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A Phase II trial looking at trimodality therapy with or without durvalumab for patients with muscle-invasive bladder cancer

Submission date 23/04/2020	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 25/11/2020	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 29/04/2025	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol

Background and study aims
Muscle invasive bladder cancer is cancer that spreads into the muscle wall of the bladder. Sometimes, cancer patients receive an initial treatment, followed by additional treatment to lower the chance of cancer coming back. The standard or usual treatment for muscle-invasive bladder cancer is observation, or surveillance, after having surgery, chemotherapy and radiation therapy. This study is looking at whether a new type of drug called durvalumab can be used in combination with the initial treatment. Durvalumab is an immunotherapy drug and not a chemotherapy drug. It has been tested in many different types of cancers. Durvalumab works by allowing the immune system to detect cancer and reactivate the immune response. This may help to slow down the growth of cancer or may cause cancer cells to die. Durvalumab has been shown to shrink tumours in animals. It has been studied in more than 5000 people and seems promising but it is not clear if it can offer better results than standard treatment so further data is required. Recently, clinical trials have shown that a drug similar to durvalumab can help some patients with bladder cancer, especially in combination with prior treatment. The aim of this study is to find out what effects durvalumab has on bladder cancer when combined with treatment patients have already received. These effects will be compared to those experienced by patients on surveillance only.

Who can participate?
Patients who have muscle-invasive bladder cancer

What does the study involve?
Participants are randomly allocated to receive durvalumab every 4 weeks for 12 months or surveillance. The duration of follow-up is until cancer recurrence or death. The following tests will be done as part of this study. Some of these tests may be done as part of standard care, in which case the results may be used. Some of these tests may be done more frequently than if participants were not taking part in this study and some may be done solely for the purpose of the study.
1. Blood tests
2. Urine tests

3. Physical examination
4. Pregnancy test (only for women of childbearing potential)
5. Magnetic resonance imaging (MRI) – a scan that uses a strong magnet to produce pictures of areas inside the body such as organs and other tissue, and inside of bones. MRI scans often involve injecting a dye into a vein
6. Computed tomography (CT) scan – a series of x-rays of the body from many angles that are turned into three-dimensional pictures on a screen. CT scans often involve injecting a dye into a vein
7. A special x-ray to study the heart (MUGA scan or ECHO)
8. A test to see how your heart is working called an ECG
9. insertion of a central venous catheter (also called central venous line, central line or central catheter). This is a small tube attached to a needle, which is inserted into a large vein (in the neck, chest or groin) that leads to the heart. It allows easy access to veins for taking blood and giving medications and transfusions through the small tube so that patients do not need a needle poke each time.
10. Cystoscopy with bladder biopsy – a procedure in which the doctor looks into the bladder with a special telescope called a cystoscope. During this procedure, a small piece of tissue is removed and sent to a lab for testing. Participants will have already undergone this test as part of standard care. This test will not be completed more often than usual during the study.
11. Positron emission tomography (PET) – a scan to help show how organs and tissues are working by tracing where a small amount of glucose (a sugar) that includes a tiny amount of radioactivity goes into body after it has been injected into a vein.

What are the possible benefits and risks of participating?
Participants are at risk of side effects if they are allocated to receive durvalumab. The study doctor will watch them closely to see if they have side effects. When possible, other drugs will be given to make side effects less serious and more tolerable. A full list of possible side effects will be made available to participants if they wish to be considered for this study. At this time the researchers cannot say if there will be any benefit to participants. This study is looking at all the possible risks and benefits for patients with muscle-invasive bladder cancer receiving durvalumab.

Where is the study run from?
Southampton Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
November 2018 to December 2026

Who is funding the study?
1. Cancer Research UK
2. AstraZeneca (UK)

Who is the main contact?
Dr Simon Crabb
uhs.urologyresearchteam@nhs.net

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-durvalumab-after-treatment-for-bladder-cancer-bl13

Study website
https://www.southampton.ac.uk/ctu/trialportfolio/listoftrials/bl13.page

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
2019-001310-42

IRAS number
261447

ClinicalTrials.gov number
NCT03768570

Secondary identifying numbers
IRAS 261447

Study information

Scientific Title
A randomized phase II trial assessing trimodality therapy with or without adjuvant durvalumab (MEDI4736) to treat patients with muscle-invasive bladder cancer

Acronym
BL13

Study objectives
To determine whether durvalumab given after standard trimodality therapy improves disease-free survival when compared to surveillance alone in patients with T2 or more muscle-invasive bladder cancer.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 22/01/2020, East of England - Cambridgeshire and Hertfordshire Research Ethics Committee (The Old Chapel, Royal Standard Place, Nottingham NG1 6FS, UK; +44 (0)207 104 8106; cambsandherts.rec@hra.nhs.uk), REC ref: 19/EE/0348

Study design
Interventional multi-centre randomized phase II trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Muscle-invasive bladder cancer

Interventions
The patients will be randomized on an electronic database at the time of registration to the durvalumab arm or the surveillance arm in a 1:1 fashion. The durvalumab arm patients will receive 1500 mg intravenous on day 1 of the 4-week cycle, every 4 weeks for 12 months. The duration of follow-up is until recurrence or death.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome measure
Disease-free survival, which is defined as the time from the randomization to the time of the first event that is either recurrent (local or distant) bladder cancer, a new primary bladder cancer or death from any cause. Measured by:
1. Time to death
2. Time to recurrence as measured by:
2.1. CT scan at baseline, weeks 8, 12, 24, 48. Post treatment/surveillance no recurrence every 3 months for the first 2 years, then at months 30 & 36, then annually. Post recurrence every 6

months until death
2.2. Cystoscopy with bladder bioscopy and urine cytology at weeks 12, 24, 48. Post treatment /surveillance no recurrence every 3 months, post recurrence every 6 months until death

Secondary outcome measures

1. Non-muscle-invasive bladder cancer recurrence rate (< T2) measured by:
1.1. CT scan at baseline, weeks 8, 12, 24, 48. Post treatment/surveillance no recurrence every 3 months for the first 2 years, then at months 30 & 36, then annually. Post recurrence every 6 months until death
1.2. Cystoscopy with bladder bioscopy and urine cytology at weeks 12, 24, 48. Post treatment /surveillance no recurrence every 3 months, post recurrence every 6 months until death
2. Loco-regional control rate (LCR) measured by cystoscopy with bladder bioscopy and urine cytology at 12 weeks
3. Overall survival and bladder-intact disease-free survival measured by:
3.1. CT scan at baseline, weeks 8, 12, 24, 48. Post treatment/surveillance no recurrence every 3 months for the first 2 years, then at months 30 & 36, then annually. Post recurrence every 6 months until death
3.2. Cystoscopy with bladder bioscopy and urine cytology at weeks 12, 24, 48. Post treatment /surveillance no recurrence every 3 months, post recurrence every 6 months until death
4. Patterns of disease recurrence between study arms measured by:
3.1. CT scan at baseline, weeks 8, 12, 24, 48. Post treatment/surveillance no recurrence every 3 months for the first 2 years, then at months 30 & 36, then annually. Post recurrence every 6 months until death
3.2. Cystoscopy with bladder bioscopy and urine cytology at weeks 12, 24, 48. Post treatment /surveillance no recurrence every 3 months, post recurrence every 6 months until death
5. Metastasis-free survival between arms measured by:
5.1. CT scan at baseline, weeks 8, 12, 24, 48. Post treatment/surveillance no recurrence every 3 months for the first 2 years, then at months 30 & 36, then annually. Post recurrence every 6 months until death
5.2. Cystoscopy with bladder bioscopy and urine cytology at weeks 12, 24, 48. Post treatment /surveillance no recurrence every 3 months, post recurrence every 6 months until death
6. Safety events recorded whenever they occur on treatment
7. Quality of life (QoL) assessed using Functional Assessment of Cancer Therapy-Bladder Cancer (FACT – BL) at baseline, weeks 8, 12, 24 and 48 or end of treatment (either therapy or surveillance)
8. Cost-effectiveness and health economics (Canadian patients only): the incremental cost-effectiveness and cost-utility of durvalumab from a government payer perspective over a DFS time horizon by prospectively collecting economic and resource utilization information:
8.1. Estimated incremental cost-effectiveness ratio reported as a difference in cost per DFS-year (DFS-LY/QALY) gained from durvalumab vs surveillance. The mean overall cost per patient for each of the two study arms will be calculated to estimate the additional cost per DFS life-year gained. The main cost components will be: cost of medications/surveillance during responsive disease (DFS phase), other medical costs during responsive disease, cost for progressive disease which will include BSC or subsequent line of treatments (if appropriate). Disease management, adverse event and disease monitoring costs will be also estimated.
8.2. A partitioned-survival model (Markov model) will be developed using data obtained from the trial. Different parametric models will be evaluated to fit data from the trial in order to evaluate the ICER/ICUR over a 3-, 5- and 10-year horizon.

Overall study start date

01/11/2018

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Histologic diagnosis of urothelial carcinoma of the bladder. Patients with mixed histology and focal differentiation are eligible but patients with pure small cell histology will be excluded
2. Stage T2-T4a N0M0 at time of diagnosis (AJCC-TNM version 8) based on trans-urethral resection of bladder tumour (TURBT), imaging, and/or bimanual examination under anesthesia (EUA)
3. CT scan of the chest/abdomen/pelvis within 8 weeks from enrollment, showing no evidence of metastatic disease
4. Patients must be ≥18 years of age
5. Patients must have a life expectancy greater than 6 months
6. Patients must have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 (see Appendix I) and a bodyweight of >30 kg
7. Patients must have adequate hematologic reserve: Platelet count ≥75 x 10e9/l, Absolute neutrophils ≥1.0 x 10e9/l. Anemia will be corrected to minimum hemoglobin of 90 g/l with red cell transfusions, if necessary
8. Patients must have an estimated creatinine clearance (Cockcroft-Gault Equation) ≥30 ml/min
9. Patients must have adequate liver function with a bilirubin ≤1.5 ULN (if confirmed Gilbert's, eligible providing bilirubin ≤3 x UNL) and AST/ALT (SGOT/SGPT) <2.5 x the upper normal limit
10. All patients must have a tumour block from their primary tumour available and consent to release the block/cores/cut slides for correlative analyses and the centre/pathologist must have agreed to the submission of the specimen(s)
11. Patients have completed prior trimodality therapy (TMT) consisting of surgery, chemotherapy and radiation therapy treatment prior to enrollment on the BL.13 study
12. Patients should begin protocol treatment within 42 days after completion of TMT
13. Prior Surgery: Patients have completed transurethral resection, prior to study enrollment
14. Prior Chemotherapy:
14.1. Patients may have completed up to 4 cycles of cisplatin-based neoadjuvant chemotherapy. Adjuvant chemotherapy is not permitted
14.2. Patients will have received cisplatin, given intravenously during the radiation therapy
OR
14..3. Patients may have received fluorouracil and mitomycin given intravenously once weekly or gemcitabine as an alternative to cisplatin during radiotherapy
15. Prior Radiation Therapy: The patient should have received radiation therapy with curative intent as part of trimodality therapy (TMT) given per institutional standards. These standards should ensure that radiotherapy treatment was delivered using: Dose and fractionation protocol considered as having curative intent; IMRT, VMAT or 4 field conformal techniques; CT-based planning; treatment volume margins specified as per institutional policy; daily imaging for treatment verification
16. Patient is able (i.e. sufficiently fluent) and willing to complete the quality of life questionnaires in either English or French. The baseline assessment must be completed within the required timelines, prior to registration/randomization. Inability (lack of comprehension in English or French, or other equivalent reason such as cognitive issues or lack of competency) to complete the questionnaires will not make the patient ineligible for the study. However, ability but unwillingness to complete the questionnaires will make the patient ineligible
17. Patient consent must be appropriately obtained in accordance with applicable local and regulatory requirements. Each patient must sign a consent form prior to enrollment in the trial

to document their willingness to participate
18. A similar process must be followed for sites outside of Canada as per their respective cooperative group's procedures
19. Patients must be accessible for treatment and follow-up. Patients registered on this trial must be treated and followed at the participating centre. This implies there must be reasonable geographical limits (for example 1 ½ hour's driving distance) placed on patients being considered for this trial. The patient's city of residence may be required to verify their geographical proximity. (Call the CCTG office (613-533-6430) if questions arise regarding the interpretation of this criterion.) Investigators must assure themselves the patients registered on this trial will be available for complete documentation of the treatment, adverse events, and follow-up
20. Patients must agree to return to their primary care facility for any adverse events which may occur through the course of the trial
21. In accordance with CCTG policy, protocol treatment is to begin within 2 working days of patient enrollment
22. Women/men of childbearing potential must have agreed to use a highly effective contraceptive method during and for 3 months following treatment. A woman is considered to be of "childbearing potential" if she has had menses at any time in the preceding 12 consecutive months. In addition to routine contraceptive methods, "effective contraception" also includes heterosexual celibacy and surgery intended to prevent pregnancy (or with a side-effect of pregnancy prevention) defined as a hysterectomy, bilateral oophorectomy or bilateral tubal ligation, or vasectomy/vasectomized partner. However, if at any point a previously celibate patient chooses to become heterosexually active during the time period for use of contraceptive measures outlined in the protocol, he/she is responsible for beginning contraceptive measures. Women of childbearing potential will have a pregnancy test to determine eligibility as part of the Pre-Study Evaluation; this may include an ultrasound to rule out pregnancy if a false-positive is suspected. For example, when beta-human chorionic gonadotropin is high and partner is vasectomized, it may be associated with tumour production of hCG, as seen with some cancers. The patient will be considered eligible if an ultrasound is negative for pregnancy
23. Prior or concurrent malignancies
24. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
190

Total final enrolment
82

Key exclusion criteria

1. Pre-existing medical conditions precluding treatment
2. Pregnancy or lactating mothers
3. Received prior therapy with an anti-programmed cell death protein 1 (anti-PD-1), anti-PD-L1, including durvalumab anti-programmed cell death-ligand 2 (anti-PD-L2), anti-CD137 (4-1BB ligand, a member of the Tumour Necrosis Factor Receptor [TNFR] family), or anti-Cytotoxic T-lymphocyte-associated antigen-4 (anti-CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways)
4. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease (e.g. colitis or Crohn's disease), diverticulitis with the exception of diverticulosis, celiac disease (controlled by diet alone) or other serious gastrointestinal chronic conditions associated with diarrhea), systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome (granulomatosis with polyangiitis), rheumatoid arthritis, hypophysitis, uveitis, etc, within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
4.1. Patients with alopecia
4.2. Patients with Grave's disease, vitiligo or psoriasis not requiring systemic treatment (within the last 2 years)
4.3. Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement
4.4. Any chronic skin condition that does not require systemic therapy
5. Patients with active or uncontrolled intercurrent illness including, but not limited to:
5.1. Cardiac dysfunction (symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia)
5.2. Active peptic ulcer disease or gastritis
5.3. Active bleeding diatheses
5.4. Psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent;
5.5. Known history of previous clinical diagnosis of tuberculosis
5.6. Known human immunodeficiency virus infection (positive HIV 1/2 antibodies)
5.7. Known active hepatitis B infection (positive HBV surface antigen (HBsAg). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody (anti-HBc) and absence of HBsAg) are eligible
5.8. Known active hepatitis C infection. Patients positive for hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA
6. History of primary immunodeficiency, history of allogenic organ transplant that requires therapeutic immunosuppression and the use of immunosuppressive agents within 28 days of randomization* or a prior history of severe (grade 3 or 4) immune-mediated toxicity from other immune therapy or grade ≥ 3 infusion reaction
* Intranasal/inhaled corticosteroids or systemic steroids that do not to exceed 10 mg/day of prednisone or equivalent dose of an alternative corticosteroid are permissible
7. Current or prior use of immunosuppressive medication within 28 days of study entry, with the exceptions of intranasal and inhaled corticosteroids or systemic chronic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid. Corticosteroids used on study for anti-emetic purpose are allowed. Corticosteroids as premedication for hypersensitivity reactions (e.g. computed tomography [CT] scan premedication) are allowed.
8. Peripheral neuropathy ≥ grade 2 (CTCAE v5.0)
9. History of allergic or hypersensitivity reactions to any study drug or their excipients
10. Mean QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥470 msec in screening ECG measured using standard institutional method or history of familial long QT

syndrome
11. History of interstitial lung disease e.g. pneumonitis or pulmonary fibrosis or evidence of interstitial lung disease on baseline CT scan
12. Any active disease condition which would render the protocol treatment dangerous or impair the ability of the patient to receive protocol therapy
13. Any condition (e.g. psychological, geographical, etc) that does not permit compliance with the protocol
14. Live attenuated vaccination administered within 30 days prior to randomization

Date of first enrolment
01/08/2020

Date of final enrolment
31/01/2023

Locations

Countries of recruitment
Canada

England

Spain

United Kingdom

Study participating centre
University Hospitals Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

Sponsor details
Southampton General Hospital
Tremona Road
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SO16 6YD

+44 (0)2381205556
bl13trial@soton.ac.uk

Sponsor type
Hospital/treatment centre

Website
http://www.uhs.nhs.uk/home.aspx

ROR
https://ror.org/0485axj58

Organisation
Canadian Cancer Trials Group

Sponsor details
Queen's University
10 Stuart Street
Kingston
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marina@ctg.queensu.ca

Sponsor type
Other

Website
http://www.ctg.queensu.ca/

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The trial will be published. The complete journal reference and, where publicly available, the direct link to the article will be posted on the Clinical Trials Results public site of the CCTG website.

Intention to publish date
01/01/2028

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No