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Assessing the safety of atezolizumab being directly administered to the bladder in bladder cancer patients undergoing radical cystectomy

Submission date 20/09/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 02/12/2022	**Overall study status** Ongoing	
Last Edited 28/07/2026	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Bladder cancer is a common disease that can be difficult to manage. For some, it can be treated using medicines given into the bladder, whilst others need the removal of their entire bladder.

In INVEST, we are investigating a drug called atezolizumab that could be used to control bladder cancer. The long-term hope is that the results from INVEST will reduce the need for bladder removal in the future. This is an immunotherapy treatment (a type of treatment that helps your immune system fight cancer), usually given directly into the bloodstream via a vein (intravenously). We are investigating whether atezolizumab can be safely given directly into the bladder and whether there is any suggestion it may work on cancer and the immune system.

Who can participate?
Adults scheduled to have bladder removal surgery (cystectomy) as a treatment for their bladder cancer

What does the study involve?
We are investigating giving atezolizumab directly into the bladder via two routes. These are introducing it directly into the bladder using a catheter (passive instillation) and injecting it directly into the tumour within the bladder (direct injection). We are also exploring which dose to use (600mg or 1200mg), and how many doses (single dose, or multiple doses: weekly for 3-6 weeks).
We will give the drug to a small number of participants (between 6-62 in total). This means we can find the best dose, check for side effects, and explore how the drug works on cancer. A larger trial will be required to fully test the performance of the drug.

Study treatment will take place between the diagnosis of bladder cancer and cystectomy. Participants will be followed up after surgery for three months, and we will collect data on participants' overall health status at the end of the study (2 years after registration of the final participant).

What are the possible benefits and risks of participating?
There is no guarantee that participants will benefit from the study treatment, but they will still receive the same cancer treatment whether or not they take part. Also, surgery will not be delayed by going into the study. It is not yet known whether atezolizumab treatment will work for localised bladder cancer. If it does work, it is hoped that it may treat the cancer and stop it from coming back or spreading into the deeper layers of the bladder. However, this cannot be guaranteed, and any benefits may be temporary.

Participation in this study may not be of direct benefit to individual participants, but it is possible that it may be of benefit to future cancer patients. Information from this study will help doctors to learn more about atezolizumab when it is administered directly in the bladder and whether this may be a step forward for the treatment of bladder cancer in the future. Without research of this sort, improvements in cancer treatments are not possible. All study participants could benefit from more close monitoring than would be possible outside of the study.
All treatment for cancer involves some risks as well as potential benefits. Side effects may be experienced from this drug, however, as this study is investigating new methods of administering the drug, we believe that these side effects may be less likely. Previous patients who have been treated with this drug have had it administered via intravenous infusion, whereas this study is administering it directly into the bladder. This may reduce the chance of experiencing side effects that affect areas other than the bladder.

In addition, the study treatment methods (passive instillation and direct injection) are well established. However, as very few patients have received atezolizumab via one of these treatment methods before, there is a chance that there may be side effects which are new, or which differ from those that doctors would usually expect to see. Participants will be monitored frequently and supportive treatment administered to minimise the side effects of treatment.

There may be additional and longer hospital visits as part of taking part in the study. We have mapped trial treatment and follow-up time points onto the existing standard of care timepoints to minimise inconvenience.
There are blood and urine samples as part of the study.
There are tissue samples taken as part of the study, but these are collected from diagnostic tissue and from the bladder following radical cystectomy (both taken as the standard of care).
There are risks from exposure to ionising radiation and procedures used to complete the CT/CT urogram scans and (optional) MRI-PET scans.
Participants will be fully informed of the potential risks and burdens involved in taking part in this research study, both by the clinical research team at their hospital and in the Participant Information Sheet, and will be given opportunities to ask questions prior to consent and during their participation.
The trial will be monitored for trial conduct and the safety of participants, and any concerns will be appropriately escalated and handled as per relevant legislation, regulatory requirements and local standard operating procedures.
The Safety Review Committee reviews accruing data at least monthly and has the authority to make changes, such as requesting extra assessments, slowing recruitment or closing.

Where is the study run from?
University of Leeds (UK)

When is the study starting and how long is it expected to run for?
August 2022 to March 2028

Who is funding the study?
Roche (Switzerland)

Who is the main contact?
ctru_invest@leeds.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-atezolizumab-before-surgery-for-urothelial-cancer-of-the-bladder-invest

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Public

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Additional identifiers

Clinical Trials Information System (CTIS)
2021-006537-19

Integrated Research Application System (IRAS)
1004693

Central Portfolio Management System (CPMS)
52636

Protocol serial number
STH21594

Study information

Scientific Title
INVEST: Phase I study of Intravesical immunotherapy for bladder cancer patients undergoing radical cystectomy

Acronym
INVEST

Study objectives
Primary objective of the trial:
The trial aims to investigate the safety and preliminary activity of both passive installations of atezolizumab (via catheter into the bladder directly) and direct injection of atezolizumab into the tumour/bladder wall.

Dose confirmation stages:
To determine the toxicity and recommended dose (RD) for further investigation of atezolizumab by passively instilled intravesical administration.
To determine the toxicity and RD for further investigation of atezolizumab when injected directly into the tumour/bladder wall via the intravesical route.

Dose expansion stages:
To evaluate the safety and toxicity of passively instilled intravesical atezolizumab at the RD.
To evaluate the safety and toxicity of directly injected atezolizumab into the tumour/bladder wall at the RD.

Secondary objectives of the trial:
All stages of the trial:
To estimate progression-free survival (the length of time from registration that a patient lives with the disease without it getting worse)
To assess treatment compliance (the feasibility of delivering trial treatment according to

protocol schedule)
To assess the pathological complete response (pCR) rate (the disappearance of all signs of cancer in the tissue samples removed during cystectomy following trial treatment, as reported by the local pathologist)

Dose confirmation stages:
To assess safety and toxicity

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 09/11/2022, London - Central Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, United Kingdom; +44 (0)207 104 8225; londoncentral.rec@hra.nhs.uk), ref: 22/LO/0651

Primary study design
Interventional

Study design
Open-label non-randomized phase Ib window of opportunity study

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Urothelial cell carcinoma of the bladder

Interventions
The study will examine two treatment routes (one for each route of administration – passive instillation and direct injection). These treatment routes are completely independent of each other and will run in parallel. Patients will be allocated to a route based on cohort availability and local logistics. Within each treatment route, the trial will be composed of two sequential dose confirmation stages (single dose of atezolizumab, then multiple doses of atezolizumab), followed by an expansion stage.
The passive instillation treatment method is regularly used in standard care for other types of earlier bladder cancer using drugs such as BCG. The bladder will be filled with a solution of atezolizumab via a urethral catheter, leaving it in place for approximately an hour, and then draining it. This will be done under local anaesthetic. Following treatment, participants will be observed and will be kept within the department for 1 hour before voiding urine/instillation, if comfortable.
For direct injection, atezolizumab is injected directly into the tumour and bladder wall within the bladder. A cystoscope is passed through the urethra into the bladder. Atezolizumab is then injected into the tumours and the bladder wall directly. This is done under local anaesthetic. This method is used regularly for Botox injections into the bladder to treat incontinence. Following treatment, participants will be observed and kept at the hospital until they have voided urine at least once.
The dose confirmation stages use a conventional 3+3 design to establish the safety of both passive instillation of intravesical atezolizumab (dose confirmation 1a: single dose, followed by dose confirmation 1b: multiple doses) and direct injection of intravesical atezolizumab (dose confirmation 2a: single dose, followed by dose confirmation 2b: multiple doses). Those in the

multiple-dose cohorts will receive one dose of atezolizumab per week for 3-6 weeks. All trial treatments will take place prior to radical cystectomy.
A 600mg dose will be used initially for both treatment routes. In line with the 3+3 design, this may be escalated to 1200mg, if well tolerated. The dose of atezolizumab administered to each cohort will be determined based on the number of dose-limiting toxicities (DLTs) experienced within the preceding cohort.
During the dose confirmation stages, recruitment to a treatment route will be paused to allow safety to be evaluated within that respective route. In addition, the first participant at each dose level and frequency will be followed up until the end of the DLT period to assess safety before additional participants are recruited. To optimise recruitment, the flip-flop (or ping-pong) design will be utilised such that when one treatment route is closed to recruitment, the other treatment route will then be opened to recruitment. This will ensure that eligible patients presenting during the dose confirmation stages are able to be recruited to one of the two treatment routes, maximising the number of patients recruited overall.
Once the RD has been established within dose confirmation 1b or 2b, the respective expansion stage will open to further characterise the safety profile and preliminary information on the activity. If we are not able to establish an RD for multiple dosing (RD1b/RD2b) we will evaluate the RD1a/RD2a single dose in the respective expansion stage.

Intervention Type
Biological/Vaccine

Phase
Phase I

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

Primary outcome(s)
Dose confirmation stages:
Number of DLTs observed during the DLT period for each dose confirmation stage. This will confirm the safety of passively instilled intravesical atezolizumab (single and multiple doses) and of atezolizumab (single and multiple doses) when injected directly into a tumour/bladder wall.
DLTs will be defined as any of the following:
1. A treatment-related toxicity that delays the radical cystectomy (RC) by more than 2 weeks.
2. Grade 3 or higher haematuria.
3. Any grade 3 or higher immune-mediated toxicity.
4. Any serious adverse event (SAE) considered treatment-related
5. Grade 4 haematological or ≥ grade 3 non-haematological toxicity that is considered treatment-related
6. Any other treatment-related event decided by the SRC to be clinically significant.
DLTs will be assessed from day 1 of trial treatment (TT) until RC, or 4 weeks after the last dose if RC does not occur.

Dose expansion stages:
For the dose expansion stages, the primary endpoints are safety and toxicity, assessed by the occurrence of adverse events (AEs), adverse reactions (ARs), adverse events of special interest (AEoSIs), serious adverse events (SAEs), serious adverse reactions (SARs), suspected unexpected serious adverse reactions (SUSARs) and related unexpected serious adverse events (RUSAEs), graded according to NCI CTCAE Version 5.0.

AEs and ARs: from day 1 of TT until 30 days post-RC (or planned RC if RC does not occur) or until initiation of new systemic anti-cancer treatment, whichever occurs first.
RUSAEs: from RC until 30 days post-RC for participants undergoing RC only
AEoSIs and SAEs: from day 1 of TT until 90 days post-RC (or planned RC if RC does not occur) or until initiation of new systemic anti-cancer treatment, whichever occurs first. SAEs will also be collected following informed consent but prior to initiation of TT, only if the SAE is caused by a protocol-mandated intervention
SARs and SUSARs: from day 1 of TT until trial end

Key secondary outcome(s)
For both dose confirmation and dose-expansion stages:
1. Progression-free survival
2. Treatment compliance as assessed by dose omissions, dose delays, dose reductions, delays to RC and RC cancellations
3. Pathological complete response rate
Progression-free survival will be assessed from the date of registration until 2 years post-¬registration of the final participant.
Treatment compliance is collected from day 1 of trial treatment to the time of RC, or until the planned RC date in the event no surgery takes place.
Pathological complete response is assessed using the local pathologist report following RC.

For dose confirmation stages only:
Safety and toxicity as assessed by the occurrence of AEs, ARs, AEoSIs, SAEs, SARs, SUSARs and RUSAEs graded according to NCI CTCAE Version 5.0.
The timing of the safety and toxicity secondary endpoints is the same as the timing for the dose expansion safety and toxicity primary endpoint given “Primary outcome measure” above.

Completion date
31/03/2028

Eligibility

Key inclusion criteria
1. Patient must be fully informed about the study and have signed the informed consent form
2. Patients with mixed histologies are required to have predominant urothelial cell carcinoma in the bladder
3. Patients with pTis to T4N0 M0 for whom radical cystectomy is planned treatment for their urothelial cell carcinoma of the bladder. Radical cystectomy must be scheduled at least 6 weeks after confirmation of eligibility. This will include both MIBC and high-grade NMIBC tumours.
4. Patients with MIBC must be ineligible for cisplatin-based neo-adjuvant chemotherapy or have declined neoadjuvant chemotherapy
5. Aged 18 years old and over
6. Performance status: Eastern Co-operative Oncology Group (ECOG) 0-2
7. Patient must be willing and able to comply with the protocol, have mental capacity and (if a woman of childbearing potential [WOCBP]) use effective contraception throughout treatment and for 5 months after treatment completion
8. Have diagnostic biopsy tissue material (i.e., transurethral resection of bladder tumour [TURBT] sample) available for use in the trial
9. Adequate organ function within 28 days prior to confirmation of eligibility and 7 days of study treatment as defined below:
9.1. White blood cell count (WBC): >2X10^9/L

9.2. Lymphocyte count: ≥ 0.5 x 10^9/L (≥ 500/µL)
9.3. Neutrophils: ≥1.5 X10^9/L
9.4. Platelets: ≥100 X10^9/L
9.5. Estimated glomerular filtration rate (eGFR): >30mL/min
9.6.Serum total bilirubin: <1.5 x upper limit of normal (ULN) OR ≤3 ULN in a patient with Gilbert's Syndrome AND direct bilirubin ≤ULN
9.7.Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT): ≤1.5 x ULN
9.8.Haemoglobin: ≥90g/L
9.9.Urine dipstick: Negative for nitrites. (If positive then a negative MSU is required. If positive MSU then infection must be treated prior to starting treatment.)

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. Active urinary tract infection in last 2 weeks prior to assessing eligibility.
2. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteraemia, or severe pneumonia, or any active infection that could impact patient safety.
3. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment. Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease (COPD) exacerbation) are eligible for the study.
4. Presence of indwelling urinary stent or history of vesico-ureteric reflux.
5. Other intravesical therapy within 2 weeks of assessing eligibility.
6. Prior radiotherapy to bladder or planned radiotherapy to bladder.
7. Reduced bladder capacity (defined as an inability to hold an intravesical instillation for 1 hour).
8. Positive pregnancy test (as eligibility assessment for WOCBP), breast-feeding women, patients intending to become pregnant during and within 5 months after last dose of atezolizumab, or patients unwilling to comply with contraception requirements.
9. Patients with active, known, or suspected autoimmune disease with the following exceptions:
9.1. Patients with vitiligo or alopecia;
9.2. Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement;

9.3. Any chronic skin condition that does not require systemic therapy;
9.4. Patients with coeliac disease controlled by diet alone;
9.5. Patients with Crohn's disease or ulcerative colitis (must be inactive stable disease).
10. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumour necrosis factor-α [TNF-α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
10.1. Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
10.2. Patients who received mineralocorticoids (e.g., fludrocortisone), inhaled or low dose corticosteroids for COPD or asthma, or low-dose corticosteroids for orthostatic hypotension or adrenal insufficiency are eligible for the study.
11. Positive test for hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV).
12. Patients considered a poor medical risk by the investigator due to a serious, uncontrolled medical disorder, non-malignant system disease or active uncontrolled infection. Examples include but are not limited to; active COVID-19 infection, any psychiatric disorder that prohibits obtaining informed consent or protocol compliance.
13. Prior systemic immune checkpoint inhibitor therapy (prior BCG is permitted).
14. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins.
15. Known hypersensitivity to Chinese hamster ovary cell products.
16. Prior allogeneic stem cell or solid organ transplantation.
17. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during atezolizumab treatment or within 5 months after the final dose of atezolizumab.
18. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest computed tomography (CT) scan (history of radiation pneumonitis in the radiation field (fibrosis) is permitted).
19. Active tuberculosis.
20. Significant cardiovascular disease (such as New York Heart Association Class II or greater cardiac disease, myocardial infarction, or cerebrovascular accident) within 3 months prior to initiation of study treatment, unstable arrhythmia, or unstable angina.
21. Major surgical procedure, other than for diagnosis or TURBT, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study (except for radical cystectomy).
22. History of leptomeningeal disease.
23. Uncontrolled or symptomatic hypercalcemia (ionized calcium >1.5 mmol/L, calcium >12 mg /dL, or corrected calcium greater than ULN).
24. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).
25. Uncontrolled tumour-related pain.
26. Current treatment with anti-viral therapy for HBV.

Date of first enrolment
04/05/2023

Date of final enrolment

31/08/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Weston Park Hospital
Cancer Clinical Trials Centre
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Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

ROR
https://ror.org/018hjpz25

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
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
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IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article		27/07/2026	28/07/2026	Yes	No
HRA research summary			26/07/2023	No	No
Participant information sheet	version 2.0	22/10/2022	01/12/2022	No	Yes