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Assessing the impact of mouth and bowel bacteria on outcomes of patients receiving chemotherapy with immunotherapy

Submission date
22/11/2022

Recruitment status
No longer recruiting

Registration date
17/01/2023

Overall study status
Ongoing

Last Edited
30/09/2026

Condition category
Cancer

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-determine-whether-number-types-bacteria-gut-affects-how-well-treatment-works-bile-duct-cancer-abc-12

Background and study aims
The aim of this study, known as ABC-12, is to analyse the bacteria that normally live in the bowel and mouth. The aim is to try and find out whether this has an effect on how well biliary tract cancer (BTC) (cancer of the bile ducts and liver) responds to treatment and how long life expectancy will be. Researchers have found that sometimes the body's own immune system may slow down or control cancer growth. Sometimes this natural immune system response stops and the cancer is not killed by your own immune system and in some patients, cancer cells and immune cells start to express signals that stop the body's immune system from killing the cancer. In this study, a new drug will be used, durvalumab, to try and block this signal to increase the immune response, in combination with standard of care cisplatin/gemcitabine chemotherapy. Durvalumab is an antibody (a protein produced by the body's defense system) and it is hoped that by blocking this signal, the immune cells will once again be able to prevent or slow down cancer growth. This drug combination has been shown in a large clinical trial to increase survival in patients with BTC where surgery is not an option.

Who can participate?
Adult patients with confirmed unresectable (cannot be removed by surgery) advanced or metastatic cancer of the biliary tract, including cholangiocarcinoma and gallbladder carcinoma

What does the study involve?
The aim will be to recruit a minimum of 50 evaluable patients across 10 UK sites over 12 months, with a 12 month follow up period.

What are the possible benefits and risks of participating?
It is hoped that the trial treatment will help you and may slow down or delay the growth of your cancer. However, there is no guarantee of this. You may not experience any direct health benefits during or following the completion of this trial. The information from this study will

help doctors learn more about treatments for biliary tract cancer. We cannot guarantee that you will personally experience benefits from taking part in this study, but you will be contributing to research that may benefit future patients with cancer with a similar disease.

The study drug durvalumab works by boosting the immune system. Durvalumab may cause side effects, which can occur when the drug is given or after the drug is given (within hours, days or weeks after). Some side effects usually get better when the treatment is stopped. However, it is possible that some side effects may become serious or life-threatening and some have resulted in death in patients who have received treatment with durvalumab. Full details of the side effects will be provided in the patient information sheet.

It is possible that the patients cancer may not improve during the study or may become even worsen. There may be risks involved in taking durvalumab that have not yet been discovered. There is always a risk involved in taking an experimental drug, but every precaution will be taken, and patients will be closely looked after by the doctors and research nurses. If a patient suffers any side effects or injuries, or their condition gets worse, they are advised to tell their doctor/nurse immediately so that they can receive appropriate care.

Possible risks associated with durvalumab:
Most of the possible side effects listed in the patient information sheet are mild to moderate. However, some side effects can be very serious and life-threatening and may even result in death. Some side effects do not need treatment, while others generally get better with treatment. Some patients may need to delay doses of durvalumab to allow the side effects to get better. The most important possible side effects, which are also fully documented in the patient information sheet, may occur because of the way durvalumab works on the immune system and they have been seen in some patients treated with durvalumab in other clinical studies. Side effects like these have also been seen in clinical studies with other drugs that are very similar to durvalumab. Management of these side effects may require the administration of drugs such as steroids or other agents that can affect your immune system and reduce inflammation (swelling).

There are also risks and burdens for participants from gemcitabine/cisplatin which is the current standard of care treatment offered. They may also cause side effects. Current side effects are listed in the patient information sheet. The patient information sheet assures the patients that their doctor will be able to explain more details about the cisplatin and gemcitabine chemotherapy that they will receive along with the study drug, durvalumab, how it will be given to the patient and what kind of side effects they may experience.

Durvalumab, when taken in combination with other medicines may be associated with other risks that are unknown at this time. Although there is limited information on how durvalumab may interact with other medications, it is important that participants share with their doctor any medications (prescription, over-the-counter and herbal supplements) that they are taking. All of the routine medications they take from the time they sign this informed consent form up until 90 days after their last dose of durvalumab, or standard chemotherapy, will be recorded by the doctor. AstraZeneca will be notified if a participant receives any medications that they are not supposed to whilst on this trial.

Risks associated with general trial procedures:
Blood Samples: Taking blood may result in pain, irritation, bruising, or bleeding, irritation at the injection site. There is also a possibility of fainting or infection
ECG: An ECG has no serious risks. It is a harmless, painless test. ECGs do not give off electrical charges. Participants may develop a mild rash where the electrodes (soft patches) were

attached. This rash often goes away without treatment.
MRI: This process is safe for most people. Participants with metal near important organs may not receive an MRI. The metal may be drawn away from the body and towards the large magnet, which could cause injury.
CT scan: Allergic reaction to the contrast median and a relatively insignificant increased exposure to radiation are the 2 main side effects of CT scanning.
Tumour biopsy: The vast majority of participants will have a tumour sample taken in the last 3 years and therefore will not need a tumour biopsy but may consent to optional biopsies. Biopsy can be provided if the participant consents to this. If a biopsy is required there is a risk of pain, bleeding, and problems with wound healing, bruising and/or infection following the biopsy.

Where is the study run from?
AstraZeneca (UK)

When is the study starting and how long is it expected to run for?
November 2022 to February 2027.

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
Mairead McNamara, mairead.mcnamara@nhs.net (UK)

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2022-000799-20

Integrated Research Application System (IRAS)
1005274

Protocol serial number
CFTSp190

Study information

Scientific Title
Exploring the microbiome in patients with advanced biliary tract cancer in a first-line study of durvalumab (MEDI4736) in combination with cisplatin/gemcitabine

Acronym
ABC-12

Study objectives
1. To determine the difference in baseline alpha diversity (number of species present in microbiome samples) between “responders” (best response of partial or complete response) and “non-responders” measured at 18 weeks (by RECIST 1.1) in patients treated with durvalumab /cisplatin/gemcitabine.
2. To investigate the association between microbiome parameters and objective response rate, tumour control (partial and complete response and stable disease), progression-free and overall survival.
3. To investigate the interaction between treatment effect and microbiome parameters on clinical outcomes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 02/08/2023, North West – Haydock (2 Redman Place, Stratford, E20 1JQ, United Kingdom; +44 (0)2071048032, (0)2071048248; haydock.rec@hra.nhs.uk), ref: 22/NW/0389

Primary study design
Interventional

Study design

Single-arm study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Biliary tract adenocarcinoma, including cholangiocarcinoma (intra- and extra-hepatic biliary ducts), and gallbladder carcinoma

Interventions
This is a single-arm study where patients will receive durvalumab plus cisplatin/gemcitabine combination therapy as follows (21-day cycles):
1. Durvalumab 1500 mg via intravenous (IV) infusion on day 1
2. Cisplatin 25 mg/m2 via IV infusion on days 1 and 8
3. Gemcitabine 1000 mg/m2 via IV infusion on days 1 and 8
Followed by durvalumab monotherapy on day 1 (28-day cycles)

On-study imaging assessments will be done Q6w ± 1w (relative to the date of registration), for the first 24 weeks (relative to the date of registration) and then Q8w ± 1w thereafter (relative to the date of registration) until RECIST 1.1-defined radiological progressive disease (PD).

Intervention Type
Biological/Vaccine

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Durvalumab, cisplatin, gemcitabine

Primary outcome(s)
Number of species present in microbiome samples (baseline alpha diversity) from both “responders” (best response of partial or complete response) and “non-responders”, defined using RECIST 1.1criteria, measured microbiome analysis at 18 weeks

Key secondary outcome(s)
The following secondary outcomes will be measured according to RECIST 1.1 criteria and recorded in patient medical notes for the duration of the study, with follow-up until 12 months after the last patient is enrolled:
1. Objective response rate
2. Disease control rate
3. Progression-free survival
4. Overall survival

Completion date
28/02/2027

Eligibility

Key inclusion criteria

1. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in the protocol
2. Provision of a signed and dated written ICF prior to any mandatory study-specific procedures, sampling, and analyses
3. Provision of a signed and dated written informed consent prior to the collection of samples (saliva and stool) for analysis
4. Age ≥18 years at the time of screening
5. Histologically biopsy-confirmed (not cytology brushings), unresectable advanced or metastatic adenocarcinoma of biliary tract, including cholangiocarcinoma (intrahepatic or extrahepatic) and gallbladder carcinoma
6. Patients with previously untreated disease if unresectable or metastatic at initial diagnosis will be eligible
7. Patients who developed recurrent disease >6 months after surgery with curative intent and, if given, >6 months after the completion of adjuvant therapy (chemotherapy and/or radiotherapy) will be eligible
8. Eastern Co-operative Oncology Group Performance Status (ECOG PS) of 0 or 1 at enrolment
9. At least 1 lesion that qualifies as a Response Evaluation Criteria RECIST 1.1 Target Lesion (TL) at baseline
10. No prior exposure to immune-mediated therapy, including, but not limited to, other Anti-cytotoxic T-lymphocyte-associated protein 4 (anti-CTLA-4), anti-programmed cell death-1 (anti-PD-1), anti-programmed cell death ligand 1 (anti-PD-L1), and anti-PD-L2 antibodies, excluding therapeutic anticancer vaccines
11. Adequate organ and marrow function, as defined below:
11.1. Haemoglobin ≥9.0 g/dL
11.2. Absolute neutrophil count ≥1.5 × 109/L
11.3. Platelet count ≥100 × 109/L
11.4. Serum bilirubin ≤1.5 × the institutional upper limit of normal (ULN). This will not apply to patients with confirmed Gilbert's syndrome, who will be allowed in consultation with their physician
11.5. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤2.5 × ULN; for patients with hepatic metastases, ALT and/or AST ≤5 × ULN
11.6. Measured creatinine clearance (CL) >50 mL/min or calculated creatinine clearance (CL) >50 mL/min as determined by Cockcroft-Gault (using actual body weight):
11.6.1. Males: Creatinine CL (mL/min) = Weight (kg) x (140-Age)/72 x serum creatinine (mg/dL)
11.6.2. Females: Creatinine CL (mL/min) = Weight (kg) x (140-Age) x 0.85/72 x serum creatinine (mg/dL)
12. Patients must have a life expectancy of at least 12 weeks at the time of screening
13. Body weight >30 kg
14. Patients must have a recent tumour biopsy or an available unstained archived tumour tissue sample in a quantity sufficient to allow for future analysis. The tumour lesions used for biopsy (if recent) should not be those used as RECIST TLs, unless there are no other lesions suitable for biopsy
15. Patients with HBV infection (as characterised by positive hepatitis B surface antigen [HBsAg] and/or anti-hepatitis B core antibodies (anti-HBc) with detectable HBV deoxyribonucleic acid (DNA) [≥10 IU/mL or above the limit of detection per local laboratory]) must receive antiviral therapy prior to registration per institutional practice to ensure adequate viral suppression. Patients must remain on antiviral therapy for the study duration and for 6 months after the last dose of study treatment. Patients who test positive for anti-HBc with undetectable HBV DNA (<10 IU/mL or under the limit of detection per local laboratory) do not require antiviral therapy unless HBV DNA exceeds 10IU/mL or reaches detectable limits per local laboratory during the course of treatment. Patients with active co-infection of HBV and HCV as evidenced by positive anti-HCV antibody and actively co-infected with HBV and hepatitis D virus are not eligible.

16. Patient must provide saliva and stool sample prior to commencement of durvalumab /cisplatin/gemcitabine
17. Patient 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
Mixed

Lower age limit
18 Years

Upper age limit
120 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Ampullary carcinoma or combined or mixed hepatocellular/cholangiocarcinoma
2. History of allogeneic organ transplantation
3. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions are:
3.1. Patients with vitiligo or alopecia
3.2. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement
3.3. Any chronic skin condition that does not require systemic therapy
3.4. Patients without an active disease in the last 5 years may be included but only after consultation with the study physician
3.5. Patients with coeliac disease controlled by diet alone
4. Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active interstitial lung disease (ILD), serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase the risk of incurring Adverse Events (AEs), or compromise the ability of the patient to give written informed consent.
5. History of another primary malignancy, except for:
5.1. Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of investigational medicinal product (IMP) and of low potential risk for recurrence
5.2. Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of

disease
5.3. Adequately treated carcinoma in situ without evidence of disease
6. History of leptomeningeal carcinomatosis
7. History of active primary immunodeficiency
8. Active infection, including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice), or human immunodeficiency virus (positive HIV 1/2 antibodies).
9. Any unresolved toxicity National Cancer Institute Common Terminology Criteria (CTC) for Adverse Event (NCI CTCAE) Grade ≥2 from a previous anticancer therapy, with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.
9.1. Patients with Grade ≥2 neuropathy will be evaluated on a case-by-case basis after consultation with the study physician.
9.2. Patients with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the study physician.
10. Brain metastases or spinal cord compression (including asymptomatic and adequately treated disease). Patients with suspected brain metastases at screening should have a Magnetic Resonance Imaging (MRI) scan (preferred) or CT scan, each preferably with IV contrast, of the brain prior to study entry.
11. Known allergy or hypersensitivity to any of the study drugs or any of the study drug excipients
12. Any concurrent chemotherapy, IMP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g., hormone replacement therapy) is acceptable.
13. Concurrent palliative radiotherapy involving target lesions used for this study (<28 days from discontinuation of radiotherapy). Radiotherapy for non-target lesions is allowed if other target lesions are available outside the involved field (previous radiotherapy given in the adjuvant setting is permitted).
14. Receipt of live attenuated vaccine within 30 days prior to the first dose of IP. Note that patients, if enrolled, should not receive live vaccine while receiving IMP and up to 30 days after the last dose of IMP.
15. Major surgical procedure (as defined by the Investigator) within 28 days prior to the first dose of IMP. Note that minor surgery of isolated lesions for palliative intent is acceptable if performed more than 14 days prior to the first dose of IMP.
16. Patients who have received prior immune-mediated therapy, including, but not limited to, other anti-PD-1, anti PD-L1, or anti CTLA-4
17. Prior locoregional therapy such as radioembolisation
18. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:
18.1. Intranasal, inhaled, or topical steroids or local steroid injections (eg, intra-articular injection)
18.2. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent.
18.3. Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

Date of first enrolment
09/11/2023

Date of final enrolment
31/12/2025

Locations

Countries of recruitment
United Kingdom

England

Wales

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
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Study participating centre
Imperial College Healthcare NHS Trust
Hammersmith Hospital
London
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W2 1BL

Study participating centre
Cambridge University Hospitals NHS Foundation Trust
Cambridge Biomedical Campus
Hills Road
Cambridge
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CB2 0QQ

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital
Pond Street
London
England
NW3 2QG

Study participating centre
Oxford University Hospitals NHS Foundation Trust
Churchill Hospital

Oxford
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OX3 9DU

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Queen Elizabeth Hospital
Mindelsohn Way
Edgbaston
Birmingham
England
B15 2GW

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Hospital
Clatterbridge Road
Bebington
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CH63 4JY

Study participating centre
Nottingham University Hospitals NHS Trust - Queen's Medical Centre Campus
Nottingham University Hospital
Derby Road
Nottingham
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NG7 2UH

Study participating centre
Velindre NHS Trust
Unit 2
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Heol Billingsley
Cardiff
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Study participating centre

University College London Hospitals NHS Foundation Trust
250 Euston Road
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Sponsor information

Organisation
Christie Hospital NHS Foundation Trust

ROR
https://ror.org/03v9efr22

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

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 datasets generated during and/or analysed during the current study will be available upon request. Requests for data would need to be formally made to The Christie as Sponsor and only after the main publication and final report are published.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		29/07/2025	30/07/2025	Yes	No