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A comparison of standard chemoradiotherapy treatment to standard chemoradiotherapy treatment given in combination with durvalumab to see if the addition of durvalumab leads to improved survival

Submission date	**Recruitment status**	[X] Prospectively registered
24/02/2020	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
03/03/2020	Ongoing	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
08/04/2025	Cancer	[X] Record updated in last year

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-chemoradiotherapy-and-durvalumab-for-invasive-bladder-cancer-radio

Background and study aims

Bladder cancer is the ninth most common cancer diagnosed worldwide. Approximately 24% of newly diagnosed patients have muscle-invasive bladder cancer (cancer that has grown into the muscle layer of the bladder wall). Five-year survival rates are around 45%. Researchers have found that the body's own immune system may slow down or control cancer growth. Sometimes, however, this response stops and the cancer is not killed by the immune system. This is because some patients' cancer cells start to produce proteins that stop the body's immune system from recognising and killing them. Programmed Death Ligand 1 (PD-L1) is one such protein. Durvalumab, a so-called immunotherapy agent, is a type of drug called a monoclonal antibody that is designed to bind to and inactivate PD-L1 thus increasing the immune response. It is hoped that by blocking this protein the immune cells will once again be able to slow down cancer growth. The current standard treatment for muscle-invasive bladder cancer consists of a combination of radiotherapy and low-dose chemotherapy using two drugs: 5-fluorouracil (5FU) and mitomycin C (MMC). This type of treatment is known as chemoradiotherapy and is used as standard of care in the UK. Studies in other cancer types have shown that chemoradiotherapy can enhance the effect of immunotherapy treatment. The aim of this study is to find out whether adding immunotherapy to chemoradiotherapy improves the outcome for patients with muscle-invasive bladder cancer. The immunotherapy drug is called durvalumab, this is a new drug currently used in the treatment of advanced lung cancer.

There are two main purposes of this study:

1. To find out if giving durvalumab in combination with chemoradiotherapy is safe and feasible.
2. To find out if durvalumab combined with chemoradiotherapy is a more effective treatment for muscle-invasive bladder cancer than chemoradiotherapy alone.

Who can participate?
Patients who are 18 years or over who have muscle-invasive bladder cancer and are fit enough to receive the trial treatment

What does the study involve?
Participants are randomly allocated to either the control group or the research group.
The control group are treated with mitomycin C + 5-fluorouracil plus radiotherapy given over a 4=week period. Patients will receive mitomycin C on the first day (day 1) of treatment and 5-fluorouracil on days 1-5 (week 1) and days 16-20 (week 4). They will have radiotherapy treatment 5 days a week (usually with a break over the weekend).
The research group are treated with durvalumab plus mitomycin C plus 5-fluorouracil plus radiotherapy Patients will receive durvalumab the day before they start their chemoradiotherapy, which will be given as described above, they will then receive treatment every 4 weeks up to a maximum of 12 months (13 doses in total).

What are the possible benefits and risks of participating?
As this treatment is new, the researchers cannot be sure that the trial treatment will be any better than the standard treatment for bladder cancer. However, it is hoped that adding durvalumab to chemoradiotherapy will improve patients' condition and prevent the return of their cancer for longer than the other treatments that are available. Patients are at risk of suffering some of the side effects associated with the chemoradiotherapy and immunotherapy used in this trial. In addition, patients taking durvalumab will have additional hospital visits due to the duration of the treatment.

Where is the study run from?
1. Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham (UK)
2. The Clatterbridge Cancer Centre NHS Foundation Trust (UK)
3. East Suffolk and North Essex NHS Foundation Trust (UK)
4. The Royal Marsden NHS Foundation Trust (UK)
5. Nottingham University Hospitals NHS Trust (UK)
7. University Hospitals Birmingham NHS Foundation Trust (UK)
8. Sheffield Teaching Hospitals NHS Foundation Trust (UK)
9. Velindre University NHS Trust (UK)
10. Grampian Health Board (UK)
11. Royal Free London NHS Foundation Trust
12. North West Anglia NHS Foundation Trust (UK)
13. The Newcastle upon Tyne Hospitals NHS Trust (UK)
14. United Lincolnshire Hospitals Trust (UK)
15. University Hospitals of North Midlands NHS Trust (UK)
16. East and North Hertfordshire NHS Trust (UK)

When is the study starting and how long is it expected to run for?
May 2017 to June 2027

Who is funding the study?
AstraZeneca UK Ltd

Who is the main contact?
RadIO Trial Office
RadIO@trials.bham.ac.uk

Study website
http://www.birmingham.ac.uk/research/activity/mds/trials/crctu/trials/RadIO

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2018-003520-37

IRAS number
251669

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 40049, IRAS 251669

Study information

Scientific Title
A multi-stage trial of durvalumab (Medi4736) with chemoradiotherapy with 5-fluorouracil and mitomycin C in patients with muscle-invasive bladder cancer

Acronym
Rad-IO

Study objectives
It is hypothesised that the known synergistic effects of chemotherapy and radiotherapy are augmented by the addition of further therapies and specifically that checkpoint inhibitors like durvalumab can augment the effect of radiotherapy and chemotherapy in muscle-invasive bladder cancer and thus can improve local control and reduce systemic spread.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 07/02/2020, York and The Humber – Sheffield Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, United Kingdom; +44 (0)207 104 8084; nrescommittee.yorkandhumber-sheffield@nhs.net), ref: 19/YH/0379

Study design
Interventional; Design type: Treatment, Drug, Radiotherapy, Immunotherapy; Randomized

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 the contact details to request a patient information sheet

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

Interventions
Current interventions as of 23/11/2023:

The study has the following stages:
Stage 1: assesses feasibility and safety.

Stage 2: assesses disease-free-survival rate at 12 months post-chemotherapy (proportion of patients that survive without any signs or symptoms of their cancer) at 12 months after the end of chemotherapy treatment in a phase II trial setting.

Randomisation will be performed according to a 1:2 ratio (control arm vs. research arm) using a minimisation program with the following stratification variables:
Neo-adjuvant chemotherapy vs. No neo-adjuvant chemotherapy

Patients will be allocated to one of the two treatment arms:
1. Control arm (MMC + 5FU plus radiotherapy)
3. Research arm (durvalumab plus MMC + 5FU plus radiotherapy)
This allocation ratio will allow the researchers to get as much information on those treated with durvalumab as possible.

The trial moved to a single arm trial in October 2023 and all patients are recruited to the Research arm.

Population available for recruitment into this study:-
For Stage 1 and 2: A maximum of 52 research arm patients will be recruited. Patients will be recruited from approximately 20 UK radiotherapy specialist centres. The trial will continue until all patients have been followed up for a minimum of 2 years after registration.

Patient pathway
Patients potentially suitable for the trial will be identified via clinical referrals or multi-disciplinary team meetings. Potential patients will be approached at oncology clinics about the trial and given a patient information sheet. After a discussion about the trial and sufficient time to consider whether they wish to take part (usually at least 24 hours), the patient will be asked to sign an informed consent form in the presence of the research doctor.

Screening investigations:
Following the informed consent process, the patient will undergo screening assessments. These will be performed within 28 days of randomisation and will include:
1. Medical history
2. Cystoscopy (examination of the lining of the bladder using a camera)
3. Physical examination and vital signs including blood pressure, pulse, temperature and respiratory rate
4. Performance status
5. Height and Weight
6. Blood tests to evaluate the functional capacity of different critical organs and systems, such as the liver and kidneys.
7. Coagulation parameters
8. Thyroid function tests
9. Urine test
10. Serum cortisol
11. For women of childbearing potential only, urine or serum pregnancy test
12. Electrocardiogram
13. CT scan chest, abdomen and pelvis or MRI scan combined with chest CT scan
14. Adverse events and toxicity assessment
15. Concomitant medications
16. Patient to complete LENT SOMA questionnaire to measure toxicity from radiotherapy
17. Patient to complete the Quality of life questionnaires

Once eligibility is confirmed patients will be randomised to one of two trial arms:
1. Control arm - standard chemoradiotherapy (radiotherapy with chemotherapy (5-fluorouracil and mitomycin C)
2. Research arm - standard chemoradiotherapy (as above) + durvalumab

In the control arm, chemoradiotherapy will be administered over a 4-week period. Mitomycin C will be given on day 1 in week 1 of treatment only, as an intravenous bolus at a dose of 12 mg /m2, prior to starting radiotherapy. 5FU will be given as a continuous intravenous infusion at 500 mg/m2/day for 5 days corresponding to fractions 1-5 (week 1 days 1-5) and 16-20 (week 4 days 22-26) of radiotherapy. During weeks 1-7 of trial treatment patients must be treated with CT planned radical radiotherapy to deliver a dose of 55 Gy in 20 fractions to the whole bladder. The radiotherapy must be delivered over 4 weeks with 5 days of treatment, followed by a 2-day break.

In the research arm, durvalumab will be administered as a pre-loading dose over a period of approx 1-hour intravenous infusion at a fixed dose of 1500 mg at week minus 1. Standard chemoradiotherapy will then be given over a 4-week period as described in treatment arm 1. Further durvalumab treatment will be administered at the start of week 4 and every 4 weeks after this up to a maximum of 12 months (a maximum of 13 doses in total).

Assessments first durvalumab dose (week -1):
If baseline laboratory assessments are performed within 3 days prior to treatment day 1 they do not need to be repeated at day 1.
1. Physical examination (based on symptoms)
2. Vital signs including blood pressure,pulse,temperature and respiratory rate
3. Performance status
4. Weight
5. Blood tests to evaluate the functional capacity of different critical organs and systems, such as the liver and kidneys
6. Thyroid function tests
7. Urine test
8. For women of childbearing potential only, urine or serum pregnancy test
9. Toxicity assessment by CTCAE version. 4.0

Assessments during treatment:
All patients will be assessed by the following methods at the start of each week whilst receiving trial treatment.

Assessments to be performed on day 1 of treatment (+/- 3 days):
1. Physical examination (based on symptoms)
2. Vital signs including blood pressure, pulse, temperature and respiratory rate
3. Performance status
4. Weight
5. Blood tests to evaluate the functional capacity of different critical organs and systems, such as the liver and kidneys
6. Toxicity assessment
7. Thyroid function tests
8. For women of childbearing potential only, urine or serum pregnancy test every 4 weeks prior to each 4 weekly treatment

Assessments during durvalumab treatment only:
1. Urine test

End of treatment assessments:
An end of treatment assessment should be performed at 30 days (+/- 7 days) after completion of protocol-defined treatment for the relevant arm. The following assessments should be made:
1. Physical examination (based on symptoms)
2. Vital signs including blood pressure, pulse, temperature and respiratory rate
3. Performance status
4. Weight
5. Blood tests to evaluate the functional capacity of different critical organs and systems, such as the liver and kidneys
6. Thyroid function tests
7. Urine test
8. Serum cortisol
9. Toxicity assessment
10. Patient to complete LENT SOMA questionnaire to measure toxicity from radiotherapy
11. Patient to complete the Quality of life questionnaires
12. For women of childbearing potential only, urine or serum pregnancy test

Assessments follow-up visits:
Patients should be followed up every 3 months (+/- 7 days*) from completion of treatment. The following assessments should be performed for all patients:
1. Cystoscopy (at 3, 6, 12, 18, 24, 30, 36, 48 and 60 month visits*) - cystoscopies can be rigid or flexible according to local policy
2. CT chest, abdomen and pelvis or MRI scan combined with chest CT (at 3, 6, 12, 18, 24, 30, 36 and 48 month visits*)
3. WHO performance status
4. Toxicity assessment by CTCAE.version 4.0 (at 3, 6, 9, 12, 15 month visits*)
5. Patients should be asked to complete the LENT SOMA questionnaire (at 3, 6, 12, 18, 24, 30, 36, 48 and 60 month visits*)
* For patients receiving durvalumab assessment at 3, 6, 9, 12 will be during treatment.
Assessments should be done within +/- 3 days.
Consenting patients should be asked to complete the QoL Booklet at each visit. The original completed Booklet should be returned to the Trial Office in the pre-paid envelope provided.
Survival status will also be assessed at each visit.

Analyses
Between 132 and 159 patients need to be randomised to observe the 70 events required to evaluate disease-free survival. Once the required number of events has occurred if the hazard ratio is less than 0.823 we would consider that sufficient evidence to warrant continuing to Stage 3 for further investigation.

Planned Interim Analysis
The primary and secondary outcome data will be analysed descriptively with point estimates and 95% confidence intervals reported and presented to an independent DMC annually, along with information relating to trial recruitment, trial conduct, data completeness, treatment compliance and safety.
Safety reports will be presented to DMC more frequently during the pilot stage including 3 months after the first 6 patients have been randomised to the research arm and 3 months following completion of treatment by those 6 patients specifically to investigate late toxicities.

Planned Final Analyses (Stages 1 and 2)
The final analysis will be conducted once 70 events have been observed. The exact timing of this

will depend on the rate of recruitment but it is expected to be between 3½ and 4 ½ years after the first site opens to recruitment.

PPI involvement
Patient advocates have helped with the review of the patient information sheet and the trial has one patient advocate as member of the Trial Management Group and one patient advocate as member of the Trials Steering Committee.

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Previous interventions as of 20/09/2023:

The study has the following stages:
Stage 1: assesses feasibility and safety.
Stage 2: assesses disease-free-survival rate at 12 months post-chemotherapy (proportion of patients that survive without any signs or symptoms of their cancer) at 12 months after the end of chemotherapy treatment in a phase II trial setting.

Randomisation will be performed according to a 1:2 ratio (control arm vs. research arm) using a minimisation program with the following stratification variables:
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Patients will be allocated to one of the two treatment arms:
1. Control arm (MMC + 5FU plus radiotherapy)
3. Research arm (durvalumab plus MMC + 5FU plus radiotherapy)
This allocation ratio will allow the researchers to get as much information on those treated with durvalumab as possible.

Population available for recruitment into this study:-
For Stage 1 and 2: A maximum of 159 patients will be recruited. The recruitment target for Stage 3 will be informed by the data collected for Stage 2. Patients will be recruited from approximately 20 UK radiotherapy specialist centres. It is estimated that Stage 1 and 2 will take 2 years to recruit. The trial will continue until all patients have been followed up for a minimum of 5 years after randomisation.

Patient pathway
Patients potentially suitable for the trial will be identified via clinical referrals or multi-disciplinary team meetings. Potential patients will be approached at oncology clinics about the trial and given a patient information sheet. After a discussion about the trial and sufficient time to consider whether they wish to take part (usually at least 24 hours), the patient will be asked to sign an informed consent form in the presence of the research doctor.

Screening investigations:
Following the informed consent process, the patient will undergo screening assessments. These will be performed within 28 days of randomisation and will include:
1. Medical history
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3. Physical examination and vital signs including blood pressure, pulse, temperature and respiratory rate
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5. Height and Weight
6. Blood tests to evaluate the functional capacity of different critical organs and systems, such

as the liver and kidneys.
7. Coagulation parameters
8. Thyroid function tests
9. Urine test
10. Serum cortisol
11. For women of childbearing potential only, urine or serum pregnancy test
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13. CT scan chest, abdomen and pelvis or MRI scan combined with chest CT scan
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7. Thyroid function tests
8. For women of childbearing potential only, urine or serum pregnancy test every 4 weeks prior to each 4 weekly treatment

Assessments during durvalumab treatment only:
1. Urine test

End of treatment assessments:
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Planned Final Analyses (Stages 1 and 2)
The final analysis will be conducted once 70 events have been observed. The exact timing of this will depend on the rate of recruitment but it is expected to be between 3½ and 4 ½ years after the first site opens to recruitment.

PPI involvement
Patient advocates have helped with the review of the patient information sheet and the trial has one patient advocate as member of the Trial Management Group and one patient advocate as member of the Trials Steering Committee.

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Previous interventions:

There are three stages to the trial:
Stage 1: assesses feasibility and safety.
Stage 2: assesses disease free-survival (length of time after treatment the patient survives without any signs or symptoms of their cancer) in a phase II trial setting.
Stage 3: if stage 2 is successful the trial will roll into a phase III, assessing overall survival (length of time from trial entry to death from any cause) with the option to add new arms.

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Population available for recruitment into this study:-
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PPI involvement
Patient advocates have helped with the review of the patient information sheet and the trial has one patient advocate as member of the Trial Management Group and one patient advocate as member of the Trials Steering Committee.

Intervention Type
Mixed

Primary outcome measure
Current primary outcome measure as of 23/11/2023:

Stage 1: Safety - Adverse Events (AEs) will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Acute toxicity defined as related AEs experienced during treatment and late toxicity defined as related AEs reported at a time more than 3 months from the completion of treatment. The number of patients experiencing each event will be reported by type and severity
Feasibility: Defined as the impact on radiotherapy treatment and assessed by days delay to start of radiotherapy, days extension in length of planned radiotherapy and stopping radiotherapy early.

Stage 2: Disease-free survival rate - Defined as the proportion of disease-free patients at 12 months post chemoradiotherapy. Disease events include:
1. Diagnosis of distant metastases
2. Diagnosis of loco-regional nodal disease
3. Diagnosis of a new muscle-invasive tumour in the bladder
4. Diagnosis of non-muscle invasive tumour in the bladder
5. Diagnosis of upper tract urothelial cancer
6. Death from bladder cancer

The trial will continue until all patients have been followed up for a minimum of 2 years after registration.

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Previous primary outcome measure as of 20/09/2023:

Stage 1: Safety - Adverse Events (AEs) will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Acute toxicity defined as related AEs experienced during treatment and late toxicity defined as related AEs reported at a time more than 3 months from the completion of treatment. The number of patients experiencing each event will be reported by type and severity
Feasibility: Defined as the impact on radiotherapy treatment and assessed by days delay to start of radiotherapy, days extension in length of planned radiotherapy and stopping radiotherapy early.

Stage 2: Disease-free survival rate - Defined as the proportion of disease-free patients at 12 months post chemoradiotherapy. Disease events include:
1. Diagnosis of distant metastases
2. Diagnosis of loco-regional nodal disease
3. Diagnosis of a new muscle-invasive tumour in the bladder
4. Diagnosis of non-muscle invasive tumour in the bladder
5. Diagnosis of upper tract urothelial cancer
6. Death from bladder cancer

The trial will continue until all patients have been followed up for a minimum of 5 years after randomisation.

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Previous primary outcome measure:

Stage 1: Safety - Adverse Events (AEs) will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Acute toxicity defined as related AEs experienced during treatment and late toxicity defined as related AEs reported at a time more than 3 months from completion of treatment. The number of patients experiencing each event will be reported by type and severity

Stage 2: Disease-free survival time - Defined as the number of whole days between the date of randomisation and the earliest date of:
1. Diagnosis of distant metastases
2. Diagnosis of loco-regional nodal disease
3. Diagnosis of new muscle-invasive tumour in the bladder

4. Diagnosis of non-muscle invasive tumour in the bladder
5. Diagnosis of upper tract urothelial cancer
6. Death from bladder cancer

Stage 3: Overall survival time - defined as the number of whole days between the date of randomisation and date of death from any cause. Patients who do not die during the course of the trial will be censored at the last date of assessment.

The trial will continue until all patients have been followed up for a minimum of 5 years after randomisation.

Secondary outcome measures

Current secondary outcome measures as of 20/09/2023:

Stage 1: Pilot
1. Feasibility, defined as the impact on radiotherapy treatment and assessed by days delay to start of radiotherapy, days extension in length of planned radiotherapy and stopping radiotherapy early.

Stage 2: Efficacy
1. Toxicity, measured by collecting adverse events graded using the CTCAE version 4.0. Acute toxicity defined as related AEs experienced during treatment and late toxicity defined as related adverse events reported at a time more than 3 months from completion of treatment. The number of patients experiencing each event will be reported by type and severity. Rate of occurrences of AEs of Grade 3 or higher will be reported along with all AESI.
2. Delivery of core target therapy (chemoradiotherapy), defined as the impact on radiotherapy treatment and assessed by days delay to start of radiotherapy, days extension in length of planned radiotherapy and stopping radiotherapy early.
3. Time to local muscle-invasive progression, defined as the number of whole days between the date of randomisation and the date of detection of local muscle-invasive bladder cancer or death from bladder cancer, whichever occurs first. Patients with no evidence of local muscle-invasive disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
4. Time to local non-muscle invasive progression, defined as the number of whole days between the date of randomisation and the date of detection of local non-muscle invasive bladder cancer or death from bladder cancer, whichever occurs first. Patients with no evidence of local non-muscle invasive disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
5. Time to regional nodal progression, defined as the number of whole days between the date of randomisation and the date of detection of loco-regional recurrence in lymph nodes within the true pelvis or death from bladder cancer, whichever occurs first. Patients with no evidence of regional nodal disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
6. Time to local progression, defined as the number of whole days between the date of randomisation and the date of the first local progression or death from bladder cancer, whichever occurs first. Local progression includes detection of local muscle-invasive disease, local non-muscle invasive disease or regional nodal disease. Patients with no evidence of local disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
7. Time to distant progression, defined as the number of whole days between the date of randomisation and the date of detection of distant progression or death from bladder cancer, whichever occurs first. Patients with no evidence of distant progression will be censored at the

last date of assessment or date of death if death is not attributed to bladder cancer.
8. Cystectomy within 1 year, defined as the proportion of patients who undergo a cystectomy within 1 year of randomisation.
9. Quality of life, assessed using the questionnaires EORTC QLQ-C30 and QLQ-BLM30 at baseline, end of treatment (30 days post-treatment discontinuation) and at 3, 6, 9, 12, 15, 18, 21, 24 months post-randomisation
10. Overall survival time , defined as the number of whole days between the date of registration /randomisation and date of death from any cause. Patients who do not die during the course of the trial will be censored at the last date of assessment.
11. Percentage of target drug delivered
Defined as the amount of durvalumab being administered as a proportion of the protocol defined dose.
12. Disease-free survival time Defined as the number of whole days between the date of registration/randomisation and the date of detection of any disease event (defined above) or death from bladder cancer, whichever occurs first. Patients with no evidence of progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer. Patients with disease still present at 3-month imaging will be categorised as having never been disease-free, these patients' disease-free survival time will be 0 days. Patients with no evidence of disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

The trial will continue until all patients have been followed up for a minimum of 2 years after randomisation.

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Previous secondary outcome measures:

Stage 1: Pilot
1. Feasibility, defined as the impact on radiotherapy treatment and assessed by days delay to start of radiotherapy, days extension in length of planned radiotherapy and stopping radiotherapy early.

Stage 2: Efficacy
1. Toxicity, measured by collecting adverse events graded using the CTCAE version 4.0. Acute toxicity defined as related AEs experienced during treatment and late toxicity defined as related adverse events reported at a time more than 3 months from completion of treatment. The number of patients experiencing each event will be reported by type and severity. Rate of occurrences of AEs of Grade 3 or higher will be reported along with all AESI.
2. Delivery of core target therapy (chemoradiotherapy), defined as the impact on radiotherapy treatment and assessed by days delay to start of radiotherapy, days extension in length of planned radiotherapy and stopping radiotherapy early.
3. Time to local muscle-invasive progression, defined as the number of whole days between the date of randomisation and the date of detection of local muscle-invasive bladder cancer or death from bladder cancer, whichever occurs first. Patients with no evidence of local muscle-invasive disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
4. Time to local non-muscle invasive progression, defined as the number of whole days between the date of randomisation and the date of detection of local non-muscle invasive bladder cancer or death from bladder cancer, whichever occurs first. Patients with no evidence of local non-muscle invasive disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.

5. Time to regional nodal progression, defined as the number of whole days between the date of randomisation and the date of detection of loco-regional recurrence in lymph nodes within the true pelvis or death from bladder cancer, whichever occurs first. Patients with no evidence of regional nodal disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
6. Time to local progression, defined as the number of whole days between the date of randomisation and the date of the first local progression or death from bladder cancer, whichever occurs first. Local progression includes detection of local muscle-invasive disease, local non-muscle invasive disease or regional nodal disease. Patients with no evidence of local disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
7. Time to distant progression, defined as the number of whole days between the date of randomisation and the date of detection of distant progression or death from bladder cancer, whichever occurs first. Patients with no evidence of distant progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
8. Cystectomy within 1 year, defined as the proportion of patients who undergo a cystectomy within 1 year of randomisation.
9. Quality of life, assessed using the questionnaires EORTC QLQ-C30 and QLQ-BLM30 at baseline, end of treatment (30 days post-treatment discontinuation) and at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48 and 60 months post-randomisation
10. Overall survival, defined as the number of whole days between the date of randomisation and date of death from any cause. Patients who do not die during the course of the trial will be censored at the last date of assessment.

Stage 3: Efficacy
1. Time to local progression, defined as the number of whole days between the date of randomisation and the date of the first local progression or death from bladder cancer, whichever occurs first. Local progression includes detection of local muscle-invasive disease, local non-muscle invasive disease or regional nodal disease. Patients with no evidence of local disease will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
2. Time to distant progression, defined as the number of whole days between the date of randomisation and the date of detection of distant progression or death from bladder cancer, whichever occurs first. Patients with no evidence of distant progression will be censored at the last date of assessment or date of death if death is not attributed to bladder cancer.
3. Toxicity, measured by collecting adverse events graded using the CTCAE version 4.0. Acute toxicity defined as related AEs experienced during treatment and late toxicity defined as related adverse events reported at a time more than 3 months from completion of treatment. The number of patients experiencing each event will be reported by type and severity. Rate of occurrences of AEs of Grade 3 or higher will be reported along with all AESI.
4. Quality of life, assessed using the questionnaires EORTC QLQ-C30 and QLQ-BLM30 at baseline, end of treatment (30 days post-treatment discontinuation) and at 3, 6, 9, 12, 15, 18, 21, 24, 30, 36, 48 and 60 months post-randomisation

The trial will continue until all patients have been followed up for a minimum of 5 years after randomisation.

Overall study start date
23/05/2017

Completion date

30/06/2027

Eligibility

Key inclusion criteria

Current inclusion criteria as of 23/11/2023:

1. Age > 18 years old
2. Bodyweight > 30 kg
3. Histologically proven invasive bladder carcinoma (adenocarcinoma, transitional cell carcinoma or squamous cell carcinoma)
4. Localised muscle-invasive carcinoma either surgically or by imaging (T2-T4a N0-2 M0)
5. World Health Organisation (WHO) performance status grade 0 to 1
6. Adequate normal organ and marrow function as defined below:
6.1. Haemoglobin > = 100 g/L
6.2. Absolute neutrophil count 1.5 x 10^9/L
6.3. Platelet count > = 100 x 10^9/L
6.4. Serum bilirubin < = 1.5 x institutional upper limit of normal (ULN).
6.5. AST or ALT < = 2.5 x institutional upper limit of normal
6.6. Calculated creatinine clearance > 40 mL/min by the Cockcroft-Gault formula
7. Available for long-term follow-up
8. Fit for a radical course of radiotherapy
9. Must have a life expectancy of at least 12 weeks
10. Evidence of post-menopausal status or negative urinary or serum pregnancy test for female pre-menopausal patients. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
10.1. Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
10.2. Women > = 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
11. Male and female patients of childbearing age willing to use highly effective contraception
12. Patient is willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits and examinations including follow up.
13. Written informed consent and any locally-required authorization obtained from the patient prior to performing any protocol-related procedures, including screening evaluations

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Previous inclusion criteria:

1. Age > 18 years old
2. Bodyweight > 30 kg
3. Histologically proven invasive bladder carcinoma (adenocarcinoma, transitional cell carcinoma or squamous cell carcinoma)

4. Localised muscle-invasive carcinoma either surgically or by imaging (T2-T4a N0 M0)
5. World Health Organisation (WHO) performance status grade 0 to 1
6. Adequate normal organ and marrow function as defined below:
6.1. Haemoglobin > = 100 g/L
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10.2. Women > = 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
11. Male and female patients of childbearing age willing to use highly effective contraception
12. Patient is willing and able to comply with the protocol for the duration of the trial including undergoing treatment and scheduled visits and examinations including follow up.
13. Written informed consent and any locally-required authorization obtained from the patient prior to performing any protocol-related procedures, including screening evaluations

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
52 research arm patients

Total final enrolment
65

Key exclusion criteria

Current participant exclusion criteria as of 20/09/2023:
1. Uncontrolled systemic disease which would preclude the patient from participating in the trial including severe or uncontrolled cardiovascular disease
2. Restrictive or obstructive disturbances to pulmonary ventilation, renal function or liver function
3. Previous pelvic radiotherapy
4. Bilateral hip replacements compromising accurate radiotherapy planning
5. Evidence of significant clinical disorder, or laboratory finding which, in the opinion of the investigator, makes it undesirable for the patient to participate in the trial
6. Widespread Carcinoma in situ (CIS), or CIS remote from the muscle-invasive tumour
7. Untreated hydronephrosis. Patients with hydronephrosis can be included if the kidney/ureter has been stented or nephrostomy has been inserted
8. Prior participation in another trial (within the previous 30 days) or concurrent enrolment in another clinical trial, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study
9. Any unresolved toxicity Common Terminology Criteria for Adverse Events (CTCAE) Grade > = 2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria (see protocol for exceptions)
10. Any previous treatment with a PD-L or PD-L1 inhibitor, including durvalumab
11. Current or prior use of immunosuppressive medication within 14 days prior to randomisation, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid (see protocol for exceptions)
12. Current use of brivudin, sorivudin, and analogues
13. Patients with an active non-infective pneumonitis
14. History of primary immunodeficiency
15. Any concurrent chemotherapy, Investigational Medicinal Product, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions is acceptable.
16. Major surgical procedure other than transurethral resection of the bladder tumour within 30 days prior to randomisation
17. History of allogenic organ transplantation
18. Active or prior documented autoimmune or inflammatory disorders (see protocol for exceptions).
19. Uncontrolled intercurrent illness (see protocol for details)
20. History of another primary malignancy (see protocol for details)
21. Metastatic disease
22. Acute, serious (e.g. Herpes zoster, chickenpox) or active infection including TB, hepatitis B (known positive Hepatitis B, Hepatitis C, or HIV
23. Bone marrow depression after radiotherapy or treatment with other antineoplastic agents
24. Pancytopenia or isolated leucopoenia/thrombopenia or haemorrhagic diathesis
25. Receipt of live attenuated vaccine within 30 days prior to randomisation
26. Serious liver impairment
27. Homozygotic for dihydropyrimidine or known complete absence of dihydrophyrimidine dehydrogenase (DPD) activity
28. Patients undergoing management for non-malignant disease
29. Female patients who are breastfeeding
30. Known allergy or hypersensitivity to any of the trial IMPs or any of the trial drug excipients
31. Judgement by the Investigator that the patient is unsuitable to participate in the trial and the patient is unlikely to comply with trial procedures, restrictions and requirements

Previous participant exclusion criteria:
1. Uncontrolled systemic disease which would preclude the patient from participating in the trial including severe or uncontrolled cardiovascular disease
2. Restrictive or obstructive disturbances to pulmonary ventilation, renal function or liver function
3. Previous pelvic radiotherapy
4. Bilateral hip replacements compromising accurate radiotherapy planning
5. Evidence of significant clinical disorder, or laboratory finding which, in the opinion of the investigator, makes it undesirable for the patient to participate in the trial
6. Widespread Carcinoma in situ (CIS), or CIS remote from the muscle-invasive tumour
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10. Any previous treatment with a PD-L or PD-L1 inhibitor, including durvalumab
11. Current or prior use of immunosuppressive medication within 14 days prior to randomisation, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid (see protocol for exceptions)
12. Current use of brivudin, sorivudin, and analogues
13. Patients with an active non-infective pneumonitis
14. History of primary immunodeficiency
15. Known history of previous clinical diagnosis of tuberculosis (TB)
16. Any concurrent chemotherapy, Investigational Medicinal Product, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions is acceptable.
17. Major surgical procedure other than transurethral resection of the bladder tumour within 30 days prior to randomisation
18. History of allogenic organ transplantation
19. Active or prior documented autoimmune or inflammatory disorders (see protocol for exceptions).
20. Uncontrolled intercurrent illness (see protocol for details)
21. History of another primary malignancy (see protocol for details)
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23. Acute, serious (e.g. Herpes zoster, chickenpox) or active infection including TB, hepatitis B (known positive Hepatitis B, Hepatitis C, or HIV
24. Bone marrow depression after radiotherapy or treatment with other antineoplastic agents
25. Pancytopenia or isolated leucopoenia/thrombopenia or haemorrhagic diathesis
26. Receipt of live attenuated vaccine within 30 days prior to randomisation
27. Serious liver impairment
28. Homozygotic for dihydropyrimidine or known complete absence of dihydrophyrimidine dehydrogenase (DPD) activity
29. Patients undergoing management for non-malignant disease
30. Female patients who are breastfeeding
31. Known allergy or hypersensitivity to any of the trial IMPs or any of the trial drug excipients
32. Judgement by the Investigator that the patient is unsuitable to participate in the trial and the patient is unlikely to comply with trial procedures, restrictions and requirements

Date of first enrolment
01/06/2020

Date of final enrolment
31/03/2025

Locations

Countries of recruitment
England

United Kingdom

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

Study participating centre
East Suffolk and North Essex NHS Foundation Trust
Colchester District General Hospital
Turner Road
Colchester
United Kingdom
CO4 5JL

Study participating centre
The Royal Marsden NHS Foundation Trust
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Nottingham University Hospitals NHS Trust
Trust Headquarters
Queens Medical Centre
Derby Road

Nottingham
United Kingdom
NG7 2UH

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
Trust HQ, PO Box 9551
Queen Elizabeth
Medical Centre
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
Sheffield
United Kingdom
S5 7AU

Study participating centre
Velindre NHS Trust
Unit 2
Charnwood Court
Heol Billingsley
Cardiff
United Kingdom
CF15 7QZ

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Royal Free London NHS Foundation Trust
Royal Free Hospital

Pond Street
London
United Kingdom
NW3 2QG

Study participating centre
Peterborough City Hospital
Edith Cavell Campus
Bretton Gate
Bretton
Peterborough
United Kingdom
PE3 9GZ

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Somerset NHS Foundation Trust
Trust Management
Lydeard House
Musgrove Park Hospital
Taunton
United Kingdom
TA1 5DA

Study participating centre
United Lincolnshire Hospitals NHS Trust
Lincoln County Hospital
Greetwell Road
Lincoln
United Kingdom
LN2 5QY

Study participating centre

Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre
Mount Vernon Hospital NHS Trust
Trust Offices
Mount Vernon Hospital
Northwood
United Kingdom
HA6 2RN

Sponsor information

Organisation
University of Birmingham

Sponsor details
c/o Dr Birgit Whitman
Research Governance
Aston Webb Building (B block), room 119
University of Birmingham
Birmingham
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United Kingdom
B15 2TT
+44 (0)121 4158011
researchgovernance@contacts.bham.ac.uk

Sponsor type
University/education

Website
http://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

Funder(s)

Funder type

Industry

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
Target meetings for the initial presentation of results would be the American Society of Clinical Oncology (ASCO), American Urology Association (AUA), European Urology Association (EAU) and European Cancer Conference (ECC). This will ensure results are disseminated to the widest possible international audiences of both oncologists and urologists. The definitive research findings would be published in peer-reviewed medical journals and presented at appropriate medical and patient meetings. The researchers would also disseminate the results via patient forums such as Fight Bladder Cancer and Action on Bladder Cancer, as well as via websites such as Cancer Research UK and social media outlets. They will establish a trial website containing materials for both patients and clinical staff. Planned publication in a peer-reviewed scientific journal.

Intention to publish date
15/01/2028

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

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 7.0	30/05/2023	20/09/2023	No	No
Protocol file	version 9.0	11/09/2024	08/04/2025	No	No