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A study to investigate if atezolizumab can reduce the size of urothelial cancer before surgery and to determine how the drug works

Submission date 09/12/2021	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 20/06/2022	**Overall study status** Ongoing	
Last Edited 18/11/2026	**Condition category** Cancer	

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-atezolizumab-for-people-with-urinary-tract-cancer-urothelial-cancer-abacus-2

Background and study aims
Urothelial cancer is the most common type of bladder cancer. This study is being carried out to see if the drug atezolizumab can reduce the size of tumours in patients with types of urothelial cancer before surgery. Atezolizumab is designed to stop a protein called PD-L1 (programmed death-ligand 1) from being expressed on the cancer, allowing the immune system to recognise the tumour cells as foreign bodies and attack them. Atezolizumab has been shown to have activity in urothelial cancer which has spread.

Who can participate?
There are strict eligibility criteria for this trial. Broadly speaking, patients aged 18 years and over with histologically confirmed urothelial cancer requiring surgery are eligible. One cohort will investigate the most common type of urothelial cancer (transitional cell carcinoma) outside the bladder, for example in the upper urinary tract. The other cohort will investigate rarer types (such as squamous cell or adenocarcinoma) of urothelial cancer throughout the entire urinary system. This study will be recruiting patients from hospitals in the UK, France and Spain.

What does the study involve?
If a patient is eligible for the study and decides to take part, they will receive up to two 3-weekly cycles of atezolizumab. 4-8 weeks after being enrolled, the patient will have an operation to remove the bladder (cystectomy) or the kidney, ureter and part of the bladder (nephroureterectomy or distal ureteral resection) as per normal practice. Following surgery, they will attend three hospital visits (4, 12 and 24 weeks after surgery) and their disease progress /survival will be followed over the next 2 years. The clinical team will compare the patient's tumour tissue samples, scan results and blood results from before and after treatment with atezolizumab in order to see how well the drug works and if it is safe. Many of the procedures involved in this study are offered as standard care and participation in this trial will not delay surgery.

What are the possible benefits and risks of participating?
Atezolizumab has significant activity in advanced bladder cancer and therefore may have beneficial outcomes. The main potential risks relate to adverse events associated with atezolizumab. In most European countries, patients currently have to wait an average of 4–8 weeks between establishing the diagnosis of urothelial cancer and surgical management. Participation in this trial of 6 weeks' preoperative treatment is not expected to result in relevant delays of surgery for participants. There is no preclinical, clinical or mechanistic evidence to suggest that atezolizumab has a relevant impact on operability or increases the risks associated with surgery.

Where is the study run from?
Queen Mary University of London (UK)

When is the study starting and how long is it expected to run for?
June 2021 to August 2027

Who is funding the study?
F. Hoffmann-La Roche (Switzerland)

Who is the main contact?
ABACUS-2 Clinical Trial Coordinator
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Contact information

Type(s)
Public

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04624399

Clinical Trials Information System (CTIS)
2019-004628-39

Integrated Research Application System (IRAS)
1003489

Central Portfolio Management System (CPMS)
47344

Study information

Scientific Title
Phase II study of neoadjuvant immune checkpoint inhibitors in urothelial cancer

Acronym
ABACUS-2

Study objectives
To determine atezolizumab's ability to reduce the size of urothelial cancer in the bladder (rare histological subtypes) and upper urinary tract before surgery (measured as pathological complete response rate), and assess the impact of the drug on the body's immune system.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 03/12/2020, Health & Social Care Research Ethics Committee A (Office for Research Ethics Committees Northern Ireland (ORECNI), Customer Care & Performance Directorate, Lissue Industrial Estate West, 5 Rathdown Walk, Moira Road, Lisburn, BT28 2RF, UK; +44 (0)28 9536 1400; RECA@hscni.net), ref: 20-NI-0148

Primary study design
Interventional

Study design

Open-label international multicentre window of opportunity Phase II trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Urothelial cancer (upper tract urothelial carcinoma and rare histological subtypes of bladder cancer)

Interventions
Eligible patients will receive 2 x 3 weekly cycles of 1200 mg atezolizumab before planned radical surgery.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Atezolizumab

Primary outcome(s)
Clinical: Efficacy of atezolizumab pre-surgery in patients with carcinoma of the bladder (rare histological subtypes) and upper urinary tract urothelial carcinoma, measured as pathological complete response rate (pCRR). PCRR is defined as no microscopic evidence of residual disease in the bladder based on histological evaluation of the resected bladder specimen collected during cystectomy (post–treatment).

Biological: Effect of 2 x 3 weekly cycles of atezolizumab pre-cystectomy on immune parameters in patients with carcinoma of the bladder (rare histological subtypes) and before radical surgery for upper tract disease in patients with high risk upper urinary tract urothelial carcinoma. Effects measured by dynamic changes in T cell subpopulations (CD8 and/or CD3) in tumour samples collected pre- and post-treatment.

Key secondary outcome(s)
1. Safety and tolerability of atezolizumab when given in the neoadjuvant setting before radical surgery, measured by incidence, nature and severity of Adverse Events graded according to NCI-CTCAE v5.0 collected during treatment and up to 24 weeks post-radical surgery. Surgical complications will be assessed by the Clavien-Dindo scoring system up to 12 weeks post-surgery.
2. Efficacy of atezolizumab given in the neoadjuvant setting before radical surgery with respect to anti-tumour effect measured by investigator-assessed radiological response pre-surgery (defined as a ≥30% decrease in tumour diameter from the baseline scan).
3. Efficacy of atezolizumab given in the neoadjuvant setting before radical surgery with respect to anti-tumour effects based on investigator-assessed disease-free survival (defined as the time between the date of enrolment to the first evidence of relapse based on local investigator assessments or death, whichever occurs first). Disease and survival information is collected up to 2 years post-surgery.
4. Efficacy of atezolizumab given in the neoadjuvant setting before radical surgery with respect to overall survival (defined as the time between the date of enrolment and death due to any cause). Disease and survival information is collected up to 2 years post-surgery.

Completion date
31/08/2027

Eligibility

Key inclusion criteria
Cohort-specific inclusion criteria:
1. Bladder cohort:
Histopathologically confirmed carcinoma of the urothelium (T1 high grade -T4a) in the bladder with mixed or rare histological subtypes such as squamous cell or adenocarcinoma. Patients with mixed histologies are required to have a dominant non-transitional cell pattern.
2. UTUC cohort:
Histopathologically confirmed high grade or high risk upper urinary tract urothelial carcinoma (renal pelvis and ureter). This cohort includes all patients with upper tract malignancy who in the opinion of the investigators qualify for radical surgery (nephroureterectomy or distal ureter resection). Urothelial carcinoma of the upper urinary tract qualifies as high-risk disease if any of the below factors are present:
2.1. Hydronephrosis
2.2. Tumour size >2 cm on cross-sectional imaging
2.3. High-grade cytology
2.4. High-grade biopsy
2.5. Multifocal disease
2.6. Variant histology
2.7. Previous radical cystectomy for urothelial cancer of the bladder
All patients undergoing radical surgery with curative intent in the opinion of the investigator are eligible. Radical surgical interventions include nephroureterectomy or distal ureteral resection.

General inclusion criteria:
Each patient must meet all of the following inclusion criteria to be enrolled in the study:
1. Willing and able to provide written informed consent
2. Ability to comply with the protocol
3. Age ≥18 years
4. Residual disease after TURBT or URS (surgical opinion, endoscopy or radiological presence)
5. Fit and planned for radical surgery with curative intent in the opinion of the investigator (according to local guidelines)
6. N0 or M0 disease CT or MRI (within 4 weeks of registration)
7. Representative formalin-fixed paraffin-embedded (FFPE) tumour samples with an associated pathology report that are determined to be available and sufficient for central testing
8. Patients who refuse neoadjuvant cisplatin-based chemotherapy or in whom neoadjuvant cisplatin-based therapy is not appropriate
9. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
10. Negative pregnancy test within 2 weeks of Day 1 Cycle 1 for female patients of childbearing potential
11. For female patients of childbearing potential to use a highly effecting form(s) of contraception (i.e. one that results in a low failure rate [<1% per year] when used consistently and correctly) and to continue its use for 5 months after the last dose of atezolizumab
12. Adequate hematologic and end-organ function within 4 weeks prior to the first study treatment defined by the following:
12.1. ANC ≥1500 cells/µl (without granulocyte colony-stimulating factor support within 2 weeks prior to Cycle 1, Day 1)

12.2. WBC counts >2500/µl
12.3. Lymphocyte count ≥500/µl
12.4. Platelet count ≥100,000/µl (without transfusion within 2 weeks prior to Cycle 1, Day 1)
12.5. Haemoglobin ≥9.0 g/dl (patients may be transfused or receive erythropoietic treatment to meet this criterion)
12.6. AST or ALT and alkaline phosphatase ≤2.5 times the institutional upper limit of normal (ULN) and serum bilirubin level ≤.5 times the institutional ULN (patients with known Gilbert disease who have serum bilirubin level ≤3 × the institutional ULN may be enrolled)
12.7. INR and aPTT ≤ 1.5 × the institutional ULN. This applies only to patients who are not receiving therapeutic anticoagulation; patients receiving therapeutic anticoagulation should be on a stable dose
12.8. Calculated creatinine clearance ≥20 ml/min (Cockcroft-Gault formula)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
1. Pregnant and lactating female patients
2. Major surgical procedure within 4 weeks prior to enrolment or anticipation of need for a major surgical procedure during the course of the study other than for diagnosis
3. Previously intravenous chemotherapy for urothelial cancer
4. Patients with prior allogeneic stem cell or solid organ transplantation
5. Prior treatment with CD137 agonists, anti-CTLA-4, anti-programmed death-1 (PD-1), or anti-PD-L1 therapeutic antibody or pathway-targeting agents
6. Patients must not have had oral or IV steroids for 14 days prior to study entry. The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed
7. Received therapeutic oral or intravenous (IV) antibiotics within 14 days prior to enrolment (patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible)
8. Administration of a live, attenuated vaccine within 4 weeks prior to enrolment or anticipation that such a live, attenuated vaccine will be required during the study
9. Treatment with systemic immunostimulatory agents (including but not limited to interferons

or interleukin [IL]–2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to enrolment
10. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 4 weeks prior to enrolment
11. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome)
12. Malignancies other than UC within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (Gleason score ≤ 3 + 4 and PSA < 10 ng/mL undergoing active surveillance and treatment naive)
13. Severe infections within 4 weeks prior to enrolment in the study including but not limited to hospitalization for complications of infection, bacteraemia, or severe pneumonia
14. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction within 3 months prior to enrolment, unstable arrhythmias, or unstable angina
15. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan (History of radiation pneumonitis in the radiation field (fibrosis) is permitted)
16. Patients with uncontrolled Type 1 diabetes mellitus. Patients with Type 1 diabetes controlled on a stable insulin regimen are eligible
17. Patients with active hepatitis infection (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA
18. Positive test for HIV
19. Patients with active tuberculosis
20. History of gastrointestinal disorders (medical disorders or extensive surgery) which may interfere with the absorption of the study drug
21. Uncontrolled hypercalcemia (>1.5 mmol/l ionized calcium or Ca >12 mg/dl or corrected serum calcium >the institutional ULN) or symptomatic hypercalcemia requiring continued use of bisphosphonate therapy or denosumab. Patients who are receiving bisphosphonate therapy or denosumab specifically to prevent skeletal events and who do not have a history of clinically significant hypercalcemia are eligible. Patients who are receiving denosumab prior to enrollment must be willing and eligible to receive a bisphosphonate instead while on study
22. History of autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis
23. Patients with a history of autoimmune-related hypothyroidism, unless on a stable dose of thyroid-replacement hormone
24. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
25. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the atezolizumab formulation

Date of first enrolment
17/06/2021

Date of final enrolment
31/05/2025

Locations

Countries of recruitment
United Kingdom

England

France

Spain

Study participating centre
St. Bartholomews Hospital
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Churchill Hospital
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Study participating centre

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Study participating centre
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Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan

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			18/11/2026	No	No