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BRAVO Study: Surgery vs. Immunotherapy – Which treatment is best in bladder cancer?

Submission date 30/08/2016	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 06/09/2016	**Overall study status** Completed	
Last Edited 27/09/2024	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-to-find-the-best-treatment-for-early-bladder-cancer-bravo

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
31724

Study information

Scientific Title
BRAVO: High risk bladder cancer: A randomised controlled feasibility study of radical cystectomy against intra-vesical immunotherapy

Acronym
BRAVO

Study objectives
The aim of this study is to investigate the feasibility of conducting a definitive phase III randomised controlled trial evaluating the efficacy of radical cystectomy against intra-vesical immunotherapy in the treatment of aggressive bladder cancer when found at an early stage.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Yorkshire & The Humber - South Yorkshire Research Ethics Committee, 12/08/2016, ref: 16/YH/0268

Study design
Randomized; Both; Design type: Treatment, Screening, Process of Care, Drug, Vaccine, Immunotherapy, Surgery, Qualitative

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
Specialty: Cancer, Primary sub-specialty: Bladder; UKCRC code/ Disease: Cancer/ Malignant neoplasms of urinary tract

Interventions
Participants will be randomised on a 1:1 basis to receive either RC or mBCG. A computer-generated adaptive minimisation algorithm that incorporates a random element will be used to ensure the treatment groups are well balanced for the following characteristics:
1. Age (<75, >=75)
2. Sex (male, female)
3. Cancer centre (Sheffield, Leeds, Bradford, Wakefield, Hull, Newcastle)
4. Tumour stage (pTa/pTis, pT1)
5. Presence of CIS (Yes, No)
6. Previous low risk bladder cancer (Yes, No)

mBCG group: Within this study, a maintenance BCG regimen is to be used. The regimen requires that at least 12 months of BCG treatment is given (starting with and including the initial dose). Treatment beyond one year is as per standard care.
Induction BCG:
Maintenance treatment should start within 2-4 weeks of randomisation (administration once a week for six weeks). Delays and deferrals due to complications or toxicity are common and allowed within this study. BCG induction should include at least 4 doses of BCG. The induction treatment should be completed within 10 weeks from the date of the first dose.
First check cystoscopy:
Following induction BCG, a check cystoscopy should be performed after a 6-week break. Within this study, the first cystoscopy should be performed using a rigid cystoscope and should include the obtainment of bladder washings or voided urinary cytology, and at least one biopsy of the bladder urothelium (either the tumour scar and/or red areas within the bladder). Fluorescence or narrow band imaging may be used, as per local hospital protocols. Histological review of the bladder biopsies and urinary cells should be performed to determine the presence or absence of BC. In the absence of carcinoma or in the presence of high risk (high grade or grade 3) non-muscle invasive bladder cancer (HRNIMBC) then the patient may continue with mBCG. The presence of an invasive BC requires the cessation of mBCG and a clinical consultation to discuss radical treatment or other treatment options.
First BCG maintenance:
Following cystoscopy, and after a wait of two weeks (and the cessation of haematuria), then three weeks of intravesical BCG is administered according to hospital practice. Unlike subsequent BCG cycles these first doses of BCG maintenance should take place in the presence

of HRNIMBC. After an eight week break from the last BCG dose either a flexible or rigid cystoscopy should be carried out. Urinary cells (either voided cytology or bladder washings) should be obtained. A biopsy of the bladder lining is not mandated after the first rigid cystoscopy.
Subsequent BCG maintenance:
As per the first BCG maintenance doses with the exception that if high risk NMIBC is detected mBCG should be discontinued and a clinical consultation should take place to discuss radical treatment or other treatment options.
mBCG and surveillance within this feasibility study ceases after one year post randomisation, or three months after the last patient is randomised. The patient should continue with their care according to standard hospital practice and applicable guidelines.
Follow up data will be collected for each cycle of treatment at the cystoscopy visits

Radical Cystectomy: Surgery can be performed by either an open, laparoscopic or robotic route as per usual practice within that unit and as per accreditation. Minimally invasive or open surgery are acceptable, however surgeons should avoid undertaking surgery within this study whilst on their learning curve for a modality. In this study surgery should take place within 8 weeks of randomisation.
Radical cystectomy should include removal of adjacent organs. In males, this includes the prostate and seminal vesicles. In females, this should include a section of adjacent anterior vaginal wall, the uterus, cervix and fallopian tubes and, if no bladder reconstruction is planned, the urethra. Oophorectomy is optional, as per local practice and individualised for each patient. Exceptions to this surgical plan are acceptable with prior approval from CTRU. Within this study, pelvic lymphadenectomy is mandated. The template for lymphadenectomy should include, at least, the regional lymph nodes up to the level of the ureteric crossing of the common iliac vessels. This includes the obturator fossa, the external iliac and internal iliac nodes. A more extended lymphadenectomy is acceptable. Excised lymphatic tissue should be submitted for histological analysis. Reconstruction through all routes is acceptable. It is anticipated this will mostly include ileal conduit and orthotopic neobladder. As for surgeon accreditation, the pattern of reconstruction should mirror the cases within the submitted RC cases. Perioperative care is to be carried out as per ERAS protocols and standard practice. Post-operative care is to be carried out as per standard practice.
Follow up frequency will be in line with current NHS practice, with data collected at routine follow up visits at 3, 6 and 12 months post randomisation +/- 2 weeks. An intravenous urogram (IVU) is carried out at approximately 2-4 weeks post RC and should be carried out per standard care.

For both study arms, follow up imaging by CT scan will be performed as per local practice and for the study should be arranged at one year post randomisation (+/-2 weeks). Wherever possible the one year post randomisation CT scan should be in the above time window to allow comparison between the two trial arms. Participants will be asked to complete questionnaires at baseline, 3 months, 6 months and at 12 months post-randomisation or until the end of the study follow-up period (one year post randomisation or three months after the last participant has been randomised if earlier).

Intervention Type
Procedure/Surgery

Primary outcome measure
1. Eligibility rate is reportedas the number of patients screened for entry to the study and considered eligible within the 18 month recruitment period

2. Recruitment rate is reported as the number of eligible patients randomised within the 18 month recruitment period

Secondary outcome measures
1. Uptake of allocated treatment is reported as the number of randomised participants starting their allocated treatment within the 21 month follow-up period
2. Treatment compliance is reported as the number of randomised participants complying with their allocated treatment regimen within the 21 month follow-up period
3. Withdrawal rate is reported as the number of randomised participants withdrawing from trial procedures within the 21 month follow-up period
4. Loss-to-follow-up rate is reported as the number of randomised participants for whom follow-up data cannot be collected within the 21 month follow-up period
5. Quality of life completion rate is reported as the number of randomised participants for whom quality of life data is available at baseline, 3, 6 and 12 months post-randomisation
6. Quality of life is measured by the EQ5D, EORTC QLQ-C30, EORTC QLQ-NMIBC24, QLQ-BLM-30 at baseline, 3, 6 and 12 months post-randomisation
7. Survival is measured at 12 months post-randomisation
8. Reasons participants / clinicians decline study entry is measured by a qualitative sub-study during the 18 month recruitment period

Overall study start date
01/10/2015

Completion date
30/09/2018

Eligibility

Key inclusion criteria
Inclusion criteria as of 23/03/2017:
1. Male or female aged ≥ 18 years old.
2. Patients with a new diagnosis of high-risk (high grade or grade 3) non-muscle invasive urothelial carcinoma (staged as either pTa, pTis or pT1). Patients with previous low grade NMIBC are suitable.
3. The tumour is either solely urothelial cell carcinoma or has urothelial cell carcinoma as the majority histological component.
4. In addition to the HRNMIBC bladder tumour, there needs to be one or more risk factor from:
4.1. Presence of pTis in the bladder
4.2. Presence of pTis in the prostatic urethra
4.3. Lymphovascular invasion
4.4. Vascular invasion
4.5. Residual Grade 3/High grade UCC on re-resection (or initial TURBT if no re-resection)
4.6. Multifocal disease (>3 tumours at initial resection)
4.7. Young age (<65 years old)
4.8. Initial tumour Size > 3cm (or >5g in histology specimen)
4.9. pT1 stage
5. Either re-resection of the bladder (following the initial diagnostic TURBT) within 3 months prior to randomisation confirming the absence of muscle invasion
OR
5.1. The initial diagnostic TURBT biopsy contains muscle, AND
5.2. The radiological and pathological stage assessment are in agreement regarding stage and

absence of muscle invasion, AND
5.3. A re-resection is not appropriate in the opinion of the treating clinician AND
5.4. The initial TURBT is within 3 months prior to randomisation
6. CT or cross sectional imaging of the abdomen and pelvis within the year prior to starting treatment.
7. Imaging of the lungs and thorax within 3 months prior to randomisation.
8. Suitable and fit for both mBCG and RC as determined by the treating clinician
9. Central MDT pathological review agrees diagnosis
10. If female, must be (as documented in patient notes):
10.1. Postmenopausal (no menses for 12 months without an alternative medical cause), or
10.2. Surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy), or
10.3. Using acceptable contraception2 (which must be continued for 7 days after the last dose of BCG or until RC is carried out). Women of child bearing potential must undergo a pregnancy test before randomisation.
10.4. Not breast feeding

Original inclusion criteria:
1. Male or female aged ≥ 18 years old
2. Patients with a new diagnosis of high-risk (high grade or grade 3) non-muscle invasive urothelial carcinoma (staged as either pTis, pTa or pT1). Patients with previous low grade NMIBC are suitable
3. The tumour is either solely urothelial cell carcinoma or has urothelial cell carcinoma as the majority histological component
4. In addition to the HRNMIBC bladder tumour, there needs to be one or more risk factor from:
4.1. Presence of pTis in the bladder
4.2. Presence of pTis in the prostatic urethra
4.3. Lymphovascular invasion
4.4. Vascular invasion
4.5. Residual Grade 3/High grade UCC on re-resection
4.6. Multifocal disease (>3 tumours at initial resection)
4.7. Young age (3cm (or >5g in histology specimen)
4.8. pT1 stage
5. Re-resection of the bladder (following the initial diagnostic TURBT) within 3 months prior to randomisation confirming the absence of muscle invasion
6. Suitable and fit for both mBCG and RC as determined by the treating clinician
7. Central MDT pathological review agrees diagnosis
8. If female, must be (as documented in patient notes):
8.1. Postmenopausal (no menses for 12 months without an alternative medical cause)
8.2. Surgically sterile (hysterectomy, bilateral salpingectomy or bilateral oophorectomy)
8.3. Using acceptable contraception (which must be continued for 7 days after the last dose of BCG or until RC is carried out)
Women of child bearing potential must undergo a pregnancy test before randomisation. d. not breast feeding

Participant type(s)
Patient

Age group
Adult

Lower age limit

18 Years

Sex
Both

Target number of participants
Planned Sample Size: 60; UK Sample Size: 60

Total final enrolment
50

Key exclusion criteria
1. Solely non-urothelial or variant urothelial pathology
2. Unable or not willing to give informed consent
3. Previous high risk (high grade or grade 3) NMI or invasive bladder cancer
4. Any previous treatment with intravesical BCG
5. Any other malignancy (excluding non-melanomatous skin cancer, low-risk prostate cancer and prior low risk bladder cancer)

Date of first enrolment
01/10/2016

Date of final enrolment
31/03/2018

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Bradford Royal Infirmary
Duckworth Lane
Bradford
United Kingdom
BD9 6RJ

Study participating centre
Castle Hill Hospital
Castle Road
Cottingham
Hull
United Kingdom
HU16 5JQ

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle Upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Pinderfields Hospital
Aberford Road
Wakefield
United Kingdom
WF1 4DG

Study participating centre
St James' University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
Airedale General Hospital
Skipton Road
Keighley
United Kingdom
BD20 6TD

Study participating centre
Barnsley Hospital NHS Foundation Trust
Gawber Road

Barnsley
United Kingdom
S75 2EP

Study participating centre
Calderdale Royal Hospital
Salterhebble
Halifax
United Kingdom
HX3 0PW

Study participating centre
Huddersfield Royal Infirmary
Acre Street
Huddersfield
United Kingdom
HD3 3EA

Study participating centre
Chesterfield Royal Hospital
Chesterfield Road
Callow
Chesterfield
United Kingdom
S44 5BL

Study participating centre
Doncaster Royal Infirmary
Armthorpe Road
Doncaster
United Kingdom
DN2 5LT

Study participating centre
Harrogate District Hospital
Lancaster Park Road
Harrogate
United Kingdom
HG2 7SX

Study participating centre
West Cumberland Hospital
Homewood Road
Whitehaven
United Kingdom
CA28 8JH

Study participating centre
Cumberland Infirmary
Newton Road
Carlisle
United Kingdom
CA2 7LT

Study participating centre
Scunthorpe General Hospital
Cliff Gardens
Scunthorpe
United Kingdom
DN15 7BH

Study participating centre
Rotherham Hospital
Moorgate Road
Rotherham
United Kingdom
S60 2UD

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

Sponsor details
Northern General Hospital
Herries Road
Sheffield
England
United Kingdom
S5 7AU

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Charity

Funder Name
Yorkshire Cancer Research

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned dissemination through peer reviewed scientific journal articles, internal reports, and conference presentations.

Intention to publish date
30/09/2020

Individual participant data (IPD) sharing plan
Not provided at time of registration

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	11/08/2017	27/11/2020	Yes	No
Results article	results	20/01/2021	17/08/2021	Yes	No

Plain English results		22/09/2022	No	Yes
HRA research summary		28/06/2023	No	No
Other publications	26/09/2024	27/09/2024	Yes	No