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A study investigating if a new medication, bintrafusp alfa, can reduce the size of urothelial carcinoma, a type of bladder cancer, before surgery to remove the bladder

Submission date 04/05/2021	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 10/05/2021	**Overall study status** Completed	
Last Edited 08/04/2026	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Urothelial carcinoma is a type of bladder cancer where cancer cells develop from the cells of the bladder lining. Urothelial carcinoma can become invasive which means that it has grown into a deeper layer of the bladder. Treatment for this type of cancer usually involves surgical removal of the bladder (cystectomy)

This study aims to investigate if a new medication, bintrafusp alfa, can reduce the size of bladder cancer before surgery.

Who can participate?
Patients recently diagnosed with urothelial carcinoma (a type of bladder cancer) requiring cystectomy (surgery to remove the bladder).

What does the study involve?
Eligible patients will receive 4 doses of bintrafusp alfa (1200mg flat dose) at 14 day intervals before undergoing surgery to remove the bladder. Patients will attend study visits at 6, 12 and 24 weeks following their surgery. After the 24-week post-surgical visit, patients will enter a follow up phase during which they will be contacted annually for 2 years after their surgery to collect survival and disease status data. Patients will have scans and tumour samples will be collected before and after treatment with bintrafusp alfa to assess how well the treatment has worked.

What are the possible benefits and risks of participating?
This trial aims to find out information that may help people with bladder cancer. There is no guarantee that there will be a benefit to participants during their treatment as this is unknown at this stage.

Participants may have side effects from the drugs or procedures carried out in this study and they will vary from person to person. Everyone taking part in the study will be followed carefully for any side effects through regular checks such as blood tests, vital signs, physical examinations and review of any illnesses or symptoms. Common side-effects (though not an exhaustive list) include, benign (not cancerous) skin growths, rash, insufficient hormone production by the adrenal glands and thyroid gland, fever, skin cancer, lung diseases which may cause inflammation or scarring of the lungs, itchy skin and infusion site reaction e.g. pain, redness, swelling or itching.

Where is the study run from?
The study is sponsored by Queen Mary University of London (UK) and is being run from coordinating centres in the UK, Spain and France.

When is the study starting and how long is it expected to run for?
April 2020 to January 2025

Who is funding the study?
Merck Healthcare KGaA (Germany)

Who is the main contact?
PEBBLE Trial Coordinator, bci-pebble@qmul.ac.uk

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT04878250

Integrated Research Application System (IRAS)
1003458

Central Portfolio Management System (CPMS)
48052

Study information

Scientific Title
A phase II study investigating preoperative bintrafusp alfa in operable urothelial carcinoma of the bladder

Acronym
PEBBLE

Study objectives
Primary:
1. To assess the efficacy of bintrafusp alfa before undergoing radical cystectomy with bilateral pelvic lymph node dissection with respect to pathological complete response rate (pCRR) in patients with T2-T4aN0-1M0 urothelial carcinoma of the bladder.

Secondary:
2. To assess the effect of 4 x doses of bintrafusp alfa at 14 day intervals before undergoing radical cystectomy with bilateral pelvic lymph node dissection on immune parameters (dynamic changes in TGFb, T-effector signatures and CD8 count) in patients with T2-T4aN0-1M0 urothelial carcinoma of the bladder.
3. To evaluate the safety and tolerability of bintrafusp alfa before undergoing radical cystectomy with bilateral pelvic lymph node dissection in this population.
4. To assess the efficacy of bintrafusp alfa given before undergoing radical cystectomy with bilateral pelvic lymph node dissection with respect to anti-tumour effects based on Investigator assessed disease free survival (DFS).
5. To assess the efficacy of bintrafusp alfa given before undergoing radical cystectomy with bilateral pelvic lymph node dissection with respect to overall survival (OS).

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 18/02/2021, North West – Greater Manchester Central Research Ethics Committee (Barlow House, 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0) 2071048007; gmcentral.rec@hra.nhs.uk), ref: 21/NW/0005

Primary study design
Interventional

Study design
Interventional non-randomized

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Bladder Cancer

Interventions
Eligible patients will receive 4 doses of bintrafusp alfa (1200mg flat dose) at 14 day intervals before undergoing radical surgery. Patients will attend study visits at 6, 12 and 24 weeks following their surgery. After the 24-week post-surgical visit, patients will enter a follow up phase during which they will be contacted annually for 2 years after their surgery to collect survival and disease status data. The efficacy of bintrafusp alfa will be assessed on CT/MRI scan images and tumour tissue samples collected at baseline and after treatment with bintrafusp alfa.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
bintrafusp alfa

Primary outcome(s)
Pathological complete response rate (pCRR) defined as no microscopic evidence (pT0/Tis/Cis) of residual disease in the bladder based on histological evaluation of the resected bladder specimen collected during radical surgery post–treatment with 4 cycles (1 cycle = 14 days) of bintrafusp alfa.

Key secondary outcome(s)
1. Dynamic changes in TGFb, T-effector signatures and CD8 count measured in tumour samples collected pre- and post-treatment with 4 cycles (1 cycle = 14 days) of bintrafusp alfa.
2. Incidence, nature and severity of adverse events (AE) graded according to NCI-CTCAE v5.0 recorded in case report forms from time of consent until the safety visit, an average of 22 weeks.
3. Disease free survival (DFS) defined as time between the date of enrolment to first evidence of relapse based on local investigator assessments or death, whichever occurs first up to 2 years using patient records.
4. Overall survival (OS) defined as the time between the date of enrolment and death due to any cause up to 2 years using patient records.

Completion date
31/01/2025

Eligibility

Key inclusion criteria
1. Willing and able to provide written informed consent
2. Ability to comply with the protocol
3. Age ≥ 18 years
4. Histopathologically confirmed urothelial carcinoma (T2-T4aN1M0) of the bladder where radical cystectomy with bilateral pelvic lymph node dissection is indicated. Patients with “variant histology” such as micropapillary,plasmocytoid,nested,sarcomatoid,microcystic,squamous and adeno variants of urothelial carcinoma are required to have more than 50% of tumor tissue with

transitional cell pattern.
5. Residual disease after TURBT or endoscopy (surgical opinion,cystoscopy or radiological presence).
6. Fit and planned for surgery (according to local guidelines).
7. N0-1 and M0 disease CT or MRI (within 4 weeks of enrolment). Patients with N2 disease on cross sectional imaging are excluded from the study.
8. Representative formalin-fixed paraffin embedded (FFPE) tumour samples with an associated pathology report that are determined to be available and sufficient for central testing.
9. Patients who refuse neoadjuvant cisplatin-based chemotherapy or in whom neoadjuvant cisplatin-based therapy is not appropriate.
10. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1
11. Negative serum pregnancy test within 14 days of Day 1 Cycle 1 for female patients of childbearing potential.
12. Highly effective method of contraception throughout the study until 2 months after the last dose of bintrafusp alfa for female patients of childbearing potential and 4 months after the last dose of bintrafusp alfa for male patients.
13. Adequate haematologic and end-organ function within 4 weeks prior to the first study treatment defined by the following:
13.1. ANC ≥ 1500 cells/μL (without granulocyte colony-stimulating factor support within 14 days prior to Cycle 1,Day 1)
13.2. WBC counts > 2500/μL
13.3. Lymphocyte count ≥ 500/μL
13.4. Platelet count ≥ 100,000/μL (without transfusion within 14 days prior to Cycle 1,Day 1)
13.5. Haemoglobin ≥ 9.0 g/dL (patients may be transfused or receive erythropoietic treatment to meet this criterion).
13.6. AST or ALT,and alkaline phosphatase ≤ 1.5 times the institutional upper limit of normal (ULN) (patients with known Gilbert disease who have serum bilirubin level ≤ 3 × the institutional ULN may be enrolled).
13.7. 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.
13.8. Calculated creatinine clearance ≥ 30 mL/min (Cockcroft-Gault formula)

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. 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. Previous intravenous chemotherapy or immune therapy for bladder 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. Has received any prior radiotherapy to the bladder.
7. Patients must not have had oral or intravenous (IV) steroids for 14 days prior to Cycle 1 Day 1. The use of inhaled corticosteroids,physiologic replacement doses of glucocorticoids (i.e.,for adrenal insufficiency),and mineralocorticoids (e.g.,fludrocortisone) is allowed at physiologic doses ≤10 mg/day of prednisone or equivalent.
8. Received therapeutic 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).
9. 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. Seasonal flu vaccines that do not contain a live virus are permitted.
10. 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.
11. Treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 4 weeks prior to enrolment.
12. 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).
13. Malignancies other than urothelial carcinoma of the bladder within 3 years prior to enrolment 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).
14. Severe infections within 4 weeks prior to enrolment including but not limited to hospitalisation for complications of infection,bacteraemia,or severe pneumonia.
15. Significant cardiovascular disease,such as New York Heart Association cardiac disease (Class II or greater),myocardial infarction within 6 months prior to enrolment,unstable arrhythmias,or unstable angina.
16. History of idiopathic pulmonary fibrosis (including pneumonitis),drug-induced pneumonitis, organising 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).
17. Patients with uncontrolled Type 1 diabetes mellitus. Patients with Type 1 diabetes controlled on a stable insulin regimen are eligible.
18. 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.
19. Positive test for HIV.
20. Patients with active tuberculosis.
21. 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. Patients with diabetes type I,vitiligo,psoriasis,or hypo- or hyperthyroid diseases not requiring immunosuppressive treatment are eligible. Replacement therapy (eg, thyroxine,insulin,or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed. Patients with a history of autoimmune-related hypothyroidism,unless on a stable dose of thyroid-replacement hormone.
22. History of bleeding diathesis or recent major bleeding events (i.e. Grade ≥ 2 bleeding events in the 30 days prior to treatment
23. Has a diagnosis of immunodeficiency.
24. Receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of study drug.
25. History of severe allergic,anaphylactic,or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
26. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of the bintrafusp alfa formulation.
27. Serious non-healing wound/ulcer/bone fracture.

Date of first enrolment
30/06/2021

Date of final enrolment
31/10/2022

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
St Bartholomew's Hospital
Barts Health NHS Trust
West Smithfield
London
England
EC1A 7BE

Sponsor information

Organisation
Queen Mary University of London

ROR
https://ror.org/026zzn846

Funder(s)

Funder type
Industry

Funder Name
Merck KGaA

Alternative Name(s)
Merck, Merck Group, Merck KGaA, Darmstadt, Germany

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
Germany

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			26/07/2023	No	No