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# Cetuximab immunotherapy combination in head and neck cancer

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| **Submission date**<br>05/11/2018 | **Recruitment status**<br>Stopped | [X] Prospectively registered<br>[ ] Protocol<br>[ ] Statistical analysis plan<br>[ ] Results<br>[ ] Individual participant data<br>[ ] Record updated in last year |
| **Registration date**<br>08/11/2018 | **Overall study status**<br>Stopped | |
| **Last Edited**<br>30/12/2021 | **Condition category**<br>Cancer | |

**Plain English summary of protocol**
Not provided at time of registration

## Contact information

**Type(s)**
Scientific

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## Additional identifiers

**Clinical Trials Information System (CTIS)**
2017-003589-28

**Protocol serial number**
39187

## Study information

## Scientific Title
Phase I/Ib trial of durvalumab (MEDI4736), tremelimumab + cetuximab in patients with recurrent /metastatic squamous cell carcinoma of the head and neck (OBERON)

## Acronym
OBERON

## Study objectives
Durvalumab and tremelimumab is safe and tolerable in combination with cetuximab in patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) and this combination is synergistic.

## Ethics approval required
Old ethics approval format

## Ethics approval(s)
West Midlands - Edgbaston Research Ethics Committee, 02/10/2018, ref: 18/WM/0225

## Primary study design
Interventional

## Study design
Non-randomised; Interventional; Design type: Treatment, Drug, Immunotherapy

## Study type(s)
Treatment

## Health condition(s) or problem(s) studied
Squamous cell carcinoma of the head and neck

## Interventions
This research study is designed to see if a combination of three anti-cancer drugs (durvalumab, tremelimumab and cetuximab) is safe and whether the side effects are manageable in patients with squamous cell carcinoma of the head and neck (SCCHN), which has recurred or spread.

This research study is also designed to see if this combination of drugs can shrink or prevent tumours of the head and neck from growing any further.

There are two parts to this study. Part A is a dose escalation study. The aim of part A is to work out the recommended dose (i.e. the dose that does not result in too many unacceptable side effects) of cetuximab in combination with durvalumab and tremelimumab. Part B will repeat the same tests on a new set of participants, using a recommended dose level that was well tolerated by participants in part A of the study. There will be 36 participants recruited to this study in total.

Participants who may be eligible to participate in the study will be identified by the team responsible for their care. The study will be explained by the study doctor and research staff at one of the research sites. Participants will be given time to consider whether to take part in the study before providing informed consent.

Participants will attend clinic during screening and then weekly for treatment visits until their cancer has been shown to progress on imaging.

Screening
The screening phase of the study will take approximately one month and will determine whether participants are eligible to take part in the study.
The screening phase will involve the following investigations:
- Assessment of inclusion and exclusion criteria
- Retrieval of an archival tumour FFPE block (taken within 12 months) or a newly acquired tumour FPPE block
- Full physical examination (including height and weight measurement)
- Collection of information on medical history
- Collection of demographic information
- Vital signs check (including blood pressure, temperature, respiratory rate and pulse rate)
- Clinical blood tests
- Urine tests
- Review of medications and adverse events
- Pregnancy test in women of childbearing age
- Electrocardiogram

Treatment
During the treatment phase, participants will attend hospital weekly. Each appointment will last approximately 3-6 hours. The following will occur:
- Cetuximab 50 mg/m2 will be administered intravenously, weekly, during hospital visits (until PD or DLT)
- Durvalumab 1500 mg will be administered intravenously, every 4 weeks, during hospital visits (until PD or DLT)
- Tremelimumab 75 mg will be administered intravenously, every 4 weeks, in combination with durvalumab for 4 cycles
- Full physical examination (including weight measurement) at each treatment visit
- Vital signs check (including blood pressure, temperature, respiratory rate and pulse rate). These will be checked before, during and after every treatment infusion
- Clinical blood tests
- Urine tests every 4 weeks
- CT or MRI scans every 8 weeks
- Review of medications and adverse events
Some further investigations may be requested during the treatment phase, if indicated clinically.

Follow up
During the follow up period participants will attend hospital for clinic visits to check on their health and manage any side effects or symptoms. CT or MRI scans will be undertaken every 12 weeks.

Samples for research
As part of the study, samples will be taken for research into head and neck cancer. These will include blood samples, skin swabs, mouth swabs and faecal samples. Where participants develop a rash, skin biopsies may also be taken. Tumour biopsies may be taken during screening and when study treatment is stopped.

The primary objective of the study is to assess safety and tolerability of durvalumab, tremelimumab and cetuximab in combination in patients with recurrent and metastatic SCCHN who have progressed beyond standard of care. Safety and tolerability of the drug combination will be assessed according to adverse events (AE), laboratory data, vital signs, electrocardiogram (ECG) changes and physical examination. Summaries of these data will be presented. The

analysis set for safety is defined as “all patients who received at least 1 dose of study treatment, and data will be summarised according to the treatment received, that is, erroneously treated patients summarised according to the treatment they actually received.

Adverse Events
The number of patients experiencing each AE will be summarised by the Medical Dictionary for Regulatory Activities (MedDRA) system organ class, MedDRA preferred term and Common Terminology Criteria for Adverse Events (CTCAE grade). The number and percentage of patients with AEs in different categories will be summarised by dose group, and events in each category will be further summarised by MedDRA system organ class and preferred term, by cohort and cetuximab dose. Serious adverse events (SAE) and adverse events of special interest (AESI), as defined in the protocol, will be summarised separately if a sufficient number occur. AEs occurring after the 28 days following discontinuation of investigational product will be listed but not included in summaries.

Clinical Data
Haematology, clinical chemistry, vital signs and ECG data will be listed individually by patient and suitably summarised. For all laboratory variables, which are included in the current version of CTCAE, the CTCAE grade will be calculated. Summary statistics of mean, median, standard deviation, minimum, maximum and number of observations will be used. Details of any deaths will be listed for all patients. For urinalysis parameters, any qualitative assessments will be summarised for all patients using the number of patients with results of negative, trace or positive. Graphical presentations of safety data will be presented as is deemed appropriate. This may include, but is not restricted to, presentation of parameters against time, concentration or shift plots. Appropriate scatter plots will also be considered to investigate trends in parameters compared to baseline.

### Intervention Type
Drug

### Phase
Phase I

### Drug/device/biological/vaccine name(s)
Cetuximab, durvalumab, tremelimumab

### Primary outcome(s)
Patient safety is measured by the total number of dose limiting toxicities that lead to discontinuation of treatment. Safety is an ongoing assessment from recruitment to end of trial participation. It will then also be reviewed across all patients at the end of the trial.

### Key secondary outcome(s)
Not provided at time of registration

### Completion date
09/11/2020

### Reason abandoned (if study stopped)
Lack of funding/sponsorship

## Eligibility

## Key inclusion criteria

1. Histologically confirmed recurrent or metastatic SCCHN (oral cavity, oropharynx, hypopharynx, or larynx) not amenable to local curative therapy with surgery or radiation therapy progressed beyond standard of care
2. Previous immunotherapy or cetuximab is permitted for part A (dose escalation) but not required. For Part B (expansion cohort), all patients must have progressed beyond treatment including immune checkpoint blockade (e.g. including but not limited to previous treatment targeting PD1/PDL1/CTLA4)
3. Able and willing to give valid written consent to provide newly acquired tumour tissue (preferred) or archival tissue. Determination of adequate tumour cell content to provide 25 slides will be undertaken by local site pathologist. Patients who do not meet this criteron may be considered eligible following discussion with the sponsor
4. For patients with oropharyngeal cancer (OPC) only: confirmed HPV status by p16 IHC, HPV PCR or ISH
5. Measurable disease by RECIST 1.1 (previously irradiated lesions must have progressed if to be used as marker lesions)
6. Written informed consent and any locally-required authorsation (e.g. HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations
7. Age ≥ 18 years at time of study entry
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
9. Life expectancy of ≥ 12 weeks
10. Body weight > 30 kg
11. Adequate normal organ and marrow functions as defined below:
11.1. Haemoglobin ≥ 9.0 g/dL
11.2. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
11.3. Platelet count ≥ 100 x 10^9/L
11.4. Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinaemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician
11.5. AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5 x ULN
11.6. Serum creatinine CL > 40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:
Males: Creatinine CL(mL/min)= Weight(kg)x(140 - Age)]/[72 x serum creatinine(mg/dL)]
Females: Creatinine CL(mL/min)=[Weight(kg)x(140 - Age)]/[72 x serum creatinine(mg/dL)]x0.85
12. Evidence of post-menopausal status, negative urinary or serum pregnancy test of female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
12.1. Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinising hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilisation (bilateral oophorectomy or hysterectomy)
12.2. Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, or underwent surgical

sterilisation (bilateral oophorectomy, bilateral salpingectomy or hysterectomy)
13. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up

## Participant type(s)
Patient

## Healthy volunteers allowed
No

## Age group
Adult

## Lower age limit
18 Years

## Sex
All

## Key exclusion criteria
Full exclusion criteria with exceptions is located in the current study protocol.
1. Involvement in the planning and/or conduct of the study
2. Participation in another clinical study with an investigational product during the last 4 weeks
3. Concurrent enrolment in another clinical study, unless it is an observational clinical study or during the follow-up period of an interventional study
4. Receipt of the last dose of anti-cancer therapy < = 28 days prior to the first dose of study drug. If sufficient wash-out time has not occurred due to the schedule or PK properties of an agent, a longer wash-out period will be required, as agreed by AstraZeneca/MedImmune and the investigator
5. Any unresolved toxicity NCI CTCAE Grade > = 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria
6. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions is acceptable
7. Major surgical procedure within 28 days prior to the first dose of IP. Note: Local surgery of isolated lesions for palliative intent is acceptable
8. History of allogeneic organ transplantation
9. Active or prior documented autoimmune or inflammatory disorders
10. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic, congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, intersitial lung disease, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent
11. History of another primary malignancy except for:
11.1. Malignancy treated with curative intent and with no known active disease > = 5 years before the first dose of IP and of low potential risk for recurrence
11.2. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
11.3. Adequately treated carcinoma in situ without evidence of disease
12. History of leptomeningeal carcinomatosis
13. Brain metastases or spinal cord compression unless the patient is stable. Following

radiotherapy and/or surgery of the brain metastases patients must wait 4 weeks following the intervention and before randomisation with imaging to confirm stability
14. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF)> = 470 ms calculated from 3 ECGs
15. History of active primary immunodeficiency
16. Active infection including tuberculosis, hepatitis B, hepatitis C or human immunodeficiency virus. Patients with a past or resolved HBV infection are eligible. Patients positive for hepatitis C antibody are eligible only if polymerase chain reaction is negative for HCV RNA
17. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab or tremelimumab
18. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP
19. Female patients who are pregnant or breastfeeding or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab + tremelimumab + cetuximab or 180 days after the last dose of durvalumab + tremelimumab + cetuximab combination therapy, whichever is the longer period
20. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients
21. Prior randomisation or treatment in a previous durvalumab and/or tremelimumab clinical study regardless of treatment arm assignment
22. Patients who have received prior anti-PD-1, anti PD-L1 or anti CTLA-4:
22.1. Must not have experienced a toxicity that led to permanent discontinuation of prior immunotherapy
22.2. All AEs while receiving prior immunotherapy must have completely resolved or resolved to baseline prior to screening for this study
22.3. Must not have required the use of additional immunosuppression other than corticosteroids for the management of an AE, not have experienced the recurrence of an AE if re-challenged, and not currently require maintenance doses of > 10 mg prednisone or equivalent per day
23. Prior grade 3 or 4 dermatological AE with cetuximab or any prior grade 4 immune related AE
24. Past medical history of ILD, drug-induced ILD, radiation pneumonitis which required steroid treatment, or any evidence of clinically active interstitial lung disease
25. Judgment by the investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements

### Date of first enrolment
14/01/2019

### Date of final enrolment
14/01/2021

## Locations

### Countries of recruitment
United Kingdom

### Study participating centre

**To be confirmed**
United Kingdom
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# Sponsor information

**Organisation**
The Christie NHS Foundation Trust

**ROR**
https://ror.org/03v9efr22

# Funder(s)

**Funder type**
Industry

**Funder Name**
AstraZeneca; Grant Codes: ESR 16-12250

**Alternative Name(s)**
AstraZeneca PLC, Pearl Therapeutics, AZ

**Funding Body Type**
Government organisation

**Funding Body Subtype**
For-profit companies (industry)

**Location**
United Kingdom

# Results and Publications

**Individual participant data (IPD) sharing plan**
The data sharing plans for the current study are unknown and will be made available at a later date.

**IPD sharing plan summary**
Data sharing statement to be made available at a later date

**Study outputs**

| Output type | Details | Date created | Date added | Peer reviewed? | Patient-facing? |
| --- | --- | --- | --- | --- | --- |
| HRA research summary | | | 26/07/2023 | No | No |