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HIVEC® HEAT - the drug mitomycin medac will be warmed to 43°C and administered through a catheter into the bladder via HIVEC® device for patients with nonmuscle-invasive bladder cancer that have previously had no response to BCG treatment

Submission date
22/06/2024

Recruitment status
Recruiting

Registration date
17/04/2025

Overall study status
Ongoing

Last Edited
20/05/2025

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
Not provided at time of registration

Who can participate?
We aim to consent and recruit 238 participants in UK hospital urology departments. These will have non-muscle-invasive Bladder Cancer (NMIBC) and have previously had BCG treatment (Bacillus Calmette-Guerin, a vaccine which is a type of immunotherapy medicine) but have not responded. The next treatment option is a cystectomy (removal of the bladder) and this trial is for those patients that are unsuitable or unwilling to undergo this procedure. There are two depths of this high-grade cancer (papillary stage Ta or T1). High-grade cancer cells can also be flat patches in the bladder called Carcinoma in Situ (CIS).

What does the study involve?
There is no randomisation into the trial but those participants entering the study will be split into one of two sub studies. The study group a participant will end up in will be largely dependent on if they have carcinoma in situ (CIS) which is a type of NMIBC. A full breakdown of the study groups can be seen below;
• Sub-Study 1: 123 participants will be required for CIS +/- completely resected papillary Ta/T1 disease that have not responded to having BCG treatment
• Sub-Study 2: 115 participants for completely resected high-grade papillary Ta/T1 disease without CIS that have not responded to having BCG treatment.

Both study groups will be allocated the same trial treatment over a 1 year period with 15 treatments of mitomycin medac drug given via a catheter into the bladder. This will be gently

warmed to 43°C using the HIVEC device, for 60 minutes The treatment schedule will be once a week for the 1st 6 weeks and after the 12 week timepoint, treatment will be given monthly for 9 months (maintenance) treatment. In Sub study 1 there will be mandatory biopsies for patients so that a retrospective analysis can be completed in an external lab. All participants will be followed up for another year after treatment to have disease assessments to ensure they remain free of cancer and to check for any treatment related adverse events.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
There is a possibility some participants may experience side effects to the drug and that it's possible to have toxicities but participants will be monitored throughout treatment and regularly followed up to check any adverse events. Treatment will be stopped if needed.
There are a lot of scheduled visits over a 2 year period, although only a few are additional to that of standard of care
Blood tests: The only blood tests in excess of standard of care are at baseline, visit 6 and visit 16.

CT Urograms: We have ensured that these are not in excess of standard of care. In the event that 12 weeks have elapsed from CT Urogram to joining the trial, the CT Urogram will be repeated. This is in the best interests of the potential participant to ensure that they are still eligible for the trial treatment and that other treatments are not now needed.

Cystoscopies: The number of cystoscopies are not in excess of standard of care

Minimising the risk from cystoscopic random bladder biopsies in Sub-Study 1: Cystoscopic random bladder biopsies will only be performed by experienced Urologists. The cystoscopic random bladder biopsies at week 24 under general/spinal anaesthetic even if no bladder recurrence has been detected is in excess of standard of care. There is a small risk of bladder perforation from bladder biopsies.

Minimising number of visits: Urine cytology, cystoscopy and HIVEC treatment will usually take place sequentially on the same day, thereby minimising the number of visits

Minimising difficulties providing a urine specimen for cytology: It is recognised that some patients have difficulty providing a timely voided urine cytology specimen. If so, a bladder washings urine cytology specimen will be collected at the time of cystoscopy

HIVEC treatments: For some UK centres, 15 HIVEC treatment visits is their standard of care. Many patients are reassured by maintenance treatments.
All reasonable participant travel for up to a maximum of 25 visits per patient will be paid.

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

When is the study starting and how long is it expected to run for?
April 2025 to March 2030

Who is funding the study?
Combat Medical Ltd (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1007375

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
0889, CPMS 55197

Study information

Scientific Title
HIVEC® HEAT (Hyperthermic intravesical mitomycin mEdac) for pAtients with BCG-unresponsive nonmuscle-invasive bladder cancer Trial

Acronym
HIVEC-HEAT

Study objectives
Primary objective:
To assess the effectiveness of Hyperthermic Intravesical Chemotherapy (HIVEC®) in BCG-unresponsive high-grade NMIBC patients.

Secondary objective:
To assess the safety of Hyperthermic Intravesical Chemotherapy (HIVEC®) in BCG-unresponsive high-grade NMIBC patients.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 04/09/2024, West Midlands - Coventry & Warwickshire Research Ethics Committee (2 Redman Place, Stratford, London, E20 1JQ, United Kingdom; +44 207 104 8263; coventryandwarwick.rec@hra.nhs.uk), ref: 24/WM/0148

Study design
Interventional non randomized

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Safety, Efficacy

Participant information sheet

Health condition(s) or problem(s) studied
Non-Muscle-Invasive Bladder Cancer (NMIBC)

Interventions
Hyperthermic Intravesical Chemotherapy (HIVEC®) in this study is conducted with the Combat BRS system (COMBRS05) and combined with Mitomycin medac administered at a concentration dose of 80 mg diluted in 40 mL of saline. Another 40 mL of saline is added to prime the BRS tubing set totalling 80 mL saline overall. Therefore, the concentration of Mitomycin medac that will be recirculated into the bladder will be 1 mg/mL. Participants will receive 80 mg Mitomycin

medac at a dose of 1 mg/mL for 12 months of treatment. The total number of HIVEC® treatments over 12 months is fifteen. Participants will be followed up for 24 months in total, including during 12 months of treatment recirculation and every 3 months thereafter for another 12 months (month 15, month 18, month 21, and month 24). The follow-up visits will follow the same schedule as standard of care. If a patient discontinues treatment early, every effort should be made to ensure treatment related AEs are recorded either by an in-person clinic visit or via the telephone at 12 months

Intervention Type
Drug

Pharmaceutical study type(s)
Therapy

Phase
Phase III

Drug/device/biological/vaccine name(s)
Mitomycin medac

Primary outcome measure
Sub-Study 1. Complete response (CR) at 3 months (negative cystoscopy without evidence of recurrent CIS in the bladder and a urine cytology test 'not positive' for high-grade urothelial carcinoma)
Sub-Study 2. Median duration of high-grade recurrence-free survival (whole days from first HIVEC treatment to first evidence of high-grade recurrence or death)

Secondary outcome measures
Timepoints are as and when the outcome occurs. Each follow-up is essential in the treatment pathway to ensure patients remain free from recurrence and/or progression. No one result/CRF will provide a definitive diagnosis and the evidence is collated across all these follow-ups to ensure these outcomes are met.
1. Freedom from high-grade Ta/T1 or CIS
2. Freedom from non-bladder recurrence of urothelial cancer
3. Progression-free survival
4. Cystectomy-free survival
5. Disease-specific survival
6. Overall survival from follow ups

In addition to those secondary outcomes listed above, those in Sub-study 1 will also look at:
1. Median duration of CR (from date of CR to first evidence of high-grade recurrence or date of last follow-up if no recurrence develops)
2. Complete response (CR) rate at 6, 12 and 24 months (negative cystoscopy without evidence of recurrent CIS in the bladder and a urine cytology test 'not positive' for high-grade urothelial carcinoma)

Overall study start date
27/03/2024

Completion date
16/03/2030

Eligibility

Key inclusion criteria

1. Under white light cystoscopy, diagnosis of urothelial carcinoma of the bladder with histologic confirmation of a tumour containing at least one (more than one allowed) of the following stage and grade categories:
1.1. Ta, high-grade
1.2. T1, high-grade
1.3. Carcinoma in situ (CIS)
2. Must be BCG-unresponsive as defined by any of the following situations:
2.1. Refractory disease (no response to BCG)
2.1.1. High-grade papillary T1 disease at 3 months following induction BCG treatment.
2.1.2. High-grade papillary Ta/T1 disease and/or CIS at 6 months after completion of adequate BCG exposure
2.1.3. (Adequate BCG is defined as at least 5 out of 6 doses of an initial induction course, plus at least 2 of 3 doses of maintenance therapy or at least 2 of 6 doses of a second induction)
2.2. Relapsing disease (relapse after initial response to BCG)
2.2.1. Within 6 months of last dose of adequate BCG exposure (defined above), the presence of recurrent high-grade papillary Ta/T1 disease is detected
2.2.2. Within 12 months of last dose of adequate BCG exposure (defined above), the presence of recurrent CIS is detected
3. Complete transurethral resection of all Ta/T1 tumour under white light within 6 weeks of first HIVEC® treatment. A complete transurethral resection consists of the removal of all visible papillary (Ta/T1) tumour.
4. Repeat white light cystoscopy is required prior to initiating HIVEC® if the time interval from the most recent TURBT to HIVEC® is > 6 weeks. This is to ensure there is no recurrent visible papillary/solid tumour.
5. Repeat (second-look) TURBT under white light is required prior to initiating HIVEC® in the following instances:
5.1. Absence of detrusor muscle in pathology specimen for high-grade Ta/T1 tumours. [If after the repeat (second-look) TURBT there is still absence of detrusor muscle in the pathology specimen for high-grade Ta, then there must be no visible papillary tumour (and confirmed as benign or remains high-grade Ta)]
5.2. High-grade T1 tumours whether detrusor muscle is present or not
6. Able and willing to provide signed and written informed consent
7. Unsuitable for cystectomy or who are unwilling to undergo cystecomy preferring a bladder-sparing approach.
8. Age ≥18 years
9. WHO performance status ≤2
10. Negative serum pregnancy test for women of child-bearing potential within 14 days of treatment initiation.
11. Women of child-bearing potential and/ or male participants must agree to use highly effective methods of birth control

Participant type(s)

Patient

Age group

Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
238

Key exclusion criteria
1. BCG-unresponsive urothelial carcinoma that has been detected with enhanced cystoscopic techniques.
2. A history of muscle-invasive (T2, T3, T4), lymph node-positive (N1, N2, N3), or metastatic (M1) bladder cancer.
3. High-grade T1 NMIBC where lymphovascular invasion is reported.
4. Histology subtypes of bladder cancer other than pure urothelial carcinoma, excluding urothelial carcinoma with squamous or glandular differentiation which are permissible.
5. Unlikely to complete or adhere to the clinical trial due to:
5.1. Life expectancy <2 years.
5.2. Unable or unwilling to receive the required follow-up care or diagnostic interventions.
6. Any condition that, in the opinion of the investigator, could lead to protocol non-compliance.
7. Any pelvic radiotherapy.
8. Prior salvage immunotherapy or chemotherapy for BCG-U NMIBC.
9. Participants must not have received any live or live attenuated vaccine within 4 weeks of the first treatment.
10. Unresolved bladder perforation
11. History of urothelial carcinoma of the upper urinary tract (ureter, renal pelvis) or prostatic urethra within 24 months of treatment initiation.
12. Mitomycin-C allergy.
13. Inability to undergo HIVEC® treatment:
13.1. Urinary frequency or urgency that precludes a 1-hour HIVEC® dwell time.
13.2. Urethral stricture preventing urethral catheterisation with the Combat BRS system 16 F catheter.
14. Uncontrolled visible haematuria.
15. Active or untreated urinary tract infection.
16. Pregnancy, breastfeeding, or planning to conceive during the treatment and/or the post-treatment period.
17. Participant must not be simultaneously enrolled in any interventional clinical trial.

Date of first enrolment
01/04/2025

Date of final enrolment
01/04/2027

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Leicester General Hospital
Gwendolen Road
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Sponsor information

Organisation
University of Leicester

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Sponsor type
University/education

Website
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ROR
https://ror.org/04h699437

Funder(s)

Funder type
Industry

Funder Name
Combat Medical Ltd

Results and Publications

Publication and dissemination plan
Peer reviewed scientific journals
Internal report
Conference presentation
Publication on website
Submission to regulatory authorities
We are requesting specific consent to share pseudonymised trial data with our research collaborators in other academic institutions and industry partners for future research.

Intention to publish date
30/03/2031

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date