ISRCTN17378733 https://doi.org/10.1186/ISRCTN17378733

Assessing the use of tailored treatments based on combinations of genes that are active in a tumour, and the impact on outcomes for bladder cancer.

Submission date
12/10/2022

Recruitment status
No longer recruiting

Registration date
27/04/2023

Overall study status
Ongoing

Last Edited
16/11/2026

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
The current approach is to treat all individual patients with bladder cancer as though they have the same type of bladder cancer, with everyone receiving the same treatment. However, treating all bladder cancers in the same way may not be best for individual patients.
The GUSTO study involves patients who need chemotherapy (drugs to kill cancer cells) before surgery to remove their bladder. GUSTO aims to understand if tailored treatments (including two different types of drugs to kill cancer cells: chemotherapy and immunotherapy) are better than the current unselected standard treatment. The GUSTO study will:
1. Look at the genetic makeup of each bladder cancer. This is done by measuring the activity of hundreds of separate genes (called gene expression profile). The results will be used to match each cancer to one of 5 subtypes of bladder cancer using a computer programme (Decipher Bladder).
2. Look at whether it is better to have treatment for bladder cancer that has grown into the surrounding muscle guided by the bladder cancer subtype or whether all patients should receive the same standard treatment regardless of cancer subtype
GUSTO will not be able to fully answer this question but will give us important information on whether a bigger study is needed.

Who can participate?
Patients aged 18 years and over with bladder cancer which has grown into the surrounding muscle and who are suitable for curative treatment (removal of the bladder)

What does the study involve?
Patients recruited will have their cancers profiled quickly (so that their treatment is not delayed). Patients will be randomly allocated to the tailored treatment or to standard treatment. The study involves the use of two standard chemotherapy drugs (gemcitabine and cisplatin) and two new immunotherapy drugs (durvalumab and tremelimumab). Not all patients in the study will receive all of these drugs.

The study will look to see how long it takes to get the subtype result and how well the test to measure the activity of the genes in each cancer works. The study will also look at how patients treated with tailored treatments respond after the bladder removal surgery.

What are the possible benefits and risks of participating?
There is no guarantee that patients will benefit from the study treatment. All patients in GUSTO will have bladder removal surgery. Most patients in the study will also receive chemotherapy or immunotherapy treatment. Those who do not receive chemotherapy or immunotherapy before bladder removal surgery will have their surgery sooner than those who receive this treatment. If, after surgery, their doctor thinks they will benefit from additional treatment they can receive this as they would if they were not in the study.
There may be additional and longer hospital visits as part of taking part in the study. Patients allocated to receive immunotherapy treatment will have more treatment visits than patients who receive chemotherapy only. Patients receiving immunotherapy treatment will have treatment after their bladder removal surgery while chemotherapy is usually only given before surgery. We have worked to minimise additional visits by suggesting that the post-cystectomy follow-up visits coincide with other visits where possible.
There are blood samples as part of the study and some are additional to the number of blood samples required in standard treatment. There are tissue samples taken as part of the study, but these are collected from surgeries that are carried out as part of standard care for this patient group.
There are risks from exposure to ionising radiation used to perform scans. This has been minimised where possible by keeping to the same schedule used in standard treatment where possible.
Participants will be monitored frequently and supportive treatment administered to minimise side effects of treatment.
Participants will be fully informed of the potential risks and burdens involved in taking part in this research study, both by the clinical research team at their hospital and in the Participant Information Sheets and Participant Supplementary Document, and will be given opportunities to ask questions prior to consent and during their participation.
The trial will be monitored for trial conduct and the safety of participants, and any concerns will be appropriately escalated and handled as per relevant legislation, regulatory requirements and local standard operating procedures. Patients have been involved in the trial design and are helping to run the trial. The results of the trial will be published in leading journals, presented at conferences and spread by charities and social media.

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

When is the study starting and how long is it expected to run for?
October 2022 to September 2027

Who is funding the study?
1. National Institute for Health Research (NIHR), Efficacy and Mechanism Evaluation (EME) Programme (Ref: NIHR 128103) (UK)
2. AstraZeneca UK Limited

Who is the main contact?
GUSTO@leeds.ac.uk

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-matching-treatment-to-the-individual-make-up-of-bladder-cancer-gusto

Contact information

Type(s)
Public

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Additional identifiers

Integrated Research Application System (IRAS)
1005487

Central Portfolio Management System (CPMS)
54256

Protocol serial number
STH20710

Study information

Scientific Title
GUSTO: Gene expression subtypes of Urothelial cancer: Stratified Treatment and Oncological outcomes

Acronym

GUSTO

Study objectives

Current hypothesis as of 30/06/2025:

The overarching aim of the GUSTO trial is to obtain information to understand whether this approach could improve outcomes, and therefore guide the design of a subsequent Phase III trial with respect to:

1. The feasibility of gene expression subtyping within routine NHS care

2. The distribution of gene expression subtypes within UK NHS populations

3. The heterogeneity of the intermediate endpoint (pCR as the primary efficacy endpoint in GUSTO) with respect to subtype following standard of care treatment (NAC)

4. To assess the activity of gene expression subtype guided neoadjuvant treatments for muscle-invasive bladder cancer (MIBC)

By providing data on disease-free survival and other time-to-event secondary endpoints, and incorporating adjuvant immunotherapy, the study will also accrue data that will inform a subsequent Phase III study to incorporate the use of adjuvant treatment for those with residual disease.

GUSTO has been designed with three stages.

Stage 1 will assess whether it is feasible to recruit patients and to carry out the gene expression subtype test within the clinical pathway for patients with muscle-invasive bladder cancer.

Stage 2 will confirm whether it is feasible to recruit patients and assess whether the assumptions made about the gene expression subtype numbers were as expected when the trial sample size was calculated.

Stage 3 will assess whether there is evidence of a treatment benefit i.e. improved complete response rate post-cystectomy as determined by pathology for patients in the gene expression subtype-guided arm.

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3. The heterogeneity of the intermediate endpoint (pCR as the primary efficacy endpoint in GUSTO) with respect to subtype following standard of care treatment (NAC)
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Stage 3 will assess whether there is evidence of a treatment benefit i.e. improved complete response rate postcystectomy as determined by pathology for patients in the gene expression subtype-guided arm.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 12/04/2023, West of Scotland REC 1 (West of Scotland Research Ethics Service, Ward 11, Dykebar Hospital, Grahamston Road, Paisley, PA2 7DE, UK; +44 (0)141 314 0212; WosRec1@ggc.scot.nhs.uk), ref: 22/WS/0153

Primary study design
Interventional

Study design
Randomized controlled open-label parallel-group study

Study type(s)
Efficacy, Safety, Treatment

Health condition(s) or problem(s) studied
Muscle invasive bladder cancer with pure or mixed urothelial (transitional) cell carcinoma

Interventions
Current interventions as of 30/06/2025:

GUSTO is a multicentre, prospective, open-label, individually randomised, controlled, parallel-group, multi-stage phase II trial of patients with T2-4a N0 M0 MIBC or T(any) N1 M0 MIBC who are suitable for NAC with cisplatin and gemcitabine prior to radical cystectomy.

The trial will assess whether the use of gene expression subtype stratified care using the GUSTO Classifier (Decipher Bladder platform and TCGA 2 classification system), to assign patients to whether they receive NAC and/or immunotherapy (durvalumab/tremelimumab), demonstrates sufficiently improved treatment activity to warrant a phase III trial.

Stage 1 will assess the feasibility of both recruitment and the embedding of gene expression subtype stratification into the clinical pathway; stage 2 will confirm feasibility of recruitment and assess the assumptions for the sample size calculation and stage 3 will involve an assessment of treatment outcomes using this stratified approach. Movement between trial stages will be dependent upon the meeting of pre-defined progression criteria.

The trial plans to recruit 320 participants over a 3-year period and the total sample size will be confirmed or re-estimated at the end of stage 2. The final sample size will depend on whether the frequencies of gene expression subtype and pCR rate in the standard care arm are as assumed based on available evidence, and whether the trial continues to stage 3. The sample size proposed (320) is based on a single-arm assessment within the gene expression subtype-guided arm, where the randomisation to the standard care arm will enable the correct design parameters to be estimated and a secondary unpowered randomised comparison to be carried out. Conducting a larger phase II study with powered randomised comparisons is considered infeasible in a reasonable timeframe.

Eligible participants will be randomised via minimisation in a 1:1 ratio to receive either:

1. Standard treatment administered intravenously: neoadjuvant chemotherapy (cisplatin 70mg /m2 on day 1, every 21 days for 4 cycles [or split dose 35 mg/m2 on day 1 and day 8 for patients with impaired creatinine clearance (40-60 ml/min)] and gemcitabine 1000mg/m2 on days 1 and 8, every 21 days for 4 cycles) prior to radical cystectomy (standard treatment)

2. Gene expression subtype-guided treatment administered intravenously:

- Basal and neuronal subtypes: neoadjuvant treatment (cisplatin: 70 mg/m2 on day 1, every 21 days, for 4 cycles, gemcitabine: 1000 mg/m2 on days 1 and 8, every 21 days, for 4 cycles, durvalumab: 1500 mg on day 1, every 21 days, for 4 cycles, tremelimumab: 75 mg on day 1, of cycles 1 and 3 only) prior to radical cystectomy. Adjuvant treatment (durvalumab: 1500 mg on day 1, every 28 days, for 8 cycles)

- Luminal infiltrated subtype: neoadjuvant treatment (durvalumab: 1500 mg on day 1, every 21 days, for 4 cycles and tremelimumab: 75 mg on day 1, of cycles 1 and 3 only) prior to radical cystectomy and adjuvant treatment (durvalumab: 1500 mg on day 1, every 28 days, for 8 cycles)

- Luminal and luminal papillary subtypes: adjuvant treatment is permitted if considered appropriate by treating clinician (not trial treatment)

Participants in the standard care arm (and local investigators) will remain blinded to gene expression subtype category.

Outcomes will be collected at cystectomy and at 3, 6, and 12 months post-cystectomy.

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Luminal infiltrated subtype: neoadjuvant treatment (durvalumab: 1500 mg on day 1, every 21 days, for 4 cycles and tremelimumab: 75 mg on day 1, of cycles 1 and 3 only) prior to radical cystectomy and adjuvant treatment (durvalumab: 1500 mg on day 1, every 28 days, for 8 cycles)

Luminal and luminal papillary subtypes: adjuvant treatment is permitted for patients with T3-4, N1-2 disease if considered appropriate by treating clinician (not trial treatment)

Participants in the standard care arm (and local investigators) will remain blinded to gene expression subtype category.

Outcomes will be collected at cystectomy and at 3, 6, and 12 months post-cystectomy.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Cisplatin, gemcitabine, durvalumab, tremelimumab

Primary outcome(s)

GUSTO has been designed with three interim stages and each stage has a separate set of objectives and endpoints:

Stage 1 (to be assessed once the trial has been open to recruitment for 6 months):
1. Recruitment, defined as the number of patients randomised within the first 6 months of the trial opening.
2. Time to return of gene expression subtype allocation, defined as the time from the date the sample is received by the Sheffield central laboratory to the date the gene expression subtype allocation is entered onto the lab-specific database.
3. Gene expression subtype allocation success rate, defined as the proportion of samples sent to the Sheffield central laboratory which are successfully allocated a gene expression subtype.

Stage 2 (be assessed once the trial has been open to recruitment for 24 months):
1. Recruitment, defined as the number of patients randomised within the first 24 months of the trial opening.
2. Gene expression subtype distribution, defined as the proportion of samples (of those successfully allocated a gene expression subtype) in each gene expression subtype.
3. Pathological complete response rate in the standard care arm by gene expression subtype, defined as the proportion of patients within each gene expression subtype who are defined as having a pathological complete response according to local pathologist report (pT0) at RC.
4. Confirmation/re-estimation of sample size

Stage 3:
Pathological complete response rate by gene expression subtype in the gene expression subtype-guided arm post-cystectomy

An interim assessment of gene-expression subtype pathological response rate will take place once all randomised participants have completed cystectomy or are known not to be proceeding to cystectomy. Final analysis will take place once all randomised participants have been followed up for 12 months post-cystectomy. At this later point, the stage 1 and 2 endpoints will be re-evaluated.

Key secondary outcome(s)

Gene expression subtype endpoints (to be assessed once all randomised participants have been followed up for 12 months post-cystectomy):
1. RNA quality and mass/yield, defined as the quality and yield of the samples tested at Sheffield central laboratory. RNA quality will be measured using two measures: the 260:230 ratio and the 260:280 ratio. RNA yield will be measured in nanograms per microlitre (ng/uL).
2. Gene expression subtype allocation re-test rate and repeat assay success rate, defined as the proportion of samples sent to the Sheffield central laboratory which require retesting, and the proportion of those re-tested samples which are successfully allocated a gene expression subtype after re-testing.
3. Time from patient consent to TURBT sample dispatch, defined as the time from a patient consenting to gene expression subtyping to the time their TURBT sample is sent for gene expression profiling.
4. Time to RNA extraction, processing and gene expression subtype allocation, defined as the time from the sample being received in Sheffield to RNA extraction/processing/gene expression subtype allocation, respectively.

Clinical secondary endpoints (to be assessed once all randomised participants have been followed up for 12 months post-cystectomy):
1. Disease-free survival (DFS) at 12 months post-cystectomy and at the end of the trial for all consenting patients registered and all patients randomised into the trial. Disease-free survival for randomised participants is defined as the time from the date of RC to the first recurrence of disease post-RC, or death due to any cause or last follow-up. DFS will be assessed in patients who undergo RC and are disease free at adjuvant baseline visit. If a participant has not had disease recurrence or is still alive at the time of analysis or lost to follow-up before disease recurrence/death is documented, they will be censored at the last date known alive. Participants discontinuing protocol treatment or receiving non-protocol treatment will still be followed for disease-free survival unless they explicitly withdraw consent. For consenting registered participants disease-free survival is defined similarly but from the date of registration.
2. Overall survival at 12 months post-cystectomy and at the end of the trial for all consenting patients registered and all patients randomised into the trial. Overall survival is defined as the time from randomisation to death from any cause or last follow-up. If a participant is still alive at the time of analysis or lost to follow-up before death is documented, they will be censored at the last date known alive. Participants discontinuing protocol treatment or receiving non-protocol treatment will still be followed for overall survival unless they explicitly withdraw consent. For consenting registered participants overall survival is defined similarly but from the date of registration.
3. Metastasis-free survival at 12 months post-cystectomy and at the end of the trial for all consenting patients registered and all patients randomised into the trial. Metastasis-free survival is defined as the time from randomisation to the first indication of a metastasis. If a participant has not had a metastasis at the time of analysis, or either died or was lost to follow-up before a metastasis is documented, they will be censored at the last date known alive without having developed a metastasis. Participants discontinuing protocol treatment or receiving non-protocol treatment will still be followed for metastasis-free survival unless they explicitly withdraw consent. For consenting registered participants metastasis-free survival is defined similarly but from the date of registration.
4. Event-free survival at 12 months post-cystectomy and at the end of the trial for all consenting patients registered and all patients randomised into the trial. Event-free survival is defined as the time from randomisation to any of the following events: failure to undergo RC (at the date the decision is made), recurrent cancer, metastasis, death from bladder cancer or commencement of further treatment for disease relapse. If a participant has not had any of these events at the time of analysis or either died from another cause or was lost to follow-up before an event was documented, they will be censored at the last date known alive without having had any of these events occur. Participants discontinuing protocol treatment or receiving non-protocol treatment will still be followed for event-free survival unless they explicitly withdraw consent. For consenting registered participants event-free survival is defined similarly but from the date of registration.
5. Histological outcomes, defined as the Tumour-Node-Metastasis (TNM) stages in both the TURBT and RC specimens. Additional parameters include margin rate (negative or positive), location of positive margins (urethra, ureteric, circumferential, soft tissue), lymph node count and number of nodes containing cancer.
6. Quality of life measured using the EQ-5D-3L and EORTC QLQ-C30 questionnaires at baseline, 6 months and 12 months post-cystectomy
7. Patient acceptability to registration and randomisation, defined as the proportion of eligible patients agreeing to registration. Acceptability to randomisation is defined as the proportion of eligible registered patients agreeing to randomisation and the proportion of randomised participants who receive their randomised treatment.
8. Pathological complete response stage by gene expression subtype in the standard and gene expression subtype-guided arms post cystectomy, defined as the proportion of participants

within each gene expression subtype with:
8.1. Complete Response (no tumour)
8.2. Partial Response (downstaging – MIBC to NMIBC)
8.3. No response (MIBC to MIBC)
8.4. Progression (Tany N0 to Tany N1-2 or M1-2)
9. Outcomes from recovery after radical cystectomy in the gene expression subtype-guided arm as determined by:
9.1. Time to cystectomy, defined as the time from randomisation to the time of RC
9.2. Safety of cystectomy, defined by blood loss, length of stay, readmission (number of patients who are re-admitted to hospital) and complications and adverse events, assessed using the Clavien-Dindo grade of complications
9.3. Pathological completeness will be assessed using the following:
9.3.1. Nodes, defined as the number in total and number that have cancer
9.3.2. Margins, defined as the proportion of positive (involved) or negative (clear)
9.3.3. Location of positive margin - Urethra. Ureteric. Circumferential. Soft tissue
10. To re-evaluate the stage 1 and 2 feasibility endpoints

Pharmacological secondary endpoints (to be assessed once all randomised participants have been followed up for 12 months post-cystectomy):
1. Toxicity and tolerability will be reported based on safety events, as graded by CTCAE V5.0 and Clavien-Dindo grade of complications where appropriate
2. Treatment compliance, defined as the number of dose omissions, dose delays, dose reductions and delays to RC and will be assessed by dose omissions, dose delays, dose reductions and delays to RC

Exploratory endpoints (to be assessed once all randomised participants have been followed up for 12 months post-cystectomy):
1. The PD-L1 status of tumour and infiltrating immune cells in pre-existing diagnostic samples in all patients, defined as the result of the Ventana/Roche SP263 PD-L1 immunohistochemistry assay, which will give a dichotomous result of either:
1.1. PD-L1 high/positive
1.2. PD-L1 low/negative
2. The utility of the Decipher RNA expression profiling (microarrays) as input to other MIBC sub-classifiers
3. The concordance of predicted subtypes for each sample across classifiers, defined as any comparisons made between the Decipher Bladder (Veracyte, USA) commercial gene expression subtyping test and any alternative classifier systems/tests

Completion date
30/09/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 30/06/2025:

Inclusion criteria for registration:
1. Age ≥18 years
2. Eastern Co-operative Oncology Group (ECOG) performance status 0 or 1
3. Currently considered for neoadjuvant chemotherapy and radical cystectomy with curative intent and suitable for all protocol defined treatment (chemotherapy and immunotherapy as

defined for all treatment groups in this protocol)
4. Confirmation of MIBC (full report not required):
- high grade pure or mixed urothelial (transitional) cell carcinoma which is at least T1 on histology AND radiological evidence of T2+ N1 cancer
OR
- high grade pure or mixed urothelial (transitional) cell carcinoma which is at least T2 on histology
5. Written informed consent for registration (PIS-1 and Participant Supplementary Document)

Inclusion criteria for randomisation:
1. Diagnosed with MIBC staged as either T2-4a N0 M0, T (any) N1 M0 or T1 on histology with radiological evidence of T2+ or N1
2. Planned for neoadjuvant chemotherapy and radical cystectomy with curative intent and suitable for all protocol defined treatment (chemotherapy and immunotherapy as defined for all treatment groups in the protocol)
3. Confirmation of a pure or mixed urothelial (transitional cell) carcinoma tumour histology based on local institutional pathology reporting
4. ECOG performance status 0 or 1
5. Estimated creatinine clearance rate (using the Cockcroft-Gault formula) of >40 ml/min according to local institutional standard methods for estimation: patients with creatinine clearance ≥ 60 ml/min are eligible for full dose cisplatin; patients with impaired creatinine clearance (40-60 ml/min) are eligible only if split dose cisplatin 35 mg/m2 is given on days 1 and 8 of neoadjuvant treatment.
6. Adequate haematological parameters
6.1. Haemoglobin ≥90 g/Lb.
6.3 Neutrophil count ≥1.5 x109 /L
6.2. Platelets ≥100 x109 /L
7. Adequate biochemical parameters:
7.1. Bilirubin ≤1.5 x ULN unless due to Gilbert's syndrome
7.2. ALT and/or AST ≤1.5 x ULN (both ALT and AST are recommended)
8. Body weight >30 kg
9. Life expectancy of at least 12 weeks
10. For women of childbearing potential, negative blood serum pregnancy test and adequate contraceptive precautions
11. For men of reproductive potential, effective contraception if the risk of conception exists
12. Written informed consent for randomisation (PIS-2 and Participant Supplementary Document)
13. Patients must be able and willing to comply with the terms of the protocol for the duration of the study including treatment, trial visits and assessments

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Previous inclusion criteria:

Inclusion criteria for registration:
1. Age ≥18 years
2. Eastern Co-operative Oncology Group (ECOG) performance status 0 or 1
3. Currently considered for neoadjuvant chemotherapy and radical cystectomy with curative intent and suitable for all protocol defined treatment (chemotherapy and immunotherapy as defined for all treatment groups in this protocol)
4. Histological confirmation of MIBC with pure or mixed urothelial (transitional) cell carcinoma (full report not required)
5. Written informed consent for registration (PIS-1 and Participant Supplementary Document)

Inclusion criteria for randomisation:
1. Diagnosed with MIBC staged as either T2-4a N0 M0 or T (any) N1 M0
2. Planned for neoadjuvant chemotherapy and radical cystectomy with curative intent and suitable for all protocol defined treatment (chemotherapy and immunotherapy as defined for all treatment groups in the protocol)
3. Confirmation of a pure or mixed urothelial (transitional cell) carcinoma tumour histology based on local institutional pathology reporting
4. ECOG performance status 0 or 1
5. Estimated glomerular filtration rate of ≥60 ml/min according to local institutional standard methods for estimation (For patients with impaired GFR (40-60 ml/min) a split dose cisplatin 35 mg/m2 on days 1 and 8 is permitted.)
6. Adequate haematological parameters
6.1. Haemoglobin ≥90 g/Lb.
6.3 Neutrophil count ≥1.5 x109 /L
6.2. Platelets ≥100 x109 /L
7. Adequate biochemical parameters
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12. Written informed consent for randomisation (PIS-2 and Participant Supplementary Document)
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Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
100 Years

Sex
All

Total final enrolment
0

Key exclusion criteria
Current exclusion criteria as of 30/06/2025:

1. Bladder tumour where a gene expression subtype classification cannot be made
2.TURBT sample processing delay such that >4 weeks from receipt of TURBT sample (from initial or repeat surgery if relevant) at central lab to receipt of gene expression subtype result at site
3. Known or suspected allergy or hypersensitivity reaction to any of the components of study treatment or their excipients for any of the treatment groups in the protocol
4. Active infection likely to impact safety of treatment delivery for any of the study treatment groups in the protocol or radical cystectomy. This includes known active tuberculosis, hepatitis B (known positive HBsAg result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). 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. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid
5. Active documented autoimmune or inflammatory disorders, including but not limited to, inflammatory bowel disease (e.g., colitis or Crohn's disease), systemic lupus erythematosus, sarcoidosis, Wegener syndrome (granulomatosis with polyangiitis), Graves' disease, rheumatoid arthritis and uveitis. Exceptions: vitiligo, alopecia, hypothyroidism that is stable on hormone replacement and any chronic skin condition not requiring systemic therapy and patients with coeliac disease controlled by diet alone.
6. Major surgical procedure <28 days prior to randomisation
7. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable angina pectoris or congestive cardiac failure (New York Heart Association > grade 2) within the last 6 months
8. Mean QT interval corrected for heart rate ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart)
9. Uncontrolled concurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise ability of the patient to give written informed consent
10. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in inclusion criteria
11. Current or prior use of immunosuppressive medications within 14 days prior to randomisation including, but not limited to, systemic corticosteroids at doses exceeding 10 mg /day of prednisolone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers. Permitted exceptions include: use prior to imaging procedures in patients with contrast allergies, use of inhaled, topical, and intranasal corticosteroids
12. Radiotherapy treatment to >30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug
13. A current separate other malignancy. Current non-melanoma skin cancer, cervical carcinoma in situ or incidental localised prostate cancer is permissible. Other prior malignancy is acceptable if treatment within GUSTO is given with curative intent
14. Any concurrent chemotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions is acceptable
15. Breastfeeding women
16. History of allogenic organ transplantation
17. History of leptomeningeal carcinomatosis
18. History of primary immunodeficiency
19. Receipt of live attenuated vaccine within 30 days prior to randomisation
20. Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment

21. Patients who received prior anti–PD-1 (including durvalumab), anti PD-L1 or anti CTLA-4 (including tremelimumab):
21.1. Must not have experienced toxicity leading to permanent discontinuation of prior immunotherapy (IO).
21.2. All AEs while receiving prior IO must have completely resolved or resolved to baseline prior to screening for this study.
21.3. Must not have experienced a ≥Grade 3 immune related AE, an immune related neurologic or ocular AE (any grade) while receiving prior IO (patients with endocrine AE of ≤Grade 2 eligible if stable on replacement therapy and asymptomatic
21.4. Must not have required the use of immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of AE if re-challenged, and not currently require maintenance doses of >10 mg prednisone or equivalent per day
22. Any contraindication to treatment with cisplatin, gemcitabine or durvalumab as described within the respective local SmPCs
23. Participation in another clinical study with an investigational product during GUSTO trial participation and follow-up.

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Previous exclusion criteria:

1. Bladder tumour where a gene expression subtype classification cannot be made
2.TURBT sample processing delay such that >4 weeks from receipt of TURBT sample at central lab to receipt of gene expression subtype result at site
3. Known or suspected allergy or hypersensitivity reaction to any of the components of study treatment or their excipients for any of the treatment groups in the protocol
4. Active infection likely to impact safety of treatment delivery for any of the study treatment groups in the protocol or radical cystectomy. This includes known active tuberculosis, hepatitis B (known positive HBsAg result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies). 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. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV ribonucleic acid
5. Active documented autoimmune or inflammatory disorders, including but not limited to, inflammatory bowel disease (e.g., colitis or Crohn’s disease), systemic lupus erythematosus, sarcoidosis, Wegener syndrome (granulomatosis with polyangiitis), Graves’ disease, rheumatoid arthritis and uveitis. Exceptions: vitiligo, alopecia, hypothyroidism that is stable on hormone replacement and any chronic skin condition not requiring systemic therapy
6. Major surgical procedure <28 days prior to randomisation
7. Coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, unstable angina pectoris or congestive cardiac failure (New York Heart Association > grade 2) within the last 6 months
8. Mean QT interval corrected for heart rate ≥470 ms calculated from 3 ECGs (within 15 minutes at 5 minutes apart)
9. Uncontrolled concurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhoea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise ability of the patient to give written informed consent
10. Any unresolved toxicity NCI CTCAE Grade ≥2 from previous anticancer therapy with the exception of alopecia, vitiligo, and the laboratory values defined in inclusion criteria

11. Current or prior use of immunosuppressive medications within 14 days prior to randomisation including, but not limited to, systemic corticosteroids at doses exceeding 10 mg /day of prednisolone or equivalent, methotrexate, azathioprine, and tumour necrosis factor-α blockers. Permitted exceptions include: use prior to imaging procedures in patients with contrast allergies, use of inhaled, topical, and intranasal corticosteroids
12. Radiotherapy treatment to >30% of the bone marrow or with a wide field of radiation within 4 weeks of the first dose of study drug
13. A current separate other malignancy. Current non-melanoma skin cancer, cervical carcinoma in situ or incidental localised prostate cancer is permissible. Other prior malignancy is acceptable if treatment within GUSTO is given with curative intent
14. Any concurrent chemotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions is acceptable
15. Breastfeeding women
16. History of allogenic organ transplantation
17. History of leptomeningeal carcinomatosis
18. History of primary immunodeficiency
19. Receipt of live attenuated vaccine within 30 days prior to randomisation
20. Prior randomisation or treatment in a previous durvalumab clinical study regardless of treatment arm assignment
21. Patients who received prior anti–PD-1 (including durvalumab), anti PD-L1 or anti CTLA-4 (including tremelimumab):
21.1. Must not have experienced toxicity leading to permanent discontinuation of prior immunotherapy (IO).
21.2. All AEs while receiving prior IO must have completely resolved or resolved to baseline prior to screening for this study.
21.3. Must not have experienced a ≥Grade 3 immune related AE, an immune related neurologic or ocular AE (any grade) while receiving prior IO (patients with endocrine AE of ≤Grade 2 eligible if stable on replacement therapy and asymptomatic
21.4. Must not have required the use of immunosuppression other than corticosteroids for the management of an AE, not have experienced recurrence of AE if re-challenged, and not currently require maintenance doses of >10 mg prednisone or equivalent per day
22. Any contraindication to treatment with cisplatin, gemcitabine or durvalumab as described within the respective local SmPCs

Date of first enrolment
31/08/2023

Date of final enrolment
30/09/2026

Locations

Countries of recruitment
United Kingdom

England

Scotland

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

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
England
SO16 6YD

Study participating centre
Royal Devon & Exeter Foundation Hospital
Barrack Road
Exeter
England
EX2 5DW

Study participating centre
St. James's University Hospital
Beckett Street
Leeds
England
LS9 7TF

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
England
NW1 2PG

Study participating centre
Guys Hospital
Guys Hospital
Great Maze Pond

London
England
SE1 9RT

Study participating centre
Derriford Hospital
Derriford Road
Plymouth
England
PL6 8DH

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
England
TS4 3BW

Study participating centre
Lister Hospital
Coreys Mill Lane
Stevenage
England
SG1 4AB

Study participating centre
Charing Cross Hospital
Fulham Palace Road
London
England
W6 8RF

Study participating centre
Nottingham City Hospital NHS Trust
Hucknall Road
Nottingham
England
NG5 1PB

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow
Scotland
G51 4TF

Study participating centre
Western General Hospital
Crewe Road South
Edinburgh
Lothian
Scotland
EH4 2XU

Study participating centre
Salford Royal
Stott Lane
Salford
England
M6 8HD

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
England
M20 4BX

Sponsor information

Organisation
Sheffield Teaching Hospitals NHS Foundation Trust

ROR
https://ror.org/018hjpz25

Funder(s)

Funder type
Government

Funder Name
National Institute for Health and Care Research (NIHR), Efficacy and Mechanism Evaluation (EME) Programme (Ref: NIHR 128103)

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics, AZ

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
De-identified individual participant data datasets generated and/or analysed during the current study will be available upon request from the Clinical Trials Research Unit, University of Leeds (contact CTRU-DataAccess@leeds.ac.uk in the first instance). Data will be made available at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete. Data will remain available from then on for as long as CTRU retains the data.

CTRU makes data available by a 'controlled access' approach. Data will only be released for legitimate secondary research purposes, where the Chief Investigator, Sponsor and CTRU agree that the proposed use has scientific value and will be carried out to a high standard (in terms of scientific rigour and information governance and security), and that there are resources available to satisfy the request. Data will only be released in line with participants' consent, all applicable laws relating to data protection and confidentiality, and any contractual obligations to which the CTRU is subject. No individual participant data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention, usually stipulating that data recipients must delete their copy of the released data at the end of the planned project.

The CTRU encourages a collaborative approach to data sharing, and believes it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets. Recipients of trial data for secondary research will also receive data dictionaries, copies of key trial documents and any other information required to understand and reuse the released datasets.

The conditions of release for aggregate data may differ from those applying to individual participant data. Requests for aggregate data should also be sent to the above email address to discuss and agree suitable requirements for release.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			20/09/2023	No	No
Protocol (other)	V3.0	29/01/2024	16/11/2026	No	No
Study website			16/11/2026	No	No
Study website			16/11/2026	No	No