor assessment.

• Overall survival defined as the time interval from the date of first study treatment administration to the date of death due to any cause. Patients alive will be censored at the date of the last documented follow-up.

• In addition, in the randomized extension of Cohort 2A safety and tolerability of EO2401/nivolumab assessed versus internal concurrent controls

Study description

Background summary

Two different primary malignancies can arise from the adrenal gland: adrenocortical carcinoma (ACC) from the adrenal cortex and malignant pheochromocytoma from the adrenal medulla.

ACC has an estimated incidence of *0.7-2 new cases per million people per year. The incidence of pheochromocytoma/paraganglioma is *2-8 per million adults per year. Approximately 10% - 15% of pheochromocytomas and paragangliomas are malignant.

The two primary malignancies arising from the adrenal glan, are tumors with quite different characteristics from many biological perspectives. However, from a general treatment perspective they show similarities:

• Surgery is of utmost importance, and the only curative treatment modality, provided radical surgery can be performed.
• Treatment options for patients with unresectable disease are few and new treatment options have not been added recently.
• The currently available first line therapies in both entities are only achieving tumor regression in approximately one in four patients at the cost of a relatively high toxicity burden
• Even though the median survival in patients with MPP (approx. 6-7 years) is longer than for patients with ACC (around 12-15 months), half of the patients with MPP have progressive disease within one year and require active management. Thus, it seems fair to conclude that for both entities there are unmet medical needs with respect to new efficacious systemic therapies.

Novel therapeutic approaches are needed to enhance the treatment outcomes for patients with adrenal malignancies.

Study objective

The objective of this trial is to evaluate safety and tolerability of an experimental drug, EO2401, in combination with another immunological treatment, nivolumab, in patients with advanced or metastatic ACC and progressive MPP.

Study design

This is an open-label, 3-cohort study. The patients will be allocated in one of the 5 cohorts (group) of the study :

• Cohort 1 : will include previously treated patients. The patients will receive a subcutaneous injection of 1 ml of EO2401 every 2 weeks during the priming phase (8 weeks) and every 4 weeks during the boosting phase, in combination with nivolumab at standard dose; patients with ACC and MPP will be included. Three to 12 evaluable patients will be included depending on the safety profile of the administered treatments. The aim of this cohort is to find the adequate dose of EO2401.

• Cohorts 2A (previously treated patients) and 2B (previously untreated patients) includes an evaluation of EO2401 at the recommended dose found in Cohort 1 in combination with nivolumab in 30 evaluable patients (15 each for Cohorts 2A and 2B) with ACC. The patients will receive a subcutaneous injection of 1 ml of EO2401 every 2 weeks during the priming phase (8 weeks) and every 4 weeks during the boosting phase. In addition, through Protocol v3.0, there is a randomized extension of cohort 2A in 3 sub-groups: 43 patients in Cohort 2A-I (EO2401 and nivolumab), 11 patients in Cohort 2A-II (EO2401 monotherapy) and 11 patients in Cohort 2A-III (nivolumab monotherapy).

• Cohorts 3A (previously treated patients) and 3B (previously untreated

patients) includes an evaluation of EO2401 at the recommended dose found in Cohort 1 in combination with nivolumab in 20 evaluable patients (no specific split between Cohorts 3A and 3B) with progressive MPP. The patients will receive a subcutaneous injection of 1 ml of EO2401 every 2 weeks during the priming phase (8 weeks) and every 4 weeks during the boosting phase.

Treatment will continue until either the disease worsens, the patient experiences intolerable study drug effects or the sponsor terminates this study.

Intervention

Cohort 1
Priming Phase
Injection of 1 ml of EO2401 every 2 weeks. EO2401 injections will be given 4 times in total during this phase. An intravenous infusion of nivolumab will be given 3 hours after treatment with EO2401. The dose of nivolumab should be 240 mg every 2 weeks for the first 3 administrations and at the dose of 480 mg on the 4th administration and onwards .

Boosting Phase
Injection of 1 ml of EO2401 every 4 weeks, in combination with an intravenous infusion of nivolumab every 4 weeks at the dosage of 480mg.

Cohorts 2 or Cohorts 3 if the EO2401 is well tolerated in Cohort 1 as follows:
Priming Phase
Injection of 1 ml of EO2401, in combination with an intravenous infusion of nivolumab every 2 weeks. The EO2401 injection in combination with the nivolumab infusion every 2 weeks will be given 4 times in total. The dose of nivolumab should be 240 mg every 2 weeks for the first 3 administrations and at the dose of 480 mg on the 4th administration and onwards.

Boosting Phase
After completing the Priming Phase, 1 subcutaneous injection of EO2401 every 4 weeks, in combination with an intravenous infusion of nivolumab every 4 weeks at the dosage of 480mg.

When EO2401 and nivolumab are administered as monotherapy (Cohorts 2A-II and 2A-III), their respective schedules of administration are the same as in combination treatment.

Study burden and risks

The risks associated with the study and study procedures are :

Blood sample collection: It may be painful when blood is drawn . Some people

get dizzy or faint from a blood draw. The patient could also get an infection, which is rare, or have bleeding, redness, or bruising at the skin puncture.

Central venous catheters (port-a-catheter): In addition to the risks described above for blood sample collection, a port-a-catheter may cause bloodstream infection and embolism.

Nivolumab: Infusion-related reactions may occur, in rare cases with fatal outcome. These infusion-related reactions may include symptoms of allergic reactions, such as tightening of the muscles in the lungs, bronchospasm, skin rash, increase or decrease in blood pressure, loss of consciousness or shock. In rare cases, chest pain or discomfort, heart attack or sudden loss of heart function may happen.

Montanide : the most common side effects related to an injection of montanide are local reactions such as local pain, tenderness, redness and granuloma at the injection site. The intensity is usually mild to moderate . The exact frequency of all these reactions is not known.
Other general reactions are mainly flu-like symptoms such as fatigue, chills, fever and headaches. Lack of energy and nausea were also observed. The intensity was usually mild or moderate. Upon subsequent vaccination using a different limb, some earlier injection sites developed new inflammatory signs, showing that they were reactivated.

EO2401: Side effects related to the administration of EO2401 may be local pain or redness or induration or even ulceration at the injection site.
These local administration site reactions could be observed in up to 54% of patients. These reactions might start a few weeks after administration, could last several weeks or months, and are usually mild to moderate, severe being uncommon.

ECGs: minor skin irritation may occur at the locations where the electrodes are placed.

CT scan: the most common CT scan side effects are:
• Potential allergic reactions to the contrast material if this material is used.
• Potential feeling of being anxious because of the uncertainty of the diagnosis and possibly scared because of the enclosed space.
• Potential increased risk of cancer which is a known medical risk after increased exposure to radiation and scans

Contacts

Public
Enterome

Avenue Ledru-Rollin 94/96
Paris 75011
FR
Scientific
Enterome

Avenue Ledru-Rollin 94/96
Paris 75011
FR

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. For inclusion in Cohort 1 patients should have adrenocortical carcinoma, or malignant pheochromocytoma/paraganglioma, as defined below for Cohorts 2A and 3A.
2. For inclusion in Cohorts 2A and 2B patients should have histologically confirmed (at primary diagnosis) unresectable locally advanced or metastatic (ENSAT/AJCC stage 3 = tumor has spread into nearby tissues or lymph nodes, or stage 4 = metastatic disease) adrenocortical carcinoma.
a. In addition, for inclusion in Cohort 2 A patients should also have received treatment with at least one line, but not more than two prior lines, of systemic therapy for established locally advanced or metastatic disease (i.e. non-adjuvant therapy), and should within these lines of therapy for advanced/metastatic disease, or as neoadjuvant/adjuvant therapy, have received mitotane therapy delivered at an adequate dose
b. In addition, for inclusion in Cohort 2B patients should not have received prior systemic therapy for established locally advanced or metastatic

disease (i.e. non-adjuvant therapy).
Note, for both cohorts 2A and 2B, neoadjuvant/adjuvant therapy (including mitotane with or without chemotherapy) for patients after complete responses to local therapy (e.g. resection) should not be counted in the definitions above for line of therapy for established disease. Patients who have received mitotane as neoadjuvant/adjuvant therapy, or therapy for advanced/metastatic disease can continue mitotane during study therapy provided definitions regarding eligibility of continued mitotane therapy are fulfilled
3. For inclusion in Cohorts 3A and 3B patients should have histologically confirmed (at primary diagnosis) unresectable malignant (defined as metastatic disease, i.e. presence of chromaffin tissue in non-chromaffin organs) pheochromocytoma/paraganglioma, and RECIST defined progression should have been documented during a maximum of an 18-months period.
a. In addition, for inclusion in Cohort 3A patients should also have received treatment with at least two prior lines of systemic therapy if the patients are eligible for radionuclide therapy, and at least one prior line of systemic therapy if the patients are not eligible for radionuclide therapy.
b. In addition, for inclusion in Cohort 3B patients should not have received prior systemic therapy for their malignant pheochromocytoma/paraganglioma.
4. Patients with an age >= 18 years old.
5. Patients who are human leukocyte antigen (HLA)-A2 positive.
6. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status <= 1 with the specific meaning of ECOG 1 being "restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house-work, office work".
7. Patients with a life expectancy > 4 months as judged by their treating physician.
8. Patients with at least one measurable lesion according to RECIST 1.1.
9. Males or non-pregnant, non-lactating, females who are:
a) female, post-menopausal (serum follicle-stimulating hormone (FSH) level > 40 mIU/mL),
b) female and male, surgically sterile (e.g. bilaterally blocked or removed fallopian tubes, vas deferens),
c) female of childbearing potential with a negative highly sensitive serum pregnancy test within 72 hours prior to first administration of study treatment and use of a highly effective contraception from signing the Informed Consent Form (ICF) through 5 months after the last study treatment dose administered; note, the male partner should in addition to the use of highly effective contraception by the female patient also use condoms,
d) male patient with female partners of childbearing potential must use condoms from signing the ICF through 5 months after the last study treatment dose administered; in addition, male patients must ensure that their partners of childbearing potential also use highly effective contraception.
Highly effective contraception include:
i) combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation: oral, intravaginal, transdermal,
ii) progestogen-only hormonal contraception associated with inhibition of

ovulation: oral, injectable, implantable, intrauterine device, and
iii) sexual abstinence when in line with the preferred and usual lifestyle of the patient (e.g. periodic abstinence is not considered a highly effective method).
10. Patients willing and able to comply with the scheduled visits, treatment plan, laboratory tests, and other study procedures indicated in the protocol.
11. Patients having received the information sheet and who have provided written informed consent prior to any study-related procedures. Note, a 2-stage consent procedure is going to be used in the trial; the first minimized consent related to the procedure of HLA-testing, and the second to all other trial details and procedures.

Exclusion criteria

1. Patients treated with dexamethasone > 2 mg/day or equivalent (i.e. 13 mg/day of prednisone, or 53 mg/day of hydrocortisone) within 14 days before the first EO2401 administration, unless required to treat an adverse event. Note, inhaled steroids and adrenal replacement steroid doses > 13 mg daily prednisone equivalents are permitted. Thus, patients needing hydrocortisone replacement therapy due to prior or ongoing mitotane therapy can receive hydrocortisone doses > 53 mg/day, i.e. also in the normally used range of 60-80 mg/day, and still be included in the trial.
2. Patients with prior treatment with compounds targeting PD-1, PD-L1, CTLA-4, or similar compounds where general resistance against therapeutic vaccination approaches might have developed (e.g. defects to the cellular antigen processing/presentation machinery, including mutations in Janus kinas [JAK] 1, JAK2, and β-2-microglobulin [B2M]) allowing tumor cells to avoid recognition and attack by immune cells.
3. Patients with prior exposure to EO2401, e.g. patients treated in Cohorts 2B or 3B of the current trial cannot be re-enrolled for treatment also in Cohorts 2A or 3A.
4. Patients treated with immunotherapy (meaning immunostimulatory or immunosuppressive therapy; beside excluded, or allowed, compounds per other inclusion/exclusion criteria specifications), radionuclide therapy, radiotherapy, cytoreductive therapy, or received treatment with any other investigational agent within 28 days before the first EO2401 administration. Note, for patients with ACC continued treatment with mitotane during this trail is allowed provided patient is eligible (see section 6.9.2). For patients with MPP, concurrent therapy with somatostatin, and somatostatin analogues is allowed provided tumor progression on this therapy has been demonstrated; concurrent therapy with bisphosphonates (e.g. zoledronic acid) or denosumab is also allowed.
5. Patients with an initial diagnosis of ACC less than 9 months from start of screening part 2.
6. Patients with ACC and any individual lesion according to RECIST 1.1 having a

maximum diameter of more than 125 mm; irrespective if the lesion is proposed as a target lesion, or not, according to RECIST 1.1.
7. Patients with ACC with more than three organs involved by disease, combined with unresectable primary tumor.
8. Patients with ACC and uncontrolled hormonal secretion (according to the judgement of the treating physician).
9. Patients with MPP and uncontrolled blood pressure (according to the judgement of the treating physician).
10. Patients with abnormal laboratory values according to the following list (note, lab ranges according to the performing laboratory's reference ranges):
a. lymphocyte count decreased, grade 2 (lymphocytes <800 - 500/mm3; <0.8 - 0.5 x 109/L), or worse grade,
b. hemoglobin < 8 g/dL (9 mmol/L) i.e. anemia Grade 2 is acceptable if judged by the Investigator as not constituting a safety risk in the individual patient,
c. white blood cell count decrease (< 3.0 × 109/L),
d. absolute neutrophil count decrease (< 1.5 × 109/L),
e. platelet count decrease (< 75 × 109/L),
f. total bilirubin > 1.5 x upper limit of normal (ULN),
g. alanine aminotransferase (ALT) > 3 x ULN; if disease metastatic to the liver > 5 x ULN,
h. aspartate aminotransferase (AST) > 3 x ULN; if disease metastatic to the liver > 5 x ULN,
i. serum creatinine increase (> 1.5 x ULN); however, if creatinine clearance (measured, or calculated according to the Cockcroft/Gault or the CKD-EPI equation) is > 40 mL/minute the patient can be enrolled, and
j. abnormal thyroid function per local laboratory levels (note, patients with hypothyroidism only requiring hormone replacement therapy are permitted to enroll, also patients with abnormal laboratory values judged by the treating physician as clinically non-relevant and related to mitotane treatment are allowed to enroll).
11. Patients with persistent Grade 3 or 4 toxicities (according to NCI-CTCAE v5.0) after prior treatments; toxicities must be resolved since at least 2 weeks before study treatment start to Grade 1 or less. However, alopecia or other persisting toxicities Grade <= 2 not constituting a safety risk based on Investigator*s judgment are acceptable.
12. Uncontrolled central nervous system (CNS) metastasis; patients with history of CNS metastases are eligible if CNS disease has been radiographically and neurologically stable for at least 6 weeks prior to ICF signing and do not require corticosteroids (of any dose; for the CNS disease specifically) for symptomatic management.
13. Other malignancy or prior malignancy with a disease-free interval of less than 3 years prior to ICF signing; except those treated with surgical intervention and an expected low likelihood of recurrence such as basal cell or squamous cell skin cancer, or carcinoma in situ, i.e. patients with adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ are eligible.

14. Patients with clinically significant active infection, cardiac disease, significant medical or psychiatric disease/condition that, in the opinion of the Investigator, would interfere with the evaluation of study results, interpretation of patient safety, or prohibit patient understanding of the informed consent procedure (i.e. only consent able patients can be enrolled in the study) or compliance with the requirements of the protocol - including (but not limited to):
a. bacterial sepsis or similarly severe infections,
b. uncontrolled or significant cardiovascular disease, including:
i. New York Heart Association > Grade 2 congestive heart failure within 6 months prior to ICF signing,
ii. myocardial infarction within 6 months prior to ICF signing,
iii. uncontrolled/unstable angina within 6 months prior to ICF signing,
iv. diagnosed or suspected congenital long QT syndrome,
v. any history of clinically significant ventricular arrhythmias (such as ventricular tachycardia, ventricular fibrillation, or Torsades de pointes),
c. stroke within 6 months prior to ICF signing,
d. concurrent neurodegenerative disease, and
e. dementia or significantly altered mental status.
15. Patients with suspected autoimmune or active autoimmune disorder or known history of an autoimmune neurologic condition (e.g. Guillain-Barré syndrome). Note, patients with vitiligo, type I diabetes mellitus, hypothyroidism due to autoimmune condition only requiring hormone replacement therapy, psoriasis not requiring systemic therapy, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
16. Patients with history of solid organ transplantation or hematopoietic stem cell transplantation.
17. Patients with history or known presence of tuberculosis.
18. Pregnant and breastfeeding patients.
19. Patients with history or presence of human immunodeficiency virus and/or potentially active hepatitis B virus/hepatitis C virus infection.
20. Patients who have received live or attenuated vaccine therapy used for prevention of infectious diseases including seasonal (influenza) vaccinations within 4 weeks of the first dose of study drug.
21. Patients with a history of hypersensitivity to any excipient present in the pharmaceutical forms of the study treatments.
22. Patients treated with herbal remedies with immunostimulating properties or known to potentially interfere with major organ function.
23. Patients with known ongoing drug and alcohol abuse.
24. Patients with known or underlying medical or psychiatric condition that, in the Investigator*s opinion, would make the administration of study drug hazardous to the patient or obscure the interpretation of toxicity determination or AEs.
25. Patients deprived of their liberty, under protective custody, or guardship.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-01-2021
Enrollment:	10
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	EO2401
Product type:	Medicine
Brand name:	OPDIVO
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-01-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-05-2020
Application type:	First submission

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-09-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-11-2020
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-04-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-04-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-11-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	06-12-2022
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-03-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-04-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-10-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	23-01-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-02-2024
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	17-05-2024
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	EUCTR2019-003396-19-NL
ClinicalTrials.gov	NCT04187404
CCMO	NL71766.000.19