A randomised phase II study comparing 3 vs 6 cycles of platinum-based chemotherapy prior to maintenance avelumab in advanced urothelial cancer [DISCUS]

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I. Contents

II. Glossary of terms and abbreviations

Abbreviation	Definition
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
APR	Annual Progress Report
aPTT	Activated Partial Thromboplastin Time
AR	Adverse Reaction
AST	Aspartate Aminotransferase
CA	Competent Authority
Ca	Calcium
CECM	Centre for Experimental Cancer Medicine
CI	Chief Investigator
CT	Computerised Tomography
CTCAE	Common Toxicity Criteria For Adverse Events
CR	Complete Response
CtDNA	Circulating Tumour Deoxyribonucleic Acid
CNS	Central Nervous System
DNA	Deoxyribonucleic Acid
DSUR	Development Safety Update Report
ECG	Electrocardiography
eCRF	Electronic Case Report Form
EDTA	Ethylenediaminetetraacetic Acid
EOT	End of Treatment
EORTC	European Organisation for Research and Treatment of Cancer
EU	European Union
FFPE	Formalin Fixed Paraffin Embedded
GCP	Good Clinical Practice
GHS	Global Health Score
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B
HCV	Hepatitis C
HIV	Human Immunodeficiency Virus
HTA	Human Tissue Act
IB	Investigator's Brochure
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IRR	Infusion Related Reaction
ISF	Investigator Site File
IV	Intravenous
JRMO	Joint Research Management Office
K	Potassium
LDH	Lactate Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic Resonance Imaging

Abbreviation	Definition
NCC	National Coordinating Centre
NCI	National Cancer Institute
NICE	National Institute for Clinical Excellence
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Patient Information Sheet
PR	Partial Response
PSA	Prostate Specific Antigen
PSF	Pharmacy Site File
QoL	Quality of Life
REC	Research Ethics Committee
RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDV	Source Data Verification
STF	Sample Transfer Form
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
TSH	Thyroid Stimulating Hormone
UC	Urothelial Carcinoma
UK	United Kingdom
ULN	Upper Limit of Normal
URS	Ureteroscopic
WBC	White Blood Cell

III. Signature page

Chief Investigator Agreement

The study as detailed within this research protocol will be conducted in accordance with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments. I delegate responsibility for the statistical analysis and oversight to a qualified statistician (see declaration below).

Chief Investigator name: Prof Thomas Powles Signature: Thomas Powles Digitally signed by Thomas Powles Date: 2023.05.26 16:40:56 +01'00' Date: _____

Statistician's Agreement

with the principles of Good Clinical Practice, the UK Policy Framework for Health and Social Care Research, the Declaration of Helsinki, and the current regulatory requirements, including the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and all subsequent amendments, and ICH E9 - Statistical principles for Clinical Trials and ICH E10 - Choice of Control Groups. I take responsibility for ensuring the statistical work in this protocol is accurate, and for the statistical analysis and oversight of this study.

Statistician's name: Fahmida Jamal Signature: Fahmida Jamal Digitally signed by Fahmida Jamal Date: 2023.05.26 16:34:17 +01'00' Date: _____

Signature of the Country Coordinating Investigator

The clinical study as detailed within this research protocol **(Version V4.0, dated 16Mar2023)**, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Country Coordinating Investigator Name: Country:

Signature: _____ Date:_____

Principal Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version 4.0, dated 16Mar2023)**, or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator Name: _____

Principal Investigator Site: _____

Signature: _____ Date:_____

IV. Synopsis

Full title	A randomised phase II study comparing 3 vs 6 cycles of platinum-based chemotherapy prior to maintenance avelumab in advanced urothelial cancer
Short title and / or acronym	DISCUS
Sponsor	Queen Mary University of London
MHRA Risk level	Type A: No higher than the risk of standard medical care (studies are those testing authorised medicinal products in accordance with the marketing authorisation in an EU member state). Avelumab is currently licensed for use in the UK, Spain and France in the treatment of metastatic merkel cell carcinoma, advanced renal cell carcinoma and locally advanced or metastatic urothelial tumours. 6 cycles of chemotherapy are given as standard prior to commencing maintenance avelumab. Whilst fewer cycles of chemotherapy are licensed, this has not been formally tested. Fewer cycles are usually given due to adverse events associated with chemotherapy. Gemcitabine is currently licensed for use in the UK, Spain and France in the treatment of bladder cancer, advanced non-small cell lung cancer, advanced pancreatic cancer, breast cancer and ovarian cancer. Cisplatin is currently licensed for use in the UK, Spain and France in the treatment of testicular, lung, cervical, bladder, head and neck, and ovarian cancer. Carboplatin is currently licensed for use in the UK, Spain and France in the treatment of advanced ovarian cancer and small cell lung cancer. Carboplatin is used as per standard of care in the treatment of urothelial carcinoma in both the UK and Spain.
Phase of the trial	Phase II
Medical condition or disease under investigation	Histologically documented, unresectable locally advanced, or metastatic urothelial cancer in patients who have not received prior systemic therapy for advanced disease.
Study design and methodology	Open-label, randomised, international, multi-centre.
Planned number of participants	224
Objectives	**Primary Objective** • To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance avelumab based on patient-reported outcomes (PROs) in the study population. **Secondary Objectives** • To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance

	avelumab based on additional patient-reported outcomes (PROs) in the study population. • To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance avelumab based on clinician reported outcomes. • To evaluate the safety and tolerability of 3 vs 6 cycles of platinum-based, front-line chemotherapy followed by maintenance avelumab therapy. • To assess the efficacy of 3 vs 6 cycles platinum based, front-line chemotherapy followed by maintenance avelumab in patients with advanced UC. **Exploratory or tertiary objectives** • An exploratory investigation of efficacy of 3 vs 6 cycles platinum based, front-line chemotherapy followed by maintenance avelumab in patients with advanced UC. **Optional substudy objectives (See Appendix A)** • An optional, exploratory investigation into the use of wearable device data as a tool for assessing quality of life in patients enrolled on the DISCUS trial. See Appendix A.
Inclusion and exclusion criteria	**Inclusion criteria** Each patient **must meet all of the following inclusion criteria** to be enrolled in the study: 1. Willing and able to provide written informed consent. 2. Ability to comply with the protocol, including but not limited to, the repeated completion of the EORTC QLQ-C30 questionnaires. 3. Age ≥ 18 years. 4. Histologically confirmed, unresectable locally advanced or metastatic urothelial carcinoma (i.e., cancer of the bladder, renal pelvis, ureter, or urethra). Patients with squamous or sarcomatoid differentiation or mixed cell types are eligible but a component of urothelial cancer is required. 5. Measurable disease by RECIST v1.1. 6. Eligible for gemcitabine/ cisplatin or gemcitabine/carboplatin. Patients meeting any of the following criteria or considered ineligible for cisplatin as per investigator discretion should be considered for gemcitabine/carboplatin (as per local standard practice): a. GFR <60 mL/min (measured by the Cockcroft-Gault formula or by local accepted standards). Subjects with a GFR ≥50 mL/min and no other cisplatin ineligibility criteria may be considered cisplatin-eligible based on the investigator's clinical judgement. Subjects are required to have a GFR ≥30 mL/min (measured by the Cockcroft-Gault

	formula or by local accepted standards) to receive carboplatin. b. ECOG or WHO performance status of 2. c. NCI CTCAE Grade ≥2 audiometric hearing loss d. NYHA Class III heart failure. d. e. . 7. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1 or 2. 8. Adequate haematologic and organ function as defined below: a. Haemoglobin ≥ 9.0g/dL b. Absolute neutrophil count (ANC) ≥1.5 x 109/L (≥1500/μL) without growth factor support c. Platelet count ≥ 100 x 109 /L (≥100,000/μL) d. Total serum bilirubin ≤1.5 x institutional upper limit of normal (ULN) (this will not apply to subjects with confirmed Gilbert's syndrome [persistent or recurrent hyperbilirubinaemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology], who will be allowed only in consultation with their physician. e. Serum transaminases (AST/ALT) ≤2.5 x the institutional ULN with the following exception in patients with documented liver metastases: AST and/or ALT ≤5 × ULN f. GFR ≥30mL/min measured by Cockroft-Gault formula, or by locally accepted standards. 9. Negative serum or urine pregnancy test within 2 weeks of Day 1 Cycle 1 for female patients of childbearing potential only. Non-childbearing potential is defined as either: a. Postmenopausal ≥ 50 years of age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments OR b. Documented irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation OR c. <50 years of age who have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels within local institution postmenopausal ranges. 10. Agreement to use adequate contraceptive measures (Refer to section 11.30 for full details).

Exclusion criteria

A patient **will not be eligible for inclusion** in this study if any of the following criteria apply:

1. Prior treatment with a PD-(L)-1 inhibitor for any advanced malignancy. Treatment with PD-(L)-1 inhibitors in the neoadjuvant or adjuvant setting for UC are permitted.
2. Prior systemic therapy for locally advanced or metastatic urothelial carcinoma with the following exceptions: a platinum containing regimen (cisplatin or carboplatin) in the neoadjuvant or adjuvant setting if more than 6 months since last cycle have occurred. Patients who received adjuvant or neoadjuvant immune therapy for muscle invasive or non-muscle invasive disease are eligible.
3. Pregnant and lactating female patients.
4. Known history of active CNS metastases. Patients with treated CNS metastases are permitted on the study if all of the following are true:
    a. CNS metastases have been clinically stable for at least 4 weeks prior to screening and baseline scans show no evidence of new or enlarged metastasis;
    b. the subject is on a stable dose of ≤10 mg/day of prednisone or equivalent for at least 2 weeks prior to C1D1 (if requiring steroid treatment);
    c. subject does not have leptomeningeal disease.
5. Prior allogeneic stem cell or solid organ transplantation.
6. Administration of a live, attenuated vaccine within 4 weeks prior to enrolment or anticipation that such a live, attenuated vaccine will be required during the study.
7. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]−2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to enrolment (see section 11.26).
8. Concurrent treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 4 weeks prior to enrolment.
9. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including, but not limited to, significant liver disease (such as cirrhosis), uncontrolled major seizure disorder, or superior vena cava syndrome.
10. Malignancies other than urothelial carcinoma within 3 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate

	cancer (Gleason score ≤ 3 + 4 and PSA < 10 ng/mL undergoing active surveillance and treatment naive). . 11. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction or cerebral vascular accident/stroke within 6 months prior to enrolment, unstable arrhythmias, or unstable angina. 12. Radiotherapy within 2 weeks prior to C1D1. Patients must have recovered adequately from toxicities resulting from the intervention prior to starting study treatment. 13. Major surgery (defined as requiring general anaesthesia and >24-hour inpatient hospitalization) within 4 weeks prior to randomisation. Patients must have recovered adequately from complications from the intervention prior to starting study treatment. 14. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan (History of radiation pneumonitis in the radiation field (fibrosis) is permitted). 15. Active hepatitis infection (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible. 16. Positive HIV test. 17. Active tuberculosis. 18. Active autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis 19. History of autoimmune-related hypothyroidism, unless on a stable dose of thyroid replacement hormone. 20. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies. 21. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of avelumab. 22. Active infection requiring systemic therapy 23. Persisting toxicity related to prior therapy (NCI CTCAE Grade > 1); however, alopecia, sensory neuropathy Grade

	≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable 24. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results 25. Participants with previous or known history of allergic reaction to cisplatin, gemcitabine, carboplatin or other platinum containing compounds, or any component of the chemotherapy formulations. 26. Patients with bleeding tumours 27. Any other contraindication for gemcitabine/ cisplatin or gemcitabine/carboplatin treatment as per SmPC.
Investigational Medicinal Product(s)	Avelumab – 800mg Q2W - Intravenous Gemcitabine – 1000mg/m^2 Q3W - Intravenous Cisplatin - 70mg/m^2 Q3W - Intravenous Carboplatin - AUC 4.5 or 5 Q3W - Intravenous
Treatment duration	**Arm A:** 3 cycles of Q3W gemcitabine (1000mg/m^2) + carboplatin (AUC 4.5 or 5, as per local practice) / cisplatin (70mg/m^2) followed by maintenance avelumab (800mg Q2W). Maintenance avelumab treatment will be given up to a maximum of 2 years from the end of chemotherapy. **Arm B:** 6 cycles of Q3W gemcitabine (1000mg/m^2) + carboplatin (AUC 4.5 or 5) / cisplatin (70mg/m^2) followed by maintenance avelumab (800mg Q2W). Maintenance avelumab treatment will be given up to a maximum of 2 years from the end of chemotherapy.
Follow up duration	Follow up duration will be until the end of avelumab treatment or for 2 years from completion of chemotherapy, whichever is longer.
End of Trial definition	Last patient last visit

1 Introduction

1.1 Background

1.1.1 Urothelial carcinoma

Urothelial cancer (UC) includes tumours originating from the urothelial cells lining the bladder, renal pelvis, ureter and urethra[1]. Bladder cancer alone accounts for 90% of UC and is the 10th most common cancer worldwide with approximately 549,000 new cases diagnosed per year, with 200,000 deaths attributed to the disease[2]. It is four times more common in men than women[2]. The incidence and mortality of bladder cancer have remained unchanged over the last 25 years[3] with high incidence particularly seen in developed countries. In the UK, it is the 11th most common cancer with around 10,200 new cases and 5,400 deaths annually [4]. However, in Mediterranean countries like Spain the incidence of new diagnoses of UC rise up to the 4th most frequent cancer with 22,350 cases and 4,400 deaths[5].

The management of bladder cancer is based on the pathological findings of the biopsy. According to the World Health Organisation (WHO) 2016 classification, there are two main pathological groups of urothelial carcinoma:[11]

- Non-muscle invasive urothelial carcinoma (NMIBC) (pTa-pT1, PTis)
- Muscle invasive urothelial carcinoma (MIBC) which infiltrates the detrusor muscle (pT2a-pT4b) and is considered high-grade.

Approximately 30% of patients with newly diagnosed UC present with high-grade, muscle-invasive UC of the bladder, which is typically aggressive and requires multimodal therapy including radical cystectomy followed by adjuvant chemotherapy[6].

5-15% of patients will be metastatic at the time of diagnosis[7], or if localised at diagnosis, metastasis will develop within 2 years when treated with radical cystectomy alone[8,9].

Survival of locally advanced or metastatic UC is poor. The five-year survival rate is around 77% for all stages of UC, although this falls to around 5% for advanced metastatic disease in the pre-immunotherapy era[10].

1.1.2 Chemotherapy

International reference guidelines are recommending first line treatment for locally advanced or metastatic UC with up to six cycles of combination chemotherapy with platinum-based regimes[11] followed by maintenance avelumab within 10 weeks of completion[1, 11, 12, 13]

A number of cisplatin containing chemotherapy regimens are acceptable, although gemcitabine and cisplatin is the most widely used in daily practice[14]. Cisplatin-containing combination chemotherapy is standard in advanced or metastatic UC patients who are fit enough to tolerate cisplatin; such as those patients otherwise fit, without comorbidities, performance status 0-1 and a creatinine clearance between 50-60ml/min[15]. Approximately 50% of patients are not deemed fit enough to tolerate cisplatin, due to not meeting the defined criteria. In these patients, gemcitabine + carboplatin combinations can be used[16] The combination of gemcitabine + cisplatin and gemcitabine + carboplatin showed comparable efficacy and better safety profile than combinations of methotrexate, vinblastine, doxorubicin and cisplatin (MVAC) used historically[17,18,19].

The Javelin Bladder 100 study looked at patient reported outcomes (PROs) using the National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index-18 (NCCN-FACT FBISI-18), NCCN-FACT FBISI-18 and subscales (disease related symptoms – physical (DRS-P), DRS-emotional (E), treatment side effects (TSE), and functional wellbeing (F/WB). This allowed total analysis and subsets of treatment specific side effects and cancer-related side effects. The mean score in Javelin was in the mid 50s out of 76 and similar scores are expected in this study[30].

One retrospective analysis of 472 patients with metastatic urothelial cancer, evaluated the impact of the number of cycles of first line platinum-based immunotherapy (fewer than 6 cycles versus standard of care 6 cycles) on the survival outcomes of patients[20]. 157 patients received 3 to 5 cycles (median 4 cycles) and 315 received 6 to 9 cycles (median 6 cycles) and showed no significant difference in overall survival (HR 1.02, 95% CI 0.78 – 1.33, p=0.91).

Fewer cycles may be therefore be adequate for some selected patients for reducing cumulative toxicity[20]. The omission of excessive cycles may also facilitate a better transition to second line therapy with immune-checkpoint inhibitors.

1.1.3 Immune checkpoint inhibitors in UC

There is a strong rationale for evaluating the role of immunotherapy in UC patients. The programmed death ligand 1 (PD-L1) pathway has emerged as a useful target in patients with UC. PD-1, a receptor on human cytotoxic CD8+ T cells, binds to PD-L1 and exerts an immune-inhibitory effect, potentiating tumour-escape mechanisms. The interaction of PD-L1 and PD1 inhibits CD8+ T cell activation, proliferation, survival and effector functions during the anti-cancer immune response. Urothelial cancers elude immune surveillance and eradication through expression of PD-L1 in the tumour microenvironment. Therefore, human monoclonal antibodies which target and bind to PD-L1, thereby blocking the interaction between PD-L1 and PD-1 and B7.1, can remove the suppressive effects of PD-L1 on anti-tumour CD8+ T cells, resulting in restoration of the cytotoxic T-cell response[21].

A Phase 1b study of pembrolizumab, a PD-1 inhibitor, in pre-treated patients with advanced UC showed durable response rates. The Overall Response Rate (ORR) in 33 patients with advanced UC was 25%, Complete response rate (CR), 10%. The median follow-up was 11 months (range 10-13 months) with a response rate ranging from 16 to over 40 weeks[22].

Similarly, data from two phase II studies suggests pembrolizumab or atezolizumab (an anti PD-L1) are reasonable alternatives to first line platinum-based chemotherapy regimens, in metastatic patients who are cisplatin ineligible but are programmed death ligand 1 (PD-L1) biomarker positive[19,23]. Biomarkers (SP142 for atezolizumab; 22C3 for pembrolizumab) should be used to match the drug, as recommended by the EMA. Well tolerated durable response (28% for atezolizumab and 47% for pembrolizumab, respectively) were observed with both drugs. Median Overall Survival (OS) extended beyond 15 months for both drugs. Treatment should continue for 2 years for pembrolizumab and until progression for atezolizumab. No consensus has been reached on whether immune checkpoint inhibitors could be recommended for PD-L1 biomarker-negative patients not eligible for chemotherapy.

Randomised front line Phase 3 trials show immune therapy to be no better than chemotherapy in PD-L1 biomarker positive patients and chemotherapy plus immune checkpoint inhibitor combinations are no better than chemotherapy alone, from a survival perspective in front-line metastatic disease.

DANUBE, a randomised phase 3 trial compared front line immune therapy with chemotherapy in patients with previously untreated, unresectable, locally advanced or metastatic urothelial carcinoma[33]. 1032 patients were enrolled into the trial and randomly allocated on a 1:1:1 basis to receive either A) durvalumab monotherapy (1500mg) IV every 4 weeks, B) durvalumab (1500mg) + tremelimumab (75mg) IV combination for 4 doses, followed by durvalumab maintenance (1500mg) IV every 4 weeks or C) standard of care chemotherapy with up to 6 cycles of gemcitabine plus cisplatin or carboplatin (depending on cisplatin eligibility). The study showed front line immune therapy to be no better than chemotherapy in the PD-L1 biomarker positive patients.

Another randomised phase 3 trial, IMvigor 130 evaluated atezolizumab alone or in combination with platinum-based chemotherapy in first-line metastatic urothelial cancer[30]. 1213 patients were randomly assigned to receive either A) 1200mg atezolizumab plus platinum-based chemotherapy, B) 1200mg atezolizumab monotherapy or C) placebo and platinum-based chemotherapy. Addition of atezolizumab to platinum-based chemotherapy as first-line treatment prolonged progression-free survival in patients with metastatic urothelial carcinoma, with an acceptable safety profile consistent with that observed with individual agents.

1.2 Avelumab in UC

Avelumab is a highly selective human monoclonal antibody which targets and binds to PD-L1, the ligand for PD-1 and B7.1, thereby blocking the interaction between PD-L1 and PD-1 and B7.1, removing the suppressive effects of PD-L1 on anti-tumour CD8+ T cells and resulting in restoration of the cytotoxic T-cell response[20].

Data from a pooled analysis of 249 patients enrolled in two advanced UC expansion cohorts in phase 1 study EMR 100070-001 was recently published[24,25]. Patients were included regardless of PD-1L expression levels. The median age was 68 years and 124 (50%) of patients received 2 more or more prior treatments for advanced or metastatic disease. At the time of analysis (cut off 10 April 2018), the median follow-up was 31.9 months (Range 24 – 43 months) and 12 (4.8%) of patients were still on treatment. Among 161 post-platinum treated patients with at least 6 months of follow-up, the ORR was 17% (95% CI 11-24%), including 9 CR and 18 partial response (PR). The disease control rate (DCR) was 40%, including 37 patients who had stable disease (SD) as their best response. An analysis using cut off of ≥ 5% for the expression of PD-L1 on tumour cells in 139 evaluable patients showed a 24% (15 out of 63) PRR in the PD-L1 positive population, and a 13% 10 out of 76) in the PD-L1 negative population, respectively. This supports the notion that avelumab has anti-tumour activity in both the PD-L1 positive and negative populations. The median PFS was 11.9 weeks (95% CI: 6.1-18.0 weeks) and 6.1 weeks (95% CI: 5.9 – 8.0 weeks) in the PD-L1 positive and negative populations, respectively. The median OS was 8.2 months (95% CI: 5.7 – 13.7 months) and 6.2 months (95% CI: 4.3 – 14.0 months) in patients with PD-L1 positive and negative tumours respectively.

Durable and complete responses following first-line chemotherapy in patients with advanced UC are uncommon. Complicated treatment regimens and adverse events limit long-term use and most patients will ultimately experience disease progression within 9 months after initial response[26]. Maintenance therapy with immune checkpoint inhibitors to promote a sustained response is therefore recommended[27]. Maintenance avelumab, started within 10 weeks of completion of first line platinum-based chemotherapy in patients with metastatic UC who have not progressed on first-line platinum-based chemotherapy is associated with an overall survival (OS) advantage compared with best supportive care; Hazard Ratio (HR) 0.69, (95% CI: 0.56-0.86)[12,27]. An increase in median OS from 14 to 21 months was observed with Avelumab. Benefit with avelumab was seen across predefined subgroups of patients, including PDL-1 status and type of response to previous therapy. Treatment was given until progression. Maintenance avelumab therapy has been approved by both US Food and Drug Administration (FDA) and European Medicines Agency (EMA).

1.2.1 Background

Avelumab is a human monoclonal antibody (mAb) of the immunoglobulin G1 isotype (IgG1). Avelumab selectively binds with high affinity to programmed death-ligand 1 (PD-L1) and competitively block its interaction with its receptors programmed death protein 1 (PD-1) and CD80 (B7-1). This removes the suppressive effects of PD-L1 on antitumor CD8+ T cells, resulting in restoration of cytotoxic T cell response. Avelumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 144kDa.

1.2.2 Summary of non-clinical experience

The non-clinical experience is fully described in the current version of the avelumab Summary of Product Characteristics[21].

The non-clinical pharmacology studies have shown that avelumab functionally enhances T cell activation in vitro and significantly inhibits the growth of PD-L1 expressing tumours in vivo.

Avelumab binds to human and murine PD-L1 with a high affinity and specificity to human PD-L1, blocking its interaction with PD-1 and CD80. In invitro studies show that by binding to PD-L1, avelumab effectively enhances T cell activation, as measured by interleukin-2 (IL-2) or interferon gamma (IFN-γ) production. Further in vitro studies demonstrate that avelumab antagonizes the inhibitory effect of PD-L1 on primary

human CD8+ T cells, resulting in their activation and restored proliferation, significantly reducing the growth of PD-L1 expressing tumours in vivo.

As a second mode of action, avelumab is capable of stimulating antibody-dependent cell-mediated cytotoxicity (ADCC) activity against PD-L1+ tumour cells in vitro and elimination of ADCC potential in vivo significantly reduced antitumor activity.

In vivo studies in mouse carcinoma models have demonstrated avelumab is capable of inhibiting tumour growth when applied as monotherapy, but also that its efficacy can be further enhanced via combination with other standard of care therapies such as cytotoxic agents (avelumab in combination with FOLFOX [folinic acid, 5 fluorouracil and oxaliplatin], cyclophosphasmide) or radiation therapy.

In vivo models using mice, rats and cynomolgus monkeys were selected for evaluation of the pharmacokinetics, pharmacodynamics and potential toxicity of avelumab.

As a monotherapy, avelumab has demonstrated antitumor activity against murine MC38 colon carcinoma tumours that are categorised by a high level of PD-L1 expression. A dose-dependent trend was observed and 400μg per dose (approximately 20mg/kg) was identified as the optimally effective dose when given every 3 days for a total of 3 doses.

Overall, the available pre-clinical data demonstrates that avelumab has the potential to offer significant clinical benefits through its ability to release antitumor CD8+ T cells from the suppressive effects of PD-L1 in the tumour microenvironment and inhibit tumour growth in vivo when applied as monotherapy. The efficacy can be further enhanced via combination with other standard of care therapies. The non-clinical safety profile for avelumab is considered adequate to support the use of avelumab in the planned therapeutic indication in humans.

1.2.3 Summary of clinical experience

Clinical experience is fully described in the current version of the avelumab Summary of Product Characteristics [21].

Avelumab is being studied in a wide variety of adult cancers, such as non-small cell lung cancer, gastric cancer, merkel cell carcinoma, renal cell carcinoma, ovarian cancer and urothelial cancer. As of 22 March 2020, a total of 18,904 patients have received avelumab in a total of 32 Phase I, II and III clinical trials across these cancer types.

A dose of 10mg/kg of avelumab via intravenous infusion (IV) every 2 weeks was selected for the expansion cohorts of Phase I studies, the Phase II pivotal study in metastatic merkel cell carcinoma (mMCC), and most ongoing Phase III studies based on the preliminary pharmacokinetic (PK), target occupancy (TO) and safety data collected in the clinical studies. In Phase II study EMR100070-003 (Part A) of mMCC, a dose of 10mg/kg every 2 weeks is associated with substantial tumour reduction, clinically meaningful efficacy with durable responses and prolonged PFS and has an acceptable safety and tolerability profile. The dose of 10mg/kg every 2 weeks has been approved (as of 22nd March 2019).

Modelling and simulation in more than 1700 patients has been used to provide a rationale for changing the regimen for avelumab from the initially approved 10mg/kg every 2 weeks to the flat dose of 800mg every 2 weeks for adults, assuming an average body weight of 75kg. Avelumab 800mg Q2W flat dose regimen is expected to maintain the established positive benefit-risk profile for avelumab 10mg/kg Q2W in the treatment of adults in the approved indications but is expected to provide more consistent dosing across body weights, minimise drug wastage, facilitate preparation and administration and reduce pharmacy errors[28]. To date, both the weight-based (10mg/kg Q2W) and the flat dose (800mg Q2W) regimes have been approved in global markets.

The 10mg/kg every 2 weeks dose of avelumab has been given in the phase 3 trial to 334 patients with locally advanced or metastatic urothelial cancer allocated to the treatment arm, via a 1-hour intravenous infusion (IV) at a dose of 10mg/kg once every 2 weeks (Q2W) together with best supportive care (BSC)[12].

It was associated with an overall survival (OS) advantage compared with best supportive care (hazard ratio [HR] 0.69, 95% confidence interval [CI] 0.56-0.86) and an acceptable safety profile[12].

1.2.4 Pharmacokinetics

Human pharmacokinetics of avelumab have been characterised using both noncompartmental analysis (NCA) and population PK (Pop PK) analyses. The PK profile of avelumab is typical for a human antibody, i.e., with a low clearance (CL) and volume of distribution.

Human pharmacokinetics data has been analysed in studies EMR 100070-001, EMR100070-002, EMR 100070-003, EMR 100070-004, EMR 100070-007, EMR 100070-008, MS100070-0035, B9991002, B9991003, B9991007 and B9991010 for different tumour types, as of March 2020.

Two Pop PK analyses were conducted. In the initial Pop PK analysis, data from 1629 subjects from ongoing studies EMR 100070-001 (data cut off 20 November 2015), EMR100070-002 (data cut off 20 November 2015) and EMR 100070-003 (data cut off 03 March 2016) were used to estimate PK parameters and evaluate the PK interindividual variability and any covariates that may be predictive of the variability.

Non-compartmental analyses on 77 mainly Caucasian patients in the dose escalation and expansion cohorts of study EMR 100070-001, revealed that the exposure of parameters of maximum concentration (C_{max}) and Area under the serum concentration-time curve (AUCt) increased with dose in a linear fashion across the 1,3, 10 and 20mg/kg doses. The apparent half-life tends to increase with dose, presumably linked to target-mediated disposition. Considering the variability, the half-lives of the 10 and 20mg/kg doses were similar (mean half-lives 102 and 120 hours, respectively), indicating that target mediated elimination dose not increase at these doses. This implies that target occupancy is likely to be high at these two doses throughout the dosing interval.

Following repeated administration of avelumab, the concentration at the end of infusion (C_{EOI}), reached the steady state approximately between the second and third dose with minimal accumulation, with less than 30% variability in C_{EOI} between day 1 and day 15.

The C_{trough} levels (concentration on the 336-hour sample) was similar across subjects with different tumour types and in dose-escalation cohorts, indicating no meaningful difference in avelumab PK among subjects with different solid tumour types.

Pop PK analyses demonstrated that age, race, baseline tumour PD-L1 status, UC tumour type or hepatic impairment had no influence on the avelumab CL or the central and peripheral volumes of distribution and no influence of renal impairment on CL. Body weight was found to positively correspond with PK exposure. The largest change in CL over time was found in subjects with mMCC; the estimated mean maximum reduction from baseline CL value at steady state was 32.1%. In subjects with the tumour type 'head and neck', CL also decreased over time, by a mean maximum reduction of 24.7% relative to baseline. The clinical impact of the change in CL over time is not known, but has been reported for other checkpoint inhibitors.

Complete PK information can be found in the avelumab Summary of Product Characteristics[21].

1.2.5 Safety

In the Phase 3 trial Javelin Bladder 100, 700 patients were randomised to avelumab group or control[12]. Among all treated patients (who received at least one dose of avelumab, adverse events of any grade occurred in 337 of 344 patients (98.0%). In the control group, adverse events occurred in 268 of 345 patients (77.7%). In the avelumab group, the most common treatment related adverse events observed of any grade were fatigue (61 patients, 17.7%), pruritis (59 patients, 17.2%), urinary tract infections (59 patients, 17.2%) and diarrhoea (57 patients, 16.6%). Grade 3 or higher adverse events occurred in 163 patients (47.4%) and 87 patients (25.2%), respectively. The most commonly observed grade 3 or higher adverse events in the avelumab group were urinary tract infection (15 patients, 4.4%), anaemia (13 patients, 3.8%) and fatigue (6 patients, 1.7%), No grade 4 or fatal immune-related adverse events occurred. Adverse events in the avelumab group led to treatment discontinuation in 41 patients (11.9%).
DISCUS Master Protocol V4.1 dated 25May2023

Death attributed to toxicity occurred in 2 patients in the avelumab group (0.6%). One event was due to sepsis from urinary tract infection and possible central venous catheter infection after receiving 11 infusions of avelumab, the other patient had an ischaemic stroke 100 days after receiving a single dose of avelumab and after disease progression and adverse events of limb venous thrombosis, pulmonary embolism and acute myocardial infarction. Median duration of trial treatment was 24.9 weeks (range, 2.0 to 159.9).

1.2.6 Efficacy

Data from a pooled analysis of 249 patients enrolled in two advanced UC expansion cohorts in phase 1 study EMR 100070-001 was recently published[29]. Patients were included regardless of PD-1L expression levels. The median age was 68 years and 124 (50%) of patients received 2 more or more prior treatments for advanced or metastatic disease. At the time of analysis (cut off 09 June 2016), the median follow-up was 9.9 months (Range 4.3 – 12.1 months) and 60 (24%) of patients were still on treatment. Among 161 post-platinum treated patients with at least 6 months of follow-up, the ORR was 17% (95% CI: 11-24%), including 9 CR and 18 PR. The DCR was 40%, including 37 patients who had stable disease as their best response. An analysis using cut off of ≥ 5% for the expression of PD-L1 on tumour cells in 139 evaluable patients showed a 24% (15 out of 63) PRR in the PD-L1 positive population, and a 13% (10 out of 76) in the PD-L1 negative population, respectively. The median PFS was 11.9 weeks (95% CI: 6.1-18.0 weeks) and 6.1 weeks (95% CI: 5.9 – 8.0 weeks) in the PD-L1 positive and negative populations, respectively. The median OS was 8.2 months (95% CI:5.7 – 13.7 months) and 6.2 months (95% CI: 4.3 – 14.0 months) in patients with PD-L1 positive and negative tumours respectively.

In the Phase 3 trial Javelin Bladder 100, maintenance avelumab, started within 10 weeks of completion of first line platinum-based chemotherapy in patients with metastatic UC who have not progressed on first-line platinum-based chemotherapy is associated with an overall survival (OS) advantage compared with best supportive care; hazard ratio (HR) 0.69, (95% CI: 0.56-0.86)[12]. An increase in median OS from 14 to 21 months was observed with avelumab. Benefit with avelumab was seen across predefined subgroups of patients, including PDL-1 status and type of response to previous therapy.

1.3 Rationale for study design

The study aims to investigate whether:

- Three cycles of platinum-based chemotherapy are superior in terms of QOL scores using PROs compared to six cycles.
- Three cycles of platinum-based chemotherapy and maintenance avelumab will be at least as active as the current standard approach of six cycles and maintenance avelumab in terms of Overall Survival.

Sequencing maintenance avelumab with up to six cycles of platinum-based chemotherapy is the current standard of care for advanced UC[12]. First-line immune checkpoint inhibitors have not proven to be superior to chemotherapy[30],[31]. No clear benefit in terms of better survival has been observed in patients who receive at least 3 cycles no matter the number of subsequent cycles are being offered but with additional toxicity[31].

There is lack of clarity on the number of cycles of chemotherapy required to maximise chemotherapy outcomes[20]. Six cycles have been given as the standard of care for historical reasons. The Javelin Bladder 100 study looked at patient reported outcomes (PROs) using the National Comprehensive Cancer Network – Functional Assessment of Cancer Therapy Bladder Cancer Symptom Index-18 (NCCN-FACT FBISI-18), NCCN-FACT FBISI-18 and subscales (disease related symptoms-physical (DRS-P), DRS-emotional [E], treatment side effects [TSE], and functional wellbeing [F/WB]). This allowed total analysis and subsets of treatment specific side effects and cancer related side effects. The mean score in Javelin was in the mid 50s out of 76 and similar scores are expected in the study.

In addition, the administration of three versus six cycles of chemotherapy followed by maintenance avelumab is particularly relevant when one considers maintenance avelumab may be more effective after a shorter period of induction chemotherapy. This is because chemotherapy and immune therapy may be

antagonistic[31.] Therefore, switching after only 3 cycles may be superior in inducing long term durable responses in subgroups of patients and better tolerated. Finally, second line agents such as Enfortumab Vedotin will be available soon[32]. As more active agents become available in UC, shorter periods of chemotherapy appear attractive in maximising the number of patients able to sequence to subsequent immune checkpoint inhibitor or antibody drug conjugate therapy. Data from the LAMB and avelumab trials suggest continued chemotherapy beyond 4 cycles is not necessarily of benefit[12,33]. Also 6 cycles appear excessive and toxicity accumulates, potentially making alternative approaches attractive. This could be problematic for the widespread adoption of maintenance avelumab, especially if other first line regimens show superiority to chemotherapy.

Overall, it is felt that patients would be keen to move away from chemotherapy toxicity as reflected in the Quality of Life (QoL) analysis. Moreover, it is possible that three cycles of chemotherapy with sequential avelumab would allow more patients with exposure to immune therapy and would be more attractive than the current standard of care. Here, we hypothesise that three cycles of platinum-based chemotherapy will be at least as active as the current standard approach of six cycles, followed by maintenance avelumab.

1.4 Assessment and management of risk

1.4.1 Potential benefits

Urothelial cancer patients have poor prognosis. 5-15% of patients will be metastatic at the time of diagnosis[7], or if localised at diagnosis, metastasis will develop within 2 years when treated with radical cystectomy alone. Upfront metastatic disease is associated with a life expectancy in the region of approximately 12 months. If progressed on front line therapy and become metastatic, life expectancy drops to around 8 months.

Sequencing maintenance avelumab with 6 cycles of platinum-based chemotherapy is the current standard of care for advanced UC and associated with a 45% response rate and 6-month PFS in the region of 50%. There is lack of clarity on the number of cycles of chemotherapy required to maximise chemotherapy outcomes and 6 cycles has been given as the standard of care for historical reasons and when looking at patient reported outcomes, QOL scores reduce with increasing number of cycles due to toxicity. It is possible that 3 cycles may achieve similar response rates from chemotherapy as 6 cycles but have positive effects on patient's quality of life.

Additionally, there is the potential benefit that maintenance avelumab may be more effective after a shorter period of chemotherapy. This is because chemotherapy and immune therapy may be antagonistic and therefore switching to maintenance avelumab earlier, after just 3 cycles of chemotherapy, may be superior in inducing long-term durable responses in subgroups of patients. It is also possible that 6 cycles of chemotherapy is required to maximise outcome. While we feel this is unlikely, this will be addressed in the randomised trial.

1.4.2 Potential risks

The side effects of both platinum-based chemotherapy with either cisplatin or carboplatin + gemcitabine and avelumab are established. Although 6 cycles of platinum-based chemotherapy before switching to maintenance avelumab is the current standard of care for advanced UC, data from studies in other tumours and unpublished data from the Javelin100 trial suggest shorter chemotherapy may be no worse[34,35, 36]

We do not expect any additional side effects from reducing the number of cycles of chemotherapy and commencing immunotherapy earlier.

Patients will not be exposed to any additional biopsies or scans compared to standard of care protocols.

1.4.3 COVID-19

Study treatment of chemotherapy followed by maintenance avelumab would be offered in this patient population as standard of care. Patients are not required to attend additional hospital visits to the standard

of care ones. In line with the safety profile of avelumab and gemcitabine, cisplatin/carboplatin, it is not expected that participation in this trial nor any of the study-related assessments or study treatments will increase the risk of COVID-19 infection or the development of severe symptoms.

Sites will only be opened to recruitment where permitted by their institution in line with national and local COVID-19 protocols. Study eligibility criteria ensure that only suitable participants who are able to comply with the protocol will be included, excluding those who would be at undue risk. Per exclusion criterion 7, administration of live attenuated vaccines is not permitted. Currently approved COVID-19 vaccines do not contain a live virus, therefore, COVID-19 vaccination is permitted and encouraged where available. Details of any COVID-19 vaccine should be recorded in the patient's medical records and concomitant medications eCRF form. The timing and administration of any COVID-19 vaccination during the study will be at the discretion of the local treating investigator in line with current national vaccination guidelines.

The CECM DISCUS coordinating team will monitor compliance centrally and onsite (where permitted) or remotely where onsite visits are not permitted as per protocol section 17.1. Only sites that are able to accommodate secure remote monitoring will be opened to recruitment, where on-site monitoring is not allowed.

The above information will be discussed with sites during set-up and site initiation.

In summary, the study team believes that the benefit outweighs the risk and that adequate precaution and mitigation is in place to conduct the trial with participant safety remaining the priority.

1.5 Trial Categorisation

This trial is categorised as Type A = No higher than the risk of standard medical care (studies are those testing authorised medicinal products in accordance with the marketing authorisation in an EU member state).

Avelumab is currently licensed for use in the UK, Spain and France in the treatment of metastatic merkel cell carcinoma, advanced renal cell carcinoma and locally advanced or metastatic urothelial tumours. 6 cycles of chemotherapy are given as standard prior to commencing maintenance avelumab. Whilst fewer cycles of chemotherapy are licensed, this has not been formally tested. Fewer cycles are usually given due to adverse events associated with chemotherapy.

Gemcitabine is currently licensed for use in the UK, Spain and France in the treatment of bladder cancer, advanced non-small cell lung cancer, advanced pancreatic cancer, breast cancer and ovarian cancer.

Cisplatin is currently licensed for use in the UK, Spain and France in the treatment of testicular, lung, cervical, bladder, head and neck, and ovarian cancer.

Carboplatin is currently licensed for use in the UK, Spain and France in the treatment of advanced ovarian cancer and small cell lung cancer. Carboplatin is used as per standard of care in the treatment of urothelial carcinoma in both the UK and Spain.

2 Trial Objectives

2.1 Primary Objective(s)

To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance avelumab based on patient-reported outcomes (PROs) in the study population.

2.2 Secondary Objective(s)

1. To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance avelumab based on additional patient-reported outcomes (PROs) in the study population.

2. To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance avelumab based on clinician reported outcomes.

3. To evaluate the safety and tolerability of 3 vs 6 cycles of platinum-based, front-line chemotherapy followed by maintenance avelumab therapy.

4. To assess the efficacy of 3 vs 6 cycles platinum based, front-line chemotherapy followed by maintenance avelumab in patients with advanced UC.

2.3 Exploratory or tertiary objective(s)

An exploratory investigation of efficacy of 3 vs 6 cycles platinum based, front-line chemotherapy followed by maintenance avelumab in patients with advanced UC.

2.4 Optional sub study objectives (see Appendix A)

An optional, exploratory investigation into the use of wearable devices as a tool for assessing quality of life in patients enrolled on the DISCUS trial. See Appendix A.

2.5 Endpoints

2.5.1 Primary Endpoint(s)

Change in GHS/QoL scale scores from baseline to completion of 6 cycles of treatment. Patients who withdraw from treatment between Cycles 4 and 6 will be included, provided an EORTC QLQ-C30 questionnaire is completed within 14 days from the date of withdrawal.

2.5.2 Secondary Endpoint (s)

The following endpoints will be assessed in relation to secondary objective 1:

1. Quality of Life assessment from baseline to the completion of 10 Cycles of treatment using the GHS/QOL scale score, as per the primary endpoint methodology.

2. Quality of Life assessment from the beginning of cycle 5 to the completion of 10 Cycles of treatment using the GHS/QOL scale score, as per the primary endpoint methodology.

3. Change in GHS/QOL scale scores from baseline to the end of assessment (wk54), as per the primary endpoint methodology.

4. The above endpoints will be repeated using the EORTC QLQ-C30 scale score.

5. GHS/QoL scale score time to deterioration (TTD), where deterioration in the GHS/QoL scale score is defined as a decrease by ≥10 points at any time point after baseline with no subsequent observations with a <10 point decrease from baseline.

6. Change in the GHS/QOL scale score from baseline as per the primary endpoint, but adjusted for baseline imbalances in GHS/QOL scale scores.

The following endpoint will be assessed in relation to secondary objective 2:

- Performance status as measured by the Karnofsky Scale on completion of 6 cycles of treatment.

The following endpoints will be assessed in relation to secondary objective 3:

1. Incidence, nature and severity of adverse events graded according to NCI-CTCAE v5.0 at the following timepoints:

    - Throughout treatment
    - On completion of Cycle 6 of treatment
    - Between Cycle 4 and the completion of Cycle 10.

2. Treatment discontinuation rate due to AEs.

The following endpoints will be assessed in relation to secondary objective 4:

1. Overall response rate in each randomised treatment arm defined as the proportion of patients who achieved complete response (CR) or partial response (PR) according to RECIST v1.1 recorded from randomisation until week 20. (investigator assessed unconfirmed best response)

2. Progression free survival rate at 20 weeks post randomisation (PFS rate) in each treatment arm defined as the proportion of patients who did not experience disease progression or death from any cause according to RECIST v1.1 recorded from randomisation until week 20.

3. Duration of response defined as the time from first documentation of CR or PR to disease progression (RECIST v1.1) or death from any cause, whichever occurs first.

4. Overall survival (OS), defined as the time between the date of randomisation and death due to any cause.

2.5.3 Exploratory or tertiary endpoints

1. Outcomes in all randomized patients determined to have PD-L1-positive tumours by a verified PD-L1 IHC test.

2. Overall survival (OS), defined as the time between the date of randomisation and date of death due to any cause, in patients who received 6 cycles of treatment versus those who received less than 6 cycles of treatment.

3. Overall survival, defined as the time between the date of randomisation and date of death due to any cause by Bajorin's risk factor group[37] at screening (0, 1 or 2).

2.5.4 Optional sub study endpoints

See appendix A.

2.6 Objectives and endpoints summary

Primary Objective	Primary Endpoint
To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance avelumab based on patient-reported outcomes (PROs) in the study population.	Change in GHS/QoL scale scores from baseline to completion of 6 cycles of treatment. Patients who withdraw from treatment between Cycles 4 and 6 will be included, provided an EORTC QLQ-C30 questionnaire is completed within 14 days from the date of withdrawal.
Secondary Objectives	**Secondary Endpoints**
To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance avelumab based on additional patient-reported outcomes (PROs) in the study population.	• Quality of Life assessment from baseline to the completion of 10 Cycles of treatment using the GHS/QOL scale score, as per the primary endpoint methodology. • Quality of Life assessment from the beginning of cycle 5 to the completion of 10 Cycles of treatment using the GHS/QOL scale score, as per the primary endpoint methodology. • Change in GHS/QOL scale scores from baseline to the end of assessment (wk54), as per the primary endpoint methodology. • The above endpoints will be repeated using the EORTC QLQ-C30 scale score. • GHS/QoL scale score time to deterioration (TTD), where deterioration in the GHS/QoL scale score is defined as a decrease by ≥10 points at any time point after baseline with no subsequent observations with a <10 point decrease from baseline. • Change in the GHS/QOL scale score from baseline as per the primary endpoint, but adjusted for baseline imbalances in GHS/QOL scale scores.
To evaluate the effect of 3 vs 6 cycles platinum-based, front-line chemotherapy followed by maintenance avelumab based on clinician reported outcomes.	Performance status as measured by the Karnofsky Scale on completion of 6 cycles of treatment.
To evaluate the safety and tolerability of 3 vs 6 cycles of platinum-based, front-line chemotherapy followed by maintenance avelumab therapy.	• Incidence, nature and severity of adverse events graded according to NCI-CTCAE v5.0 at the following timepoints: o Throughout treatment o On completion of Cycle 6 of treatment o Between Cycle 4 and the completion of Cycle 10. • Treatment discontinuation rate due to AEs.

To assess the efficacy of 3 vs 6 cycles platinum based, front-line chemotherapy followed by maintenance avelumab in patients with advanced UC.	**Overall response rate** in each randomised treatment arm defined as the proportion of patients who achieved complete response (CR) or partial response (PR) according to RECIST v1.1 recorded from randomisation until week 20. (investigator assessed unconfirmed best response) **Progression free survival rate at 20 weeks post randomisation (PFS rate)** in each treatment arm defined as the proportion of patients who did not experience disease progression or death from any cause according to RECIST v1.1 recorded from randomisation until week 20. **Duration of response** defined as the time from first documentation of CR or PR to disease progression (RECIST v1.1) or death from any cause, whichever occurs first. **Overall survival (OS)**, defined as the time between the date of randomisation and death due to any cause.
Exploratory Objectives	**Exploratory Endpoints**
An exploratory investigation of efficacy of 3 vs 6 cycles platinum based, front-line chemotherapy followed by maintenance avelumab in patients with advanced UC.	• Outcomes in all randomized patients determined to have PD-L1-positive tumours by a verified PD-L1 IHC test. • Overall survival (OS), defined as the time between the date of randomisation and date of death due to any cause, in patients who received 6 cycles of treatment versus those who received less than 6 cycles of treatment. • Overall survival, defined as the time between the date of randomisation and date of death due to any cause by Bajorin's risk factor group[38] at screening (0, 1 or 2).
Optional Sub Study Objectives	**Optional Sub Study Endpoints**
An additional and optional sub study will be conducted on a subset of patients who provide additional consent. See Appendix A for details on objectives.	An additional and optional sub study will be conducted on a subset of patients who provide additional consent. See Appendix A for details on endpoints.

3 Study design

This is an adaptive, open-label, randomised phase II trial that aims to evaluate the impact of 3 vs 6 cycles of first-line platinum-based chemotherapy followed by maintenance avelumab in the quality of life of patients with locally advanced or metastatic UC. Initially, 224 eligible and evaluable patients (112 in each arm) will receive 3 cycles vs 6 cycles of 3-weekly gemcitabine plus cisplatin/carboplatin, followed by 2-weekly maintenance avelumab until disease progression or intolerable toxicities. Avelumab treatment will be given up to a maximum of 2 years from the end of chemotherapy. Patients who continue to derive benefit at the end of the 2-year avelumab period, can be switched to local supply as per standard of care and at the discretion of the local investigator. Patients completing the entire duration of the study will be

expected to attend a maximum of approximately 70 visits. It is estimated that on average approximately 80% of patients will receive a minimum of 5 months of treatment and 20% of patients will remain on treatment for the full duration.

Patients will be stratified by (a) Investigator choice of platinum-based first line chemotherapy (cisplatin vs carboplatin) for advanced disease and (b) presence of liver metastasis (present vs not present). On completion of treatment or sooner if disease progression or toxicities occur, patients will be contacted 12-weekly to collect survival and disease status data. All patients will be followed up until the end of avelumab treatment or for 2 years from completion of chemotherapy, whichever is longer.

The primary endpoint of the study is QoL as measured by the change from baseline in EORTC QLQ-C30 questionnaire GHS/QoL scale scores from baseline to the completion of 6 cycles of treatment. Patients who withdraw from treatment between cycles 4 and 6 will be included in the primary endpoint analysis provided they have completed an EORTC QLQ-C30 assessment within 14 days after the date of withdrawal. Secondary endpoints include additional patient-reported outcomes, performance status, safety analysis and efficacy analysis (ORR, PFS, DoR, OS).

The study also includes extensive biomarker analysis using archival tissue samples as well as translational blood collection including but not limited to circulating tumour DNA (ctDNA) analysis before and on treatment. Sequential urine samples will be collected for urinary microbiome and urinary ctDNA analysis. All biomarker analysis will be covered by a separate biomarker protocol and will be completed separately to this study. Samples are also collected in this study for future ethically approved research.

There is an additional, optional sub study using wearable device data. Further details are provided in Appendix A.

Figure 1: Trial Schema

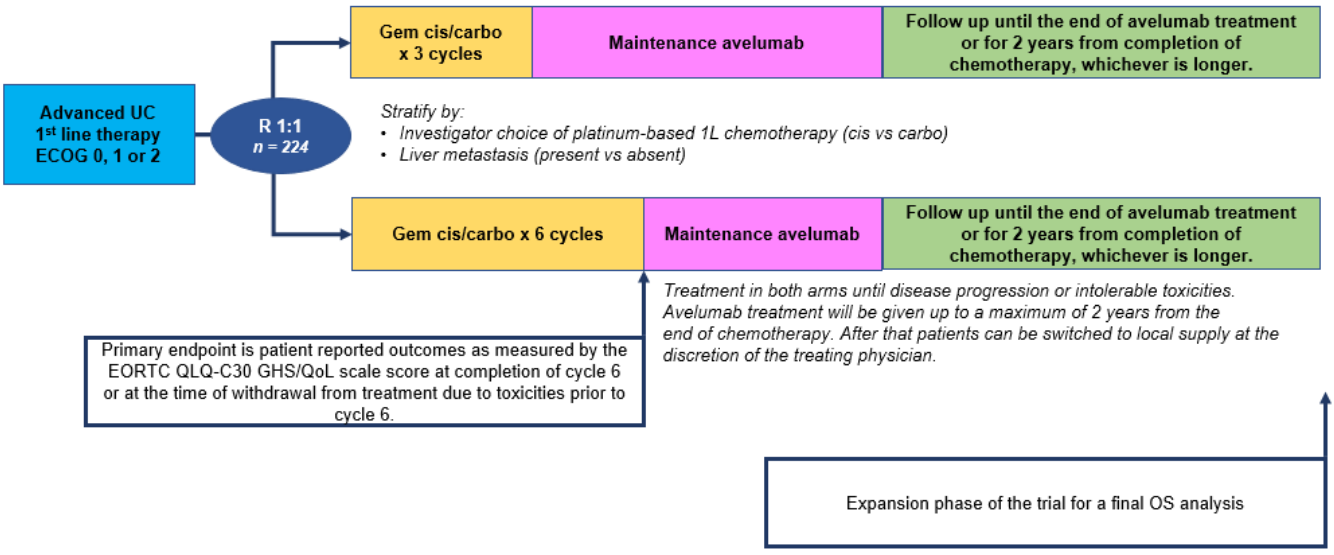
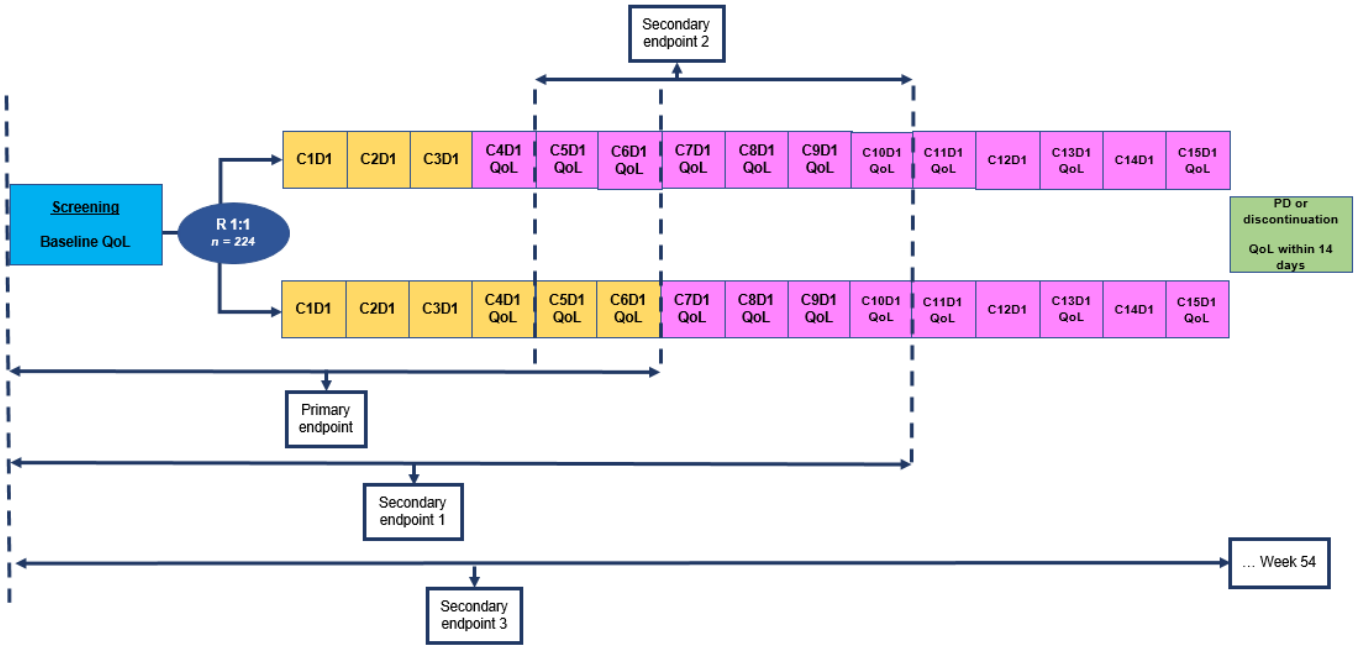


Figure 2: Trial Quality of Life Endpoint Schema



This trial may in the future have an expansion phase based on the results of the overall survival analysis. If an overall survival signal is determined, recruitment could be expanded to allow further investigation of the signal. The design of the expansion phase will remain the same but will focus on OS instead of QoL. The TSC, TMG, the Sponsor and funder will need to agree before the expansion phase proceeds. A substantial protocol amendment will be submitted prior to the expansion phase being implemented. For each expansion to the current study design, new sample size calculations will be performed based on the latest literature available.

3.1 Study setting

This international, multi-centre study will be conducted in both the United Kingdom, Spain and France. The National Coordinating Centre for the United Kingdom will be the Centre for Experimental Cancer Medicine located at Barts Cancer Institute, Queen Mary University of London. In Spain, the National Coordinating Centre will be ADKNOMA Health Research S.L. located in Barcelona. In France, the National Coordinating Centre will be UNICANCER located in Paris.

Initially 40 sites (from the UK, France and Spain) are planned, with all study procedures taking place within the site's setting. Additional sites and countries may be added to the study via a future protocol amendment. In the UK, patients will be recruited from within the NHS setting. In Spain and France, patients will be recruited from within the national health care system.

Sites will be selected following robust feasibility procedures to ensure that all sites are qualified to participate in the DISCUS study. Sites must be adequately resourced to properly conduct the trial, have the potential to recruit eligible participants, generate high quality study data and conduct the trial within the national regulations and to the standards set out in the Sponsor Standard Operating Procedures. Each Principal Investigator must be qualified in education, training and experience in order to conduct the trial at a participating site. Potential investigators will be assessed and selected based on previous experience in the therapeutic area and clinical trial settings.

A list of participating sites can be obtained from the DISCUS Clinical Trial Coordinator.

4 Patient Evaluability and Replacement

4.1 Target Accrual

224 evaluable patients with histologically documented, unresectable locally advanced, or metastatic urothelial cancer in patients who have not received prior systemic therapy for advanced disease will be enrolled from sites in the UK, France and Spain. Patients who do not receive the 4th cycle of treatment will be replaced, irrespective of treatment arm.

4.2 Participant identification and recruitment

Patients will be identified in the secondary care setting via multi-disciplinary team meetings or in out-patient clinics by their direct clinical care team. Potential participants will most likely be known to the study investigators and their research teams. Potential participants will be approached as they attend routine clinical appointments. There is also a possibility that outside referrals may come from external oncologists should they have a potentially suitable participant for the trial. Once a potential participant has been identified, the clinician will discuss the study with them and a member of the research team will offer the participant the trial participant information sheet. Participants must meet all the inclusion criteria and none of the exclusion criteria in order to be eligible for the trial. Eligibility for the DISCUS trial will be confirmed by a delegated clinician within the site team.

5 Informed consent procedures

Informed consent will be obtained prior to the participant undergoing procedures that are specifically for the purposes of the study and are outside standard, routine care at participating sites. This includes collection of identifiable participant data.

The Principal Investigator (PI) has overall responsibility for the informed consent of participants at their site and will ensure that any person delegated responsibility to participate in the informed consent process is duly authorised, trained, and competent to participate according to the ethically approved protocol, principles of Good Clinical Practice (GCP), and Declaration of Helsinki. If delegation of consent occurs, then details will be provided in the site delegation log.

It is the responsibility of the Investigator, or a medically qualified person delegated by the Investigator, to obtain written informed consent from each subject **prior** to participation in this study, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Ample time must be given for consideration by the patient before taking part. Written informed consent will only be obtained from those who the Investigator feels assured have understood the implications of participation in the study. Patients lacking mental capacity will not be included in this study. The Principal Investigator (PI) or appropriately delegated sub-investigator must document in the patient's notes when the PIS was given to the patient and when informed consent was obtained.

The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the study without giving reasons and without prejudicing their further treatment and will be provided with a contact point where they may obtain further information about the study. If new safety information becomes available the Chief Investigator (CI), in conjunction with the sponsor and the Trial Steering Committee (TSC) will review the study, update the PIS accordingly and resubmit for relevant regulatory approvals. The CI will review the new safety information and assess whether an urgent TSC meeting should be convened or whether this information can be reviewed at the next scheduled meeting. All patients, including those already being treated, should be informed of the new information, given a copy of the revised PIS and asked to give their consent to continue in the study. Patients will not be re-consented following amendments that do not affect safety or number of assessments / visits required. Where a participant is required to re-consent (for example if new Research Safety Information becomes available during the study, or following an amendment that affects the participant, or

new information needs to be provided to a participant) it is the responsibility of the PI to ensure this is done in a timely manner and prior to the next dose of IMP (where applicable).

5.1 Vulnerable participant considerations

Vulnerable participants will not be consented or recruited into the DISCUS study.

5.2 Writing, reading, and translation considerations

Arrangements for an official hospital translator for any participant who is not competent or comfortable with communication in English (or local language for non-UK sites) will be made by participating sites in line with their local hospital policy. The translator will be asked to read through the Patient Information Sheet (PIS) and Consent Form and to translate each section for the participant. A record of the translator used will be documented in the medical notes by the study investigator.

Written informed consent will only be obtained from those who the Investigator feels assured have understood the implications of participation in the study.

5.3 Participants lacking capacity

Not applicable.

5.4 Minors

Not applicable.

6 Participant allocation

PIs must keep a record of all patients screened for entry into this study, including those deemed ineligible after screening. Copies of the screening logs should be filed in the Investigator Site File (ISF). For each patient the primary reason for exclusion should be recorded. Diagnostic data obtained as part of the patient's standard care can be used to determine eligibility, provided they fall within the protocol-defined timelines. Written informed consent must be obtained prior to the patient undergoing any study specific procedures.

After ensuring that a patient has consented to participate in the study, the registration electronic Case Report Form (eCRF) must be completed. All patients will be assigned a unique trial ID for use in all correspondence. To ensure patient confidentiality patients will only be identified on eCRFs, other trial specific forms and all communication to the DISCUS CECM coordinating team and participating national coordinating centres (NCC) using their assigned trial ID. It is the PI's responsibility to maintain a confidential record of the identity (i.e., full name, date of birth and hospital number) and assigned trial ID for the patients enrolled in this study. At the end of the study this record should be archived along with the ISF.

Full details of the patient enrolment and randomisation procedure can be found in the DISCUS enrolment procedure manual.

7 Participant eligibility criteria

7.1 Inclusion criteria

Each patient **must meet all of the following inclusion criteria** to be enrolled in the study:

1. Willing and able to provide written informed consent.
2. Ability to comply with the protocol, including but not limited to, the repeated completion of the EORTC QLQ-C30 questionnaires.

3. Age ≥ 18 years.
4. Histologically confirmed, unresectable locally advanced or metastatic urothelial carcinoma (i.e., cancer of the bladder, renal pelvis, ureter, or urethra). Patients with squamous or sarcomatoid differentiation or mixed cell types are eligible but a component of urothelial cancer is required.
5. Measurable disease by RECIST v1.1.
6. Eligible for gemcitabine/ cisplatin or gemcitabine/carboplatin. Patients meeting any of the following criteria or considered ineligible for cisplatin as per investigator discretion, should be considered for gemcitabine/carboplatin (as per local standard practice):
    a. GFR <60 mL/min (measured by the Cockcroft-Gault formula or by local accepted standards). Subjects with a GFR ≥50 mL/min and no other cisplatin ineligibility criteria may be considered cisplatin-eligible based on the investigator's clinical judgement. Subjects are required to have a GFR ≥30 mL/min (measured by the Cockcroft-Gault formula or by local accepted standards) to receive carboplatin.
    b. ECOG or WHO performance status of 2.
    c. NCI CTCAE Grade ≥2 audiometric hearing loss.
    d. NYHA Class III heart failure.
7. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1 or 2.
8. Adequate haematologic and organ function as defined below:
    a. Haemoglobin ≥ 9.0g/dL
    b. Absolute neutrophil count (ANC) ≥1.5 x 109/L (≥1500/μL) without growth factor support
    c. Platelet count ≥ 100 x 109 /L (≥100,000/μL)
    d. Total serum bilirubin ≤1.5 x institutional upper limit of normal (ULN) (this will not apply to subjects with confirmed Gilbert's syndrome [persistent or recurrent hyperbilirubinaemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology], who will be allowed only in consultation with their physician.
    e. Serum transaminases (AST/ALT) ≤2.5 x the institutional ULN with the following exception in patients with documented liver metastases: AST and/or ALT ≤5 × ULN
    f. GFR ≥30mL/min measured by Cockcroft-Gault formula, or locally accepted standards.
9. Negative serum or urine pregnancy test within 2 weeks of Day 1 Cycle 1 for female patients of childbearing potential only. Non-childbearing potential is defined as either:
        a. Postmenopausal ≥ 50 years of age and amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments OR
        b. Documented irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation OR
        c. <50 years of age who have been amenorrhoeic for 12 months or more following cessation of exogenous hormonal treatments and with LH and FSH levels within local institution postmenopausal ranges.
10. Agreement to use adequate contraceptive measures (Refer to section 11.30 for full details).

7.2 Exclusion criteria

A patient **will not be eligible for inclusion** in this study if any of the following criteria apply:

1. Prior treatment with a PD-(L)-1 inhibitor for any advanced malignancy. Treatment with PD-(L)-1 inhibitors in the neoadjuvant or adjuvant setting for UC are permitted.
2. Prior systemic therapy for locally advanced or metastatic urothelial carcinoma with the following exceptions: a platinum containing regimen (cisplatin or carboplatin) in the neoadjuvant or adjuvant

setting if more than 6 months since last cycle have occurred. Patients who received adjuvant or neoadjuvant immune therapy for muscle invasive or non-muscle invasive disease are eligible.

3. Pregnant and lactating female patients.
4. Known history of active CNS metastases. Patients with treated CNS metastases are permitted on the study if all of the following are true:
    a. CNS metastases have been clinically stable for at least 4 weeks prior to screening and baseline scans show no evidence of new or enlarged metastasis;
    b. the subject is on a stable dose of ≤10 mg/day of prednisone or equivalent for at least 2 weeks prior to C1D1 (if requiring steroid treatment);
    c. subject does not have leptomeningeal disease.
5. Prior allogeneic stem cell or solid organ transplantation.
6. Administration of a live, attenuated vaccine within 4 weeks prior to enrolment or anticipation that such a live, attenuated vaccine will be required during the study.
7. Treatment with systemic immunostimulatory agents (including but not limited to interferons or interleukin [IL]−2) within 4 weeks or five half-lives of the drug, whichever is shorter, prior to enrolment (see section 11.26).
8. Concurrent treatment with any other investigational agent or participation in another clinical trial with therapeutic intent within 4 weeks prior to enrolment.
9. Evidence of significant uncontrolled concomitant disease that could affect compliance with the protocol or interpretation of results, including significant liver disease (such as cirrhosis, uncontrolled major seizure disorder, or superior vena cava syndrome).
10. Malignancies other than urothelial carcinoma within 3 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, or ductal carcinoma in situ treated surgically with curative intent) or localized prostate cancer treated with curative intent and absence of prostate-specific antigen (PSA) relapse or incidental prostate cancer (Gleason score ≤ 3 + 4 and PSA < 10 ng/mL undergoing active surveillance and treatment naive). .
11. Significant cardiovascular disease, such as New York Heart Association cardiac disease (Class II or greater), myocardial infarction or cerebral vascular accident/stroke within 6 months prior to enrolment, unstable arrhythmias, or unstable angina.
12. Radiotherapy within 2 weeks prior to C1D1. Patients must have recovered adequately from toxicities resulting from the intervention prior to starting study treatment.
13. Major surgery (defined as requiring general anaesthesia and >24-hour inpatient hospitalization) within 4 weeks prior to randomisation. Patients must have recovered adequately from complications from the intervention prior to starting study treatment.
14. History of idiopathic pulmonary fibrosis (including pneumonitis), drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia), or evidence of active pneumonitis on screening chest CT scan (History of radiation pneumonitis in the radiation field (fibrosis) is permitted).
15. Active hepatitis infection (defined as having a positive hepatitis B surface antigen [HBsAg] test at screening) or hepatitis C. Patients with past hepatitis B virus (HBV) infection or resolved HBV infection (defined as having a negative HBsAg test and a positive antibody to hepatitis B core antigen [anti-HBc] antibody test) are eligible.
16. Positive HIV test.
17. Active tuberculosis.

18. Active autoimmune disease including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis.
19. History of autoimmune-related hypothyroidism, unless on a stable dose of thyroid replacement hormone.
20. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies.
21. Known hypersensitivity or allergy to biopharmaceuticals produced in Chinese hamster ovary cells or any component of avelumab.
22. Active infection requiring systemic therapy.
23. Persisting toxicity related to prior therapy (NCI CTCAE Grade > 1); however, alopecia, sensory neuropathy Grade ≤ 2, or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable.
24. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results
25. Participants with previous or known history of allergic reaction to cisplatin, gemcitabine, carboplatin or other platinum containing compounds, or any component of the chemotherapy formulations.
26. Patients with bleeding tumours
27. Any other contraindication for gemcitabine/ cisplatin or gemcitabine/carboplatin treatment as per SmPC.

8 Study Schedule

8.1 Randomisation method

Once confirmed that a patient meets all eligibility criteria, they will be randomised in a 1:1 ratio using the minimisation method to receive one of the following treatments:

- 3 cycles of Q3W gemcitabine (1000mg/m^2) D1&D8 + carboplatin (AUC 4.5 or 5, as per local practice) D1 / cisplatin (70mg/m^2) D1 followed by maintenance avelumab (800mg Q2W).
- 6 cycles of Q3W gemcitabine (1000mg/m^2) D1&D8 + carboplatin (AUC 4.5 or 5) D1/ cisplatin (70mg/m^2) D1 followed by maintenance avelumab (800mg Q2W).

Randomisation will be stratified by the following factors:

a) Investigator choice of platinum- based first line chemotherapy for advanced disease: cisplatin vs carboplatin
b) Presence of liver metastasis: present vs not present

8.2 Randomisation procedure

Full details of the patient enrolment and randomisation procedure can be found in the DISCUS enrolment procedure manual.

In summary, on identifying and consenting a suitable patient, participating sites should notify the CECM DISCUS Team via email that a patient is due to be randomised. Site staff must then fully complete the screening eCRFs and confirm eligibility. The CECM DISCUS coordinator will check the screening eCRF data against the protocol and randomise the patient using the eCRF. Patients will be randomised to receive either treatment arm on a 1:1 ratio as per the methods described in section 8.1.

Site and Pharmacy staff will receive a confirmation of randomisation via email. The email confirming randomisation and cohort allocation must be retained with the patient medical notes and ISF.

Patients should receive their first dose of study treatment no later than 3 days after randomisation.

8.3 Cohort allocation / sequential allocation

Not applicable

8.4 Blinding

Not applicable

8.5 Unblinding

Not applicable

8.6 Schedule of assessments (in diagrammatic format)

While participating in the study patients will have to attend visits as described in Table 1 (3 cycles of chemotherapy) or Table 2 (6 cycles of chemotherapy). For logistical reasons it may be difficult for participating sites to carry out all screening assessments on one day. Patients will be fully informed about the number of visits required to confirm eligibility in the trial. For a summary of assessments see Table 1 and Table 2.

Table 1: Schedule of assessments for 3 cycles of gemcitabine + cisplatin/carboplatin followed by avelumab

Visit	**SCR**	**Chemotherapy Cycles 1 to 3**		**Maintenance Avelumab Cycles 4 to 29**		**Safety Visit**		**Post treatment FU [1]**
Assessment window	**Wk - 4 to 0**	**Day 1** *(± 3 days)*	**Day 8** *(± 3 days)*	**Day 1**[2] *(± 3 days)*	**Day 15** *(± 3 days)*	**30 – 37 days after last IMP dose**	**83-90 days after last IMP dose**[3]	**12weekly** *(± 1wk)*
Informed consent	X							
Demographic data and medical history	X							
Physical examination, weight, vital signs[4]**, height *(screening only)*, Karnofsky scale**	X	X		X	Vital signs only	X		
12-lead ECG	X							
Haematology & Biochemistry, Urinalysis [5]	X	X	X	X		X		
HIV, HBV, HCV serology	X[6]							
TSH, free T4[5]	X			X		X		
Pregnancy test	X	X		X		X		

[1] On completion of treatment or sooner if disease progression or toxicities occur, patients will be contacted 12-weekly to collect survival and disease status data. All patients will be followed up until the end of avelumab treatment or for 2 years from completion of chemotherapy, whichever is longer.
[2] C4D1 avelumab infusion should commence within 10 weeks after the last dose of chemotherapy.
[3] Assessments to be performed via telephone, a subsequent site visit should be requested in case any concerns noted during the telephone call.
[4] Vital signs to be determined up to 60 min before infusion
[5] Safety bloods and urinalysis may be carried out up to ≤72 hours before the day of treatment. Cycle 1 assessments do not need to be repeated if screening sampling took place ≤72 hours before C 1 D1.
[6] HBV DNA is required on or before Cycle 1, Day 1 if patient has negative serology for HBsAg and positive serology for anti-HBc

(women childbearing potential)								
CT/MRI chest, abdomen and pelvis [1]	X[2]	C4D1[2], then 10 weekly (± 7 days) for the first 5 scans and at the investigator's discretion thereafter						
Adverse events *(CTCAE v5.0)*		X	X	X	X	X	X	
Serious adverse events *(CTCAE v5.0)*				X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	
Gemcitabine/platinum infusion		X	Gem only					
Avelumab infusion				X	X			
Archival tumour tissue	X							
Research bloods sample	X	C4D1, at each imaging timepoint & at PD						
Research urine sample	X	C4D1, at each imaging timepoint & at PD						
Quality of Life (QoL) assessment [3]	X	On Day 1 of C4 to C11 and every 2 cycles thereafter (C13D1, C15D1, C17D1 etc) as well as on PD/treatment discontinuation.						
Survival, disease, anti-cancer treatment [4]						X	X	X

Table 2: Schedule of assessments for 6 cycles of gemcitabine + cisplatin/carboplatin followed by avelumab

Visit	**SCR**	**Chemotherapy Cycles 1 to 6**		**Maintenance Avelumab Cycles 7 to 32**		**Safety Visit**		**Post treatment FU[5]**
Assessment window	**Wk - 4 to 0**	**Day 1** *(± 3 days)*	**Day 8** *(± 3 days)*	**Day 1[6]** *(± 3 days)*	**Day 15** *(± 3 days)*	**30 – 37 days after last IMP dose**	**83-90 days after last IMP dose[7]**	**12weekly** *(± 1wk)*
Informed consent	X							
Demographic data and medical history	X							
Physical examination, weight, vital signs[8], height *(screening only)*, Karnofsky scale	X	X		X	Vital signs only	X		
12-lead ECG	X							
Haematology & Biochemistry, Urinalysis [9]	X	X	X	X		X		

[1] Screening CT/MRI of head only in cases of clinical suspicion of brain mets – as per clinical practice.
[2] C4D1 CT/MRI assessment can occur at any time point between C3D1 and C4D1.
[3] Assessment should occur ± 1 week of planned cycle time point. From Cycle 11 onwards QoL questionnaires will be completed every 2 cycles (8 weeks) (C13D1, C15D1, C17D1 etc). A QoL assessment should also occur within 14 days of treatment discontinuation (platinum based chemotherapy or avelumab) or progression. This should be conserved to be the next time point QOL assessment. QoL assessments will only be completed for a maximum of 1 year post randomisation.
[4] Can be collected over telephone or from medical records. Follow up will continue for a maximum of 2 years post end of treatment.
[5] On completion of treatment or sooner if disease progression or toxicities occur, patients will be contacted 12-weekly to collect survival and disease status data. All patients will be followed up until the end of avelumab treatment or for 2 years from completion of chemotherapy, whichever is longer.
[6] C7D1 avelumab infusion should commence within 10 weeks after the last dose of chemotherapy.
[7] Assessments to be performed via telephone, a subsequent site visit should be requested in case any concerns noted during the telephone call.
[8] Vital signs to be determined up to 60 min before infusion
[9] Safety bloods and urinalysis may be carried out up to ≤72 hours before the day of treatment. Cycle 1 assessments do not need to be repeated if screening sampling took place ≤72 hours before C 1 D1.

HIV, HBV, HCV serology	X[1]							
TSH, free T4[5]	X			X		X		
Pregnancy test (women childbearing potential)	X	X		X		X		
CT/MRI chest, abdomen and pelvis [2]	X[2]	C4D1[3], then 10 weekly (± 7 days) for the first 5 scans and at investigator's discretion thereafter						
Adverse events (CTCAE v5.0)		X	X	X	X	X	X	
Serious adverse events *(CTCAE v5.0)*				X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	
Gemcitabine/platinum infusion		X	Gem only					
Avelumab infusion				X	X			
Archival tumour tissue	X							
Research bloods sample	X	C4D1. at each imaging timepoint & at PD						
Research urine sample	X	C4D1, at each imaging timepoint & at PD						
Quality of Life (QoL) assessment [4]	X	On Day 1 of C4 to C11 and every 2 cycles thereafter (C13D1, C15D1, C17D1 etc) as well as on PD/treatment discontinuation.						
Survival, disease, anti-cancer treatment [5]						X	X	X

8.7 Study assessments

8.7.1 Demographics and medical history

Demographic data collected will depend on the data protection laws of each country and will include age, sex, date of birth and self-reported race/ethnicity, where possible and with the patient's consent.

A standard medical history will be obtained including details of any relevant medical conditions occurring prior to consent, surgeries and cancer history (including prior cancer therapies and procedures). Details will also be collected on the patient's urothelial cancer diagnosis including site, histological type, date of diagnosis, tumour size, grade and TNM staging.

8.7.2 Height, physical examination, vital signs and Karnofsky scale

Height (cm) will be measured at baseline only.

A standard physical examination should include a weight (kg) measurement and physical assessment and should take place at the time points indicated in the table of assessments. Results should be recorded on the relevant eCRF as normal or clinically abnormal and details should be provided for clinically abnormal results.

Vital signs will include the measurements of heart rate, systolic and diastolic blood pressure (while the patient is in a seated position) and temperature. Vital signs should be determined within 60mins before

[1] HBV DNA is required on or before Cycle 1, Day 1 if patient has negative serology for HBsAg and positive serology for anti-HBc
[2] Screening CT/MRI of head only in cases of clinical suspicion of brain mets – as per clinical practice.
[3] C4D1 CT/MRI assessment can occur at any time point between C3D1 and C4D1.
[4] Assessment should occur ± 1 week of planned cycle time point. From Cycle 11 onwards QoL questionnaires will be completed every 2 cycles (8 weeks) (C13D1, C15D1, C17D1 etc). A QoL assessment should also occur within 14 days of treatment discontinuation (platinum based chemotherapy or avelumab) or progression. This should be conserved to be the next time point QoL assessment. QoL assessments will only be completed for a maximum of 1 year post randomisation.
[5] Can be collected over telephone or from medical records. Follow up will continue for a maximum of 2 years post end of treatment.

each infusion. Patients will be informed about the possibility of delayed post- avelumab infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Performance status will be assessed at screening, day 1 of every cycle and at the safety visit using the Karnofsky scale according to Table 3 and will be recorded on the eCRF.

Table 3: Karnofsky Scale

Definition	%	Criteria
Able to carry on normal activity and to work. No special care is needed.	100	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, care for most personal needs. A varying amount of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospitalisation is indicated although death not imminent.
	20	Very sick; hospitalisation necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead.

8.7.3 ECG

Baseline 12-lead ECG reading (single) will be taken at screening and when clinically indicated. To minimise variability in autonomic tone and heart rate, it is important that patients are resting quietly for at least 5 minutes prior to recording ECGs. Blood draws and other procedures should be avoided during the period immediately before ECG measurement, and activity should be controlled as much as possible to minimise variability due to the effects of physiologic stress. If possible, the same machine should be used for all ECGs for a specific patient. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

8.7.4 Haematology, biochemistry and urinalysis

Blood samples for haematology and clinical chemistry tests will be taken at screening and at the visits described in the table of assessments and analysed at the local site's laboratory using standard methods for routine tests. The following variables will be measured:

- **Haematology:** (approximately 8ml of blood) haemoglobin, WBC count with differential (absolute neutrophil count, lymphocytes) and platelet count.
- **Biochemistry:** (approximately 6ml of blood), urea, creatinine, sodium, potassium, calcium, phosphorus, total bilirubin, ALT or AST, LDH and albumin
- **Thyroid function testing**: thyroid-stimulating hormone (TSH), free T4.

The following variables will only be assessed during the screening period:

- **HIV test**: All patients will be tested for HIV prior to inclusion into the study and HIV-positive patients will be excluded from the study.

- **HBV serology** (HBsAg, antibody to HBsAg [anti-HBs], anti-HBc). HBV DNA is required on or before Cycle 1, Day 1 if patient has negative serology for HBsAg and positive serology for anti-HBc.
- **HCV serology** (anti-HCV).

Blood volumes for haematology, clinical chemistry and coagulation tests may vary according to local practice. The date and result for each test must be recorded in the appropriate eCRF. Abnormal laboratory values that are considered to be of clinical significance must be recorded as an AE as described in section 12.5. All patients with clinically significant abnormal laboratory results are to be followed until the results return to normal ranges or until a valid reason, other than a drug-related adverse event, is identified.

Urinalysis: specific gravity, pH, glucose, protein, ketones and blood.

8.7.5 Pregnancy test

Female patients of childbearing potential must have a negative serum pregnancy test within 14 days prior to the first dose of IMP (Cycle 1 Day 1) and preferably as close as possible to the first dose. Further pregnancy tests (serum or urine) will be performed as per the table of assessments. The discussion about contraception will be recorded in the medical notes.

8.7.6 Tumour assessments

Tumour assessments will be performed using CT scans (with oral/IV contrast) of the chest, abdomen and pelvis (and brain at screening for those patients with a known history of, or clinical suspicion of CNS metastases-as per clinical practice). If contrast CT is contraindicated (e.g., patients with contrast allergy or impaired renal clearance), MRI scans and non-contrast CT scans of the chest may be used.

RECIST v1.1 criteria will be used to assess patient response to treatment by determining tumour size/response and PFS. Screening assessments should be performed no more than 28 days prior to the first dose of IMP. Screening assessments will include the chest abdomen, pelvis and also a CT/MRI of the brain (for those patients with a known history of, or clinical suspicion of CNS metastases – if part of standard clinical practice).

Following the screening assessment, subsequent assessments of the chest, abdomen and pelvis will be carried at Cycle 4 Day 1 (can occur at any time point between C3D1 and C4D1) and 10 weekly thereafter (± 7 days) for the following 5 scans. Thereafter, subsequent tumour assessments will be performed at the investigator's discretion. If an unscheduled assessment is performed and the patient has not progressed, the results should be reported at the next scheduled visit. The method of tumour assessment used at baseline, e.g., CT or MRI scans, must be used at each subsequent follow-up assessment.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to NTL (nontarget lesion) or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm disease progression, then the date of the initial indeterminate scan should be declared as the date of progression.

Patients will not be treated through progression.

8.7.7 Concomitant medication

All medications and vaccines (including prescription medications and over the counter preparations) taken by the patient during the screening period i.e., at least 4 weeks prior to the start of study medications, will be documented as concomitant medications. Note all medications and vaccines should be recorded clearly to allow for identification of prohibited medications. Please refer to section 1.4.3 for information regarding COVID-19 vaccination.

If a patient is taking any of the medications defined as prohibited for use during the study according to section 11.26, then these will be documented during screening. Patients must stop taking any prohibited medications prior to starting study treatment for a period that is equal to 4 weeks or 5 times the half-life of the prohibited medication (see Section 11.26). The following details will be collected: drug name, reason for treatment, dose/units, route of administration, frequency, start and end date of therapy.

8.7.8 Quality of life assessment

To capture quality of life data, the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) measure has been selected. Patients will complete the EORTC QLQ-C30 questionnaire as per the timepoints described in the schedule of assessments detailed in Table 1 and Table 2 above.

The EORTC QLQ-C30 questionnaire will be self-administered by the patient before the patient sees the physician (i.e., at the start of the visit). Patients will be given the questionnaires that are available in their local language. Repeated completion of the EORTC QLQ-C30 is a mandatory requirement in order for a patient to take part in the DISCUS study. However, in situations whereby a questionnaire is not completed, the reason for the missing questionnaire should be documented in the eCRF. Upon completion, a copy of the EORTC QLQ-C30 questionnaire should be returned to the CECM DISCUS coordinating team. The original copy of the EORTC QLQ-C30 questionnaire should be retained in the patient's trial records.

The EORTC QLQ-C30 is composed of both multi-item scales and single-item measures. These include a global health status (GHS)/Quality of Life (QoL) scale, five functional scales, three symptom scales, and six single items. The EORTC QLQ-C30 has been carefully developed in a multi-cultural setting and is easily understood by most patients and is quick to complete (mean time 11 minutes) [39,40].

The primary endpoint of the study is QoL as measured by the change in EORTC QLQ-C30 from baseline to completion of 6 cycles of treatment. Patients who withdraw from treatment between cycles 4 and 6 will be included in they have completed an EORTC QLQ-C30 assessment within 14 days post the date of withdrawal. The GHS/QoL scale score is composed of two of the thirty items collected on the EORTC QLQ-C30 (questions 29 and 30). The average of these two items is taken (known as the raw score) and a linear transformation is applied to standardise the raw score so that the score ranges from 0 to 100 where a high GHS/QoL scale score represents a high QoL. Imputations and rules for creating a GHS/QoL scale score with missing data will follow those detailed in the EORTC QLQ-C30 scoring manual[41].

The list below outlines guidance for site staff when administering the EORTC QLQ-C30 to patients:

- During the first administration of the questionnaire, patients may not understand the instructions or may find certain questions confusing, site staff should be available to provide verbal explanations.

- When patients are unable to fill in the questionnaire themselves for practical reasons (e.g. too frail or forgot glasses), then site staff can choose to read out the questions and fill in the questionnaire on the patient's behalf. All such instances must be recorded on the questionnaire.

- Upon completion, questionnaires should be checked for missing data and it should be ascertained whether this is accidental or deliberate. In the former case, the patient can be asked to complete the missing questions. In the latter case, the questionnaire should be marked that the patient did not wish to answer a particular question.

- The first QoL assessment should occur at screening (week -4 to 0), thereafter, QoL assessments should occur ± 1 week of the planned cycle time point. From Cycle 11 onwards QoL questionnaires will be completed every 2 cycles (8 weeks) (C13D1, C15D1, C17D1 etc). A QoL assessment should also occur within 14 days of treatment discontinuation (platinum based chemotherapy or avelumab)

or progression. QoL assessments will only be completed for a maximum of 1 year post randomisation.

There is an additional and optional sub study utilising wearable devices as a means of assessing patient QoL. Further details of this sub study are provided in Appendix A. Patients can optionally consent to participate in this sub study, providing they are eligible and enrolled on the DISCUS study. The sub-study will meet its primary data collection endpoint if patients generate at least 3 data points (over 3 distinct cycles) during cycle 1 to cycle 6. Please refer to Appendix A.

8.7.9 Adverse events

AEs will be collected throughout the study, from the time the patient signs the informed consent form to the safety visit (83 - 90 days after the last dose of IMP) and recorded in the eCRF. Any AEs that remain unresolved after the safety visit should be followed until resolution and recorded in the eCRF. If an AE is unresolved at the termination of the study the AE should be followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. Details about the assessment of AEs are given in Section 12.2. The following details will be collected: AE term, date of onset, date of resolution, CTCAE grade (maximum intensity), seriousness, Investigator causality rating against the study medication (yes or no), action taken with regards to study medication, outcome.

AEs meeting the criteria for 'serious' (SAEs) that occur whilst on gemcitabine/cisplatin or gemcitabine/carboplatin chemotherapy only are excluded from expedited recording/reporting on SAE form, however they should be recorded as AEs on the eCRF and in the medical records. All SAEs that occur once the subject has moved on to receive avelumab should be recorded and reported to the Sponsor (JRMO or agreed representative) within 24 hours of the PI or co-investigator becoming aware of the event, as per standard SAE reporting guidance.

8.7.10 Study drug administration

Gemcitabine and cisplatin/carboplatin will be dispensed to patients on day 1 of each 21-day cycle of chemotherapy (3 cycles or 6 cycles depending on the allocated arm). Gemcitabine will additionally be dispensed to patients on day 8 of each 21-day cycle of chemotherapy. Please refer to tables Table 4 and

Table **5** in section 11.17 for study drug dosing schedule.

Following completion of gemcitabine and cisplatin/carboplatin chemotherapy, patients will then receive maintenance avelumab within 10 weeks of completing chemotherapy, on day 1 and 15 of each 28-day cycle for up to 2 years after the end of chemotherapy. Date and time of administration, drug name and drug dose will be collected and documented in the patient's medical records.

All patients will receive study treatment until disease progression or intolerable toxicities. Avelumab treatment will be given up to a maximum of 2 years from the end of chemotherapy. Patients who continue to derive benefit at the end of the 2-year avelumab period, can be switched to local supply as per standard of care and at the discretion of the local investigator.

Patients who discontinue platinum based chemotherapy due to toxicity will be permitted to switch to on-study maintenance avelumab if in the opinion of the local investigator benefit will be derived. Switching to on-study maintenance avelumab will be permitted provided that the treatment discontinuation quality of life assessment is completed within 14 days of the date of treatment discontinuation. The CECM DISCUS coordinating team must be notified in all instances of patients switching to on-study maintenance avelumab.

8.7.11 Follow up procedures

All patients will be followed for survival, disease status and new anti-cancer treatment information unless the patient requests to be withdrawn from follow-up (this request must be documented in the source documents and signed by the Investigator) or the study is terminated by the Sponsor. Follow-up information will be collected via telephone calls or review of patient medical records 12 weekly. Follow up will be until the end of avelumab treatment or for 2 years from completion of chemotherapy, whichever is longer.

On completion of the study, participating patients will be considered for further treatment at the discretion of the treating physician.

9 Participant, Study, and Site discontinuation

9.1.1 Participant Discontinuation

The Investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time and for any reason. Reasons for withdrawal from the study may include but are not limited to the following*:*

- Patient withdrawal of consent at any time
- Any medical condition that the Investigator or Sponsor determines may jeopardise the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient noncompliance

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn.

Any data or samples collected up to the point that the patient withdraws from the study will be retained and analysed in the study.

9.1.2 Discontinuation from Study Drug

Treatment with study drug should be discontinued if it is considered to be in the best interest of the patient. Reasons for treatment discontinuation include:

- Intolerable toxicity related to study treatment
- Any medical condition that may jeopardise the patient's safety if he or she continues on study treatment in the judgment of the Investigator
- Use of another systemic anti-cancer therapy
- Treatment delay >12 weeks because of IMP related toxicity (chemotherapy or avelumab)
- Pregnancy – for female patients only
- Patient request
- Protocol violations or non-compliance
- Radiographic evidence of disease progression

Please discuss with the CI prior to premature treatment discontinuation. The primary reason for study drug discontinuation should be documented on the appropriate eCRF.

9.1.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study or an individual site at any time.

Reasons for terminating the study may include but are not limited to the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients
- Patient enrolment is unsatisfactory
- Futility

Reasons for terminating an individual site may include but are not limited to the following:

- Non-compliance with study procedures which compromise patient safety and/or study integrity.
- Upon the recommendation of the regulatory authorities.

Study or site discontinuation will be discussed with the TSC and sponsor to ensure there is no conflict with the immediate needs of the patients.

9.1.4 Discontinuation from optional substudy

Participation in the sub study is entirely optional. Patients who have consented to participate in the sub-study have the right to withdraw from the sub study at any time and for any reason.

Any data or samples collected up to the point that the patient withdraws from the study will be retained and analysed in the study.

10 Laboratories and samples

10.1 Central laboratories

The DISCUS study will utilise central laboratories to perform the exploratory endpoint analysis and for the storage of samples for future ethically approved research. Full contact details can be found in the protocol study contacts section:

- **CECM Central Sample Repository:** Barts and the London Queen Mary School of Medicine and Dentistry Tissue Bank (HTA Licensing number: 12199)

- **Sub-contracted Vendor**: HistoGeneX N.V. for PD-L1 analysis.

Additional sub-contracted vendors maybe approached and utilised throughout the course of the study. Additional central analysis will be covered by a separate biomarker protocol.

10.2 Local laboratories

Please refer to section Haematology, biochemistry and urinalysis8.7.4 for details regarding local laboratory testing in the DISCUS study.

If a site is no longer able to support a local laboratory test as required in the DISCUS study (e.g. testing procedure is outside of a site's UKAS accreditation), then the site should notify the DISCUS CECM Coordinating team.

10.3 Sample collection, labelling, and logging

Tumour Tissue: A representative archival tumour tissue (FFPE tumour block) with anonymised pathology report compromising of muscle-invasive urothelial carcinoma, or a biopsy of metastatic urothelial carcinoma will be collected from each patient. If an FFPE tumour sample is not available then at least 15 unstained slides with an anonymised pathology report will be collected. Fine needle aspiration, brushing, cell pellets from pleural effusion, and lavage samples are not acceptable. For core-need biopsy specimens, at least three cores should be submitted.

Blood and Urine Samples: All patients will be asked to donate 2 x 6mL of blood and 50ml urine at each time point indicated in the table of assessments for analysis of the study's exploratory objectives and future ethically approved research. This part of the study is not optional. Further details on sample processing, handling and shipment are provided in the DISCUS laboratory manual.

All patients will be consented for the collection and use of tissue, blood and urine samples. All samples will be linked anonymised and only identified by the trial ID and unique sample number allocated by the CECM coordinating team.

Tumour tissue, blood and urine samples will be retained by the CECM DISCUS coordinating team. Further details about sample collection, labelling and logging are provided in the DISCUS laboratory manual.

Wearable device data: All patients who wish to participate in the optional substudy using wearable device data will complete an additional and optional consent form. Patients will be asked to consent to having wearable device data collected at various time points including, but not limited to, heart rate, step count, peripheral oximetry and electronic patient reported outcome (ePRO) questionnaires, via a synced mobile application.

10.4 Sample transfer, chain of custody, and accountability

Further details about sample transfer are provided in the DISCUS laboratory manual.

In all cases, patients will be consented for the collection and use of their biological samples and a full chain of custody will be maintained for all samples throughout their lifecycle. The Investigator at each site is responsible for maintaining a record of full traceability of biological samples collected from patients while these are in storage at the site, either until shipment or disposal. Any sample receiver e.g., sub-contracted service provider will keep full traceability of samples from receipt of arrival to further shipment or disposal (as appropriate).

10.5 Sample analysis procedures

Central analysis of PD-L1 will be carried out on all baseline archival FFPE tumour samples using the Ventana methodology (≥5% immune cells staining using SP263 antibody, Ventana[12]). All sample analysis will be carried out under a biomarker protocol separate to this trial. These may include the following:

- To evaluate candidate predictive biomarkers of sensitivity or resistance to sequential chemotherapy and avelumab in pre-treatment tumour tissue in each of the co-primary UC patient populations treated.
- Expression profiling of tumour and/or tumour infiltrating immune cells.
- Identification of immunogenic neo-antigens which potentially could promote anti-tumour T-cell response upon treatment.
- Profiling of immune cell infiltration in tumour, blood and/or urine samples with specific focus on T cell exhaustion upon chemotherapy (CyTOF, multiplex immunohistochemistry analysis, flow cytometry, TCR repertoire/neoantigens.
- Circulating tumour DNA (ctDNA) analysis at baseline, on treatment and at progression.
- Cytokine assessment
- Tumour and urinary tract microbiome analysis

Additional assessments including genetic and/or molecular tests may be conducted either within the scope of the biomarker protocol or within future ethically approved studies. Patients will not be notified of the results of these analyses due to the preliminary nature of the results. The test results will not be distributed to the patient's insurance company, employer, GP/family doctor or any other future or current treating physician. Patients will be notified of this via information in the PIS/ICF.

10.6 Sample Storage Procedures

Details about sample storage are provided in the DISCUS laboratory manual. Research blood and urine samples should be stored in a -20ºC or -80ºC freezer as defined in the DISCUS laboratory manual. FFPE samples should be stored at room temperature. The Sponsor will arrange for samples to be collected from sites and shipped to the central sample repository.

10.7 Sample and result recording and reporting

The format and timelines for result reporting will be documented in the DISCUS Analytical Plan or vendor sub-contract as appropriate. All results will be retained in the DISCUS TMF.

Samples, and any data deriving from any analysis, may be shared with commercial and non-commercial collaborators, upon contractual agreement. Samples may be transferred within or outside the UK and EU after being linked anonymised using only the DISCUS trial ID and unique sample number allocated by the CECM coordinating team. Patients will be notified of this via information in the PIS/ICF.

10.8 Sample Management at End of Study

In the event that a patient withdraws their consent from the study no further data or samples will be collected. The investigational site team must ask the patient if samples and data collected up to the date of withdrawal can be used in the study. All samples and data collected up to the date of withdrawal will be destroyed, if requested by the patient. In all other instances, samples and data collected up to the date of withdrawal will be used in the study.

Queen Mary University of London as the Sponsor will keep overall oversight of the entire lifecycle through internal procedures and monitoring of study sites, the CI will be the custodian of the samples. Samples will be transferred from participating sites to Barts Cancer Institute, Queen Mary University of London. Those retained for further ethically approved research will be registered with the Barts and the London Queen Mary's School of Medicine and Dentistry Tissue Bank (HTA Licensing number: 12199). Subject to relevant approvals, samples may be transferred to organisations (including commercial organisations) within or outside the EU for analysis.

11 Study medication

Refer to the avelumab Summary of Product Characteristics (SmPC), gemcitabine (SmPC), carboplatin (SmPC), cisplatin (SmPC) and DISCUS Pharmacy Manual for further details.

11.1 Name and description of Investigational Medicinal Product(s) (IMP)

Avelumab, gemcitabine, carboplatin and cisplatin are considered IMPs in this study.

Refer to the current version of the avelumab SmPC, gemcitabine SmPC, carboplatin SmPC, cisplatin SmPC for information regarding the physical and chemical properties and the lists of excipients of each IMP.

11.2 Legal status of IMP

Avelumab is currently licensed for use in the UK, Spain and France in the treatment of metastatic merkel cell carcinoma, advanced renal cell carcinoma and locally advanced or metastatic urothelial tumours.

Gemcitabine is currently licensed for use in the UK, Spain and France in the treatment of bladder cancer, advanced non-small cell lung cancer, advanced pancreatic cancer, breast cancer and ovarian cancer.

Cisplatin is currently licensed for use in the UK, Spain and France in the treatment of testicular, lung, cervical, bladder, head and neck, and ovarian cancer

Carboplatin is currently licensed for use in the UK, Spain and France in the treatment of advanced ovarian cancer and small cell lung cancer. Carboplatin is used as per standard of care in the treatment of urothelial carcinoma in both the UK, Spain and France..

The trial will be carried out under a Clinical Trial Authorisation (CTA). The drug is therefore only to be used by the named investigators, for the participants specified in this protocol, and within the trial.

11.3 Name and description of each Non-Investigational Medicinal Product (NIMP)

No NIMPs will be used in the DISCUS study.

11.4 Legal Status of NIMP

No NIMPS will be used in the DISCUS study.

11.5 IMP Manufacturer(s) and supply arrangements

Avelumab is manufactured by Merck Healthcare KGaA and will be supplied to participating sites as concentrate for solution for infusion by Merck Healthcare KGaA. Stock will be allocated and released specifically for use in the DISCUS study. Packaged and labelled avelumab will be distributed to UK sites by Fisher Clinical Services UK Limited (Fisher UK). Fisher Clinical Services GmbH (Fisher Germany) will distribute packaged and labelled avelumab to all EU (Spain and France) sites.

Commercial supplies of gemcitabine, cisplatin and carboplatin will be obtained locally by the investigating sites in keeping with standard local practice. The need for ring fencing will be assessed on a site-by-site basis.

Please refer to the DISCUS Pharmacy Manual for further details regarding avelumab IMP ordering, supply and distribution arrangements.

11.6 Packaging and labelling of IMP(s)

All study drugs will be packaged and labelled in accordance with local regulations and Good Manufacturing Practice Annex 13, stating that the drug is for clinical trial use only and should be kept out of reach of children.

Avelumab will be packaged and labelled by Fisher Clinical Services.

11.7 Packaging

The investigational product avelumab is a sterile, clear, colourless and non-pyrogenic solution for intravenous infusion. It is presented in Type I glass vials filled with 10 mL of liquid (200 mg/vial), closed with a rubber septum and sealed with an aluminium flip off seal. Each single-use vial contains 200 mg of avelumab, formulated as a 20 mg/mL preservative-free acetate buffered solution at pH 5.2 in presence of Polysorbate 20 and Mannitol. The product requires further dilution prior to IV infusion.

Gemcitabine, cisplatin/carboplatin will be obtained locally by the investigating sites in keeping with standard local practice. Please refer to the current SmPC for each gemcitabine, cisplatin/carboplatin for information on packaging.

11.8 Labelling

Avelumab will be distributed and labelled by Fisher Clinical Services and supply will be managed by them in conjunction with the CECM. Fisher Clinical Services UK Limited (Fisher UK) will distribute packaged and labelled avelumab to all UK sites. Fisher Clinical Services GmbH (Fisher Germany) will distribute packaged and labelled avelumab to all EU (Spain and France) sites.

Gemcitabine, cisplatin/carboplatin will be labelled locally in line with Annex 13 requirements by the respective Pharmacy departments of participating sites. These IMPs are used within their marketing authorisation or are recognised treatment options within established clinical practice. Dispensing labels will be locally applied by participating pharmacies to finished products and this text will comply with Annex 13 requirements. This is in line with MHRA type A risk adaptation whereby IMP being used within the terms of its marketing authorisation, has not been repackaged and is dispensed according to the prescription given by an authorised healthcare professional can be labelled according to Annex 13 requirements.

No labelling risk adaptations will be applied to avelumab as the IMP has been repackaged by the IMP manufacturer for clinical trial use.

11.9 Preparation of IMP(s)

For administration in clinical studies, avelumab infusion solution should be prepared by dilution in 0.9% Sodium Chloride (Normal Saline), 0.45% Sodium Chloride (half normal saline), Dextrose 5% (D5W) or Dextrose 10% (D10W). The verified avelumab concentration range in the infusion solution diluted with 0.9% and 0.45% NaCl is 0.016 mg/mL to 8 mg/mL, while the verified avelumab concentration range in the infusion solution diluted with D5W and D10W is 1.0 mg/mL to 8 mg/mL.

If not used immediately, the diluted drug product can be stored up to 8 hours at room temperature (15-25^{o}C, 59-77^{o}F), including infusion time. Alternatively, the diluted drug product may be stored up to 24 hours at 2°C to 8°C/36 – 46^{o}F, including infusion time. If not used immediately, storage requirements, expiry date and time of the diluted product as per the aforementioned timelines are the responsibility of the user(s) and must be appropriately documented on the product and the preparation documentation e.g. worksheets. Please refer to the DISCUS Pharmacy Manual for detailed information on preparation on avelumab for administration.

Gemcitabine, cisplatin/carboplatin will be obtained locally by the investigating sites in keeping with standard local practice. Please refer to the current SmPC for each gemcitabine, cisplatin/carboplatin for information on preparation. Dose banding according to local institution policy is acceptable for gemcitabine, cisplatin/carboplatin in the UK NHS England dose banding guidance may be used. Gemcitabine, cisplatin/carboplatin are used within their marketing authorisation or are recognised treatment options within established clinical practice. The sponsor has risk assessed and permitted that use of generic product, and the use of local policies for dose-banding is acceptable for these IMPs.

11.10 Accountability

The Site Principal Investigator must ensure that the study drugs are stored and dispensed in accordance with hospital standard operating procedures and applicable regulatory requirements. The PI may delegate this task to a suitable individual (e.g., pharmacist) but retains overall responsibility. Full drug accountability records must be maintained for avelumab, gemcitabine, cisplatin/carboplatin using the IMP accountability logs provided. Sites may amend the IMP accountability log provided or use their own documentation if it captures all the information required by the Sponsor. If the site is using their own documents, or changes the sponsor provided template, these need to be approved by the Sponsor Research Pharmacist or NCC delegate before use. The medication provided for this study is for use only as directed in the protocol. Drug distribution and accountability logs will be provided to the site in a pharmacy pack. It is the Investigator's responsibility to establish a system for handling the investigational product to ensure that:

- Deliveries of investigational products are correctly received by a responsible person (e.g., pharmacist or suitable pharmacy designee) and are handled and stored correctly and safely.
- Investigational products are dispensed only to study participants, and in accordance with the protocol.
- A dispensing record (which will include the identification of the participant to whom the investigational product was dispensed, the date of dispensing, the quantity of investigational product dispensed, and the date and quantity of any unused investigational product returned to the pharmacy) is accurately maintained. Any discrepancies must be accounted for on the appropriate form. This record is in addition to any drug accountability information recorded in the eCRF.

In the case that IMP is damaged, please contact the CECM for reconciliation and replacement. At the termination of the study or at the request of the Sponsor, all unused drugs will be accounted for and destroyed locally at the study sites as per local policies. Certificates of delivery and destruction or return for avelumab must be signed and copies retained in the PSF. Further guidance will be provided in the DISCUS Pharmacy Manual.

11.11 Assessment of compliance

Pharmacy departments will be monitored in accordance with the DISCUS study monitoring plan. On-site monitoring will be used to provide assurance that all procedures related to patient treatment are being carried out in accordance with the protocol and all applicable SOPs.

11.12 Drug storage

11.12.1 Drug Receipt

Avelumab will be distributed to UK sites by Fisher Clinical Services UK Limited (Fisher UK). Fisher Clinical Services GmbH (Fisher Germany) will distribute packaged and labelled avelumab to all EU (Spain and France) sites.

Avelumab will be received by the pharmacy department at the participating site. Avelumab will be shipped via a temperature controlled shipper (2 – 8^{o}C, 36 – 46^{o}F) that is monitored with a temperature monitoring device. Further instructions regarding shipment temperature monitoring and the operation of the temperature monitoring devices are contained within the DISCUS pharmacy manual. The pharmacy department should acknowledge receipt of avelumab as per the DISCUS Pharmacy Manual.

Ordering and delivery records for avelumab will be retained in the Pharmacy Site File. Shipments of avelumab received at the pharmacy will be logged onto the accountability log. The accountability log will be kept in the Pharmacy Site File (PSF). No risk adaptation regarding shipment records will be applied to avelumab as the IMP has been repackaged by the IMP manufacturer for clinical trial use.

Gemcitabine, cisplatin/carboplatin will be obtained locally by the investigating sites in keeping with standard local practice. Gemcitabine, cisplatin/carboplatin are commercial supplies locally sourced by local pharmacies by the routine medicines supply chain. These IMPs are used within their marketing authorisation or are recognised treatment options within established clinical practice. Therefore, as per MHRA type A risk adaptations, shipment records for these IMPs will not be retained within the PSF for this study.

11.12.2 Drug Storage Conditions

The IMP must be kept in a secure place under appropriate storage conditions. A description of the appropriate storage and shipment conditions are specified on the investigational labels. The PI at each participating site or a delegated person e.g., pharmacist, is responsible for ensuring that the IMP is stored in a secure place and under the recommended storage conditions. Temperature monitoring records

(manual or automated) for all IMPs must be maintained and will be made available to the sponsor upon request e.g., monitoring visits.

- Avelumab drug product must be stored at 2°C to 8°C/36 to 46ºF until use. Avelumab drug product must not be frozen. Rough shaking of the solution must be avoided. Please refer to section 11.9 for storage conditions post-preparation.
- Gemcitabine, cisplatin/carboplatin will be obtained locally by the investigating sites in keeping with standard local practice. Please refer to the current SmPC for each gemcitabine, cisplatin and carboplatin for information on storage requirements.

11.13 Drug Temperature Excursions

Please refer to the DISCUS pharmacy manual for both in-transit and on-site temperature excursion reporting procedures for avelumab, gemcitabine, cisplatin and carboplatin. All temperature excursions affecting study IMP must be reported to the CECM DISCUS coordinating team as soon as possible.

11.14 Prescription and Dispensing of IMP(s)

Study IMP will be dispensed by the pharmacy (or by staff delegated by the PI) at the participating site in accordance with the trial-specific prescription. A prescription template will be provided in the pharmacy file, although sites will be permitted to use their own clinical trial template prescription if suitable. Prior approval of the final prescription template by the Sponsor Research Pharmacist or NCC delegate is required.

Study IMP must only be dispensed if prescribed by delegated prescribing healthcare professions as listed on the current site delegation log. Site staff are responsible for ensuring that the local pharmacy has access to the current site delegation log (if required as per local SOP). For sites whereby alternative arrangements are in place, this will be assessed by the CECM coordinating team during site feasibility.

11.15 Administration of IMP(s)

Avelumab will be administered at a flat dose of 800mg on day 1 and day 15 of each 28-day cycle from cycle 4 onwards (arm A) or cycle 7 onwards (arm B). Please refer to section 11.24 for guidance on pre-medications to be administered prior to avelumab infusions. Avelumab will be administered for a maximum of 2 years post chemotherapy. Both arm A and arm B will receive a maximum of 26 cycles (52 biweekly infusions) of avelumab within 10 weeks of completion of chemotherapy.

Avelumab concentrate for solution for infusion should be diluted in 0.9% saline (sodium chloride injection) supplied in an infusion bag; alternatively, a 0.45% saline solution (half normal saline), Dextrose 5% (D5W) or Dextrose 10% (D10W) can be used if needed.

Avelumab will be delivered by IV infusion over 60 minutes (± 10-20 minutes) using IV infusion bags (polyethylene, polypropylene, ethylene vinyl acetate or low density polyethylene) connected to an infusion set equipped with a low protein binding 0.2 micro polyether sulfone (PES) in-line filter (or PSU but only if PES membrane is not available) and an appropriate gauge standard venous catheter for the subject. Alternatively, a permanent venous catheter or implantable port may be used. Prior to infusion, the assembly should be primed with dosing solution.

Following avelumab infusions, subjects must be observed for 30 minutes for potential infusion reactions. Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Gemcitabine, cisplatin and carboplatin will be administered via Intravenous (IV) infusion as per local procedures

11.16 Destruction, return, and recall of IMP(s) and placebo(s)

Any avelumab expired or remaining at the end of the trial must be destroyed according to the site's local standard operating procedures and only following permission by the Sponsor. Certificates or logs of destruction must be provided by the site and copies retained in the PSF. No site IMP destruction risk adaptations will be applied to avelumab as the IMP has been repackaged by the IMP manufacturer for clinical trial use. Full destruction records will be maintained for this IMP.

Gemcitabine, cisplatin/carboplatin are commercial supplies locally sourced and dispensed by local pharmacies. These IMPs are used within their marketing authorisation or are recognised treatment options within established clinical practice. Therefore, as per MHRA type A risk adaptations, site IMP destruction records for these IMPs will not be retained within the PSF for this study. In the event of local supplies of gemcitabine, cisplatin and carboplatin being subject to a product recall, this will be as per local site procedure. Sites should inform the sponsor of any such recall request.

Details regarding measures to take in the event of avelumab being subject to a product recall will be documented in the DISCUS pharmacy manual.

11.17 Dosage schedules

Table 4 below describes the dosing schedule for the 3 chemotherapy cycle arm.

Table 4: Dosing Schedule – 3 chemotherapy cycle arm.

IMP	Dose	Cycle Length	3 chemotherapy cycle arm	
			Frequency	Duration
Gemcitabine	1000 mg/m2	21 days	Day 1 & 8	Cycles 1 - 3
+				
Cisplatin	70 mg/m2	21 days	Day 1	Cycles 1-3
Or[1]				
Carboplatin	AUC 4.5, or AUC of 5	21 days	Day 1	Cycles 1-3
Followed by ⬇				
Avelumab	800mg	28 days	Day 1[3] & 15	Cycle 4 onwards[2]

[1] As per investigator choice

[2]Until disease progression or intolerable toxicities up to a maximum of 2 years following gemcitabine + cisplatin/carboplatin chemotherapy.

[3] C4D1 avelumab infusion should commence within 10 weeks after the last dose of chemotherapy.

Table 5 below describes the dosing schedule for the 6 chemotherapy cycle arm

3 C4D1 avelumab infusion should commence within 10 weeks after the last dose of chemotherapy.

Table **5 Dosing Schedule – 6 chemotherapy cycle arm**

IMP	Dose	Cycle Length	6 chemotherapy cycle arm

			Frequency	Duration
Gemcitabine	1000 mg/m2	21 days	Day 1 & 8	Cycles 1 - 6
+				
Cisplatin	70 mg/m2	21 days	Day 1	Cycles 1 - 6
Or[1]				
Carboplatin	AUC 4.5, or AUC of 5	21 days	Day 1	Cycles 1 - 6
Followed by ⬇				
Avelumab	800mg	28 days	Day 1[3] & 15	Cycle 7 onwards[2]

[1] As per investigator choice

[2] Until disease progression or intolerable toxicities up to a maximum of 2 years following gemcitabine + cisplatin/carboplatin chemotherapy.

[3] C7D1 avelumab infusion should commence within 10 weeks after the last dose of chemotherapy.

11.18 Dosage modifications and delays

There will be no dose modification permitted for avelumab. Dose modifications or delays for gemcitabine and cisplatin/carboplatin should follow local guidelines on this study. Please refer to the table of assessments for the windows permitted at each infusion timepoint.

Please refer to section 11.19 for guidance on management of avelumab specific adverse events. Please refer to section 11.21 for guidance on the management of avelumab infusion related/hypersensitivity reactions and avelumab related tumour lysis syndrome.

Gemcitabine and cisplatin/carboplatin related toxicities will be managed as per local practice.

Patients who have a treatment delay of more than 12 weeks due to treatment related toxicity should discontinue study treatment and receive a quality of life assessment within 14 days of discontinuation, unless there is a specific agreement between the Investigator and the CI. Please refer to section 8.7.8 for further details on quality of life assessment.

11.19 Management of avelumab specific adverse events

The following section provides guidance on the management of avelumab specific adverse events. Treatment of irAEs should follow guidelines set forth in Table 6.

Table 6 Management of avelumab Immune-Related Adverse Events

11.19.1 Gastrointestinal irAEs

Severity of Diarrhoea/Colitis (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Diarrhoea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (e.g., oral fluids, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2, 3 or 4.

Grade 2 Diarrhoea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with activities of daily living (ADL) Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment	If improves to Grade ≤ 1: Resume avelumab therapy If persists > 5-7 days or recurs: Treat as Grade 3 or 4.
Grade 3 to 4 Diarrhoea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 h; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. 1.0 to 2.0 mg/kg/day prednisone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower endoscopy	If improves: Continue steroids until Grade ≤ 1, then taper over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5mg/kg (if no contraindication). Note: infliximab should not be used in cases of perforation or sepsis.

11.19.2 Dermatological irAEs

Grade of Rash (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 to 2 Covering ≤ 30% body surface area	Continue avelumab therapy Symptomatic therapy (for example, antihistamines, topical steroids)	If Grade 2 persists > 1 to 2 weeks or recurs: Withhold avelumab therapy Consider skin biopsy Consider 0.5-1.0 mg/kg/day prednisone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: Life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisone or equivalent	If improves to Grade ≤ 1: Taper steroids over at least 1 month; resume avelumab therapy following steroids taper (for initial Grade 3).

	Add prophylactic antibiotics for opportunistic infections	

11.19.3 Pulmonary irAEs

Grade of Pneumonitis (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4.
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily; consider hospitalization 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤ 1, taper steroids over at least 1 month, and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening or for recurrent Grade 2: Treat as Grade 3 to 4.
Grade 3 to 4 Grade 3: Severe new symptoms; New/worsening hypoxia; Grade 4: Life-threatening	Permanently discontinue avelumab therapy. Hospitalize. Pulmonary and Infectious Disease consults. 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤ 1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)

11.19.4 Hepatic irAEs

Grade of Liver Test Elevation (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1	Continue avelumab therapy	Continue liver function monitoring If worsens: Treat as Grade 2 or 3 to 4.

Grade 1 AST or ALT > ULN to 3.0 x ULN and/or Total bilirubin > ULN to 1.5 x ULN		
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days.	If returns to Grade ≤ 1: Resume routine monitoring; resume avelumab therapy. If elevation persists > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and/or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist/ hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤ 1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines.

11.19.5 Renal irAEs

Grade of Creatinine Increased (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections	If returns to Grade ≤1: Taper steroids over at least 1 month.

	Consider renal biopsy Nephrology consult	

11.19.6 Cardiac irAEs

Myocarditis	Initial Management	Follow-up Management
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g., troponin, CK-muscle/brain, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy. Hospitalise. In the presence of life-threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish aetiology and rule-out immune-related myocarditis. Guideline based supportive treatment as per cardiology consult. * Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-related aetiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-related etiology is suspected or confirmed following cardiology consult, manage as immune-related myocarditis.
Immune-related myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate as per cardiology consult. * 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month. If no improvement or worsening, consider additional immunosuppressants (e.g., azathioprine, cyclosporine A).

*Local guidelines, or e.g., European Society of Cardiology or American Heart Association guidelines

European Society of Cardiology guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines

American Heart Association guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001

11.19.7 Endocrine irAEs

Endocrine Disorder	Initial Management	Follow-up Management
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalization Endocrinology consult Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for type I diabetes mellitus) as appropriate. Rule out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and/or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement/suppression). Continue hormone replacement/suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and/or adrenal insufficiency is confirmed (i.e. subnormal serum thyroxine with inappropriately low thyroid-stimulating hormone and/or low serum cortisol with inappropriately low adrenocorticotropic hormone):	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented.

Endocrine Disorder	Initial Management	Follow-up Management
	• Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated **If hypophysitis confirmed:** • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and/or abnormal MRI. Consider hospitalization. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Continue hormone replacement/suppression therapy as appropriate.

11.19.8 Other irAEs (not described above)

Grade of other irAEs (NCI-CTCAE v4)	Initial Management	Follow-up Management
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential irAE	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent	If improves to Grade ≤ 1: Taper steroids over at least 1 month.

	Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	
Grade 4	Permanently discontinue avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent and/or other immunosuppressant as needed Add prophylactic antibiotics for opportunistic infections Specialty consult.	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency **Persistent Grade 2 or 3 irAE lasting 12 weeks or longer**	Permanently discontinue avelumab therapy Specialty consult	
Suspected pancreatitis	Withhold avelumab therapy	
Confirmed pancreatitis	Permanently discontinue avelumab therapy	
Suspected Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)	Withhold avelumab therapy)	
Confirmed Stevens-Johnson syndrome (SJS) or Toxic epidermal necrolysis (TEN)	Permanently discontinue avelumab therapy	

Abbreviations: ADL=activities of daily living; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BNP=B-type natriuretic peptide; CK- =creatine kinase; CT= computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE=immune related adverse event; IV=intravenous; LH=luteinizing hormone; MRI=magnetic resonance imaging; NCI CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PRL=prolactin; ULN=upper limit of normal.

11.20 Known drug reactions and interventions with other therapies

The following section provides guidance on the management of avelumab infusion related/ hypersensitivity reactions and avelumab related tumour lysis syndrome.

11.21 Management of avelumab infusion related reactions

In order to mitigate infusion-related reactions, premedication with an antihistamine and with paracetamol (acetaminophen) approximately 30 to 60 minutes prior to the first 4 infusions of avelumab is mandatory (for example, 25-50 mg diphenhydramine and 500-650 mg paracetamol [acetaminophen] IV or oral equivalent). Premedication should be administered for subsequent avelumab doses based upon clinical judgment and presence/severity of prior infusion reactions. The premedication regimen may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids.

Since avelumab is administered IV, infusion-related reactions may occur (with symptoms such as fever, chills, rigors, diaphoresis, and headache). Treatment of the infusion-related reaction and modifications of avelumab infusion are mainly dependent upon severity, as indicated in Table 7.

Table 7: Treatment Modification for Symptoms of avelumab Infusion Related Reactions

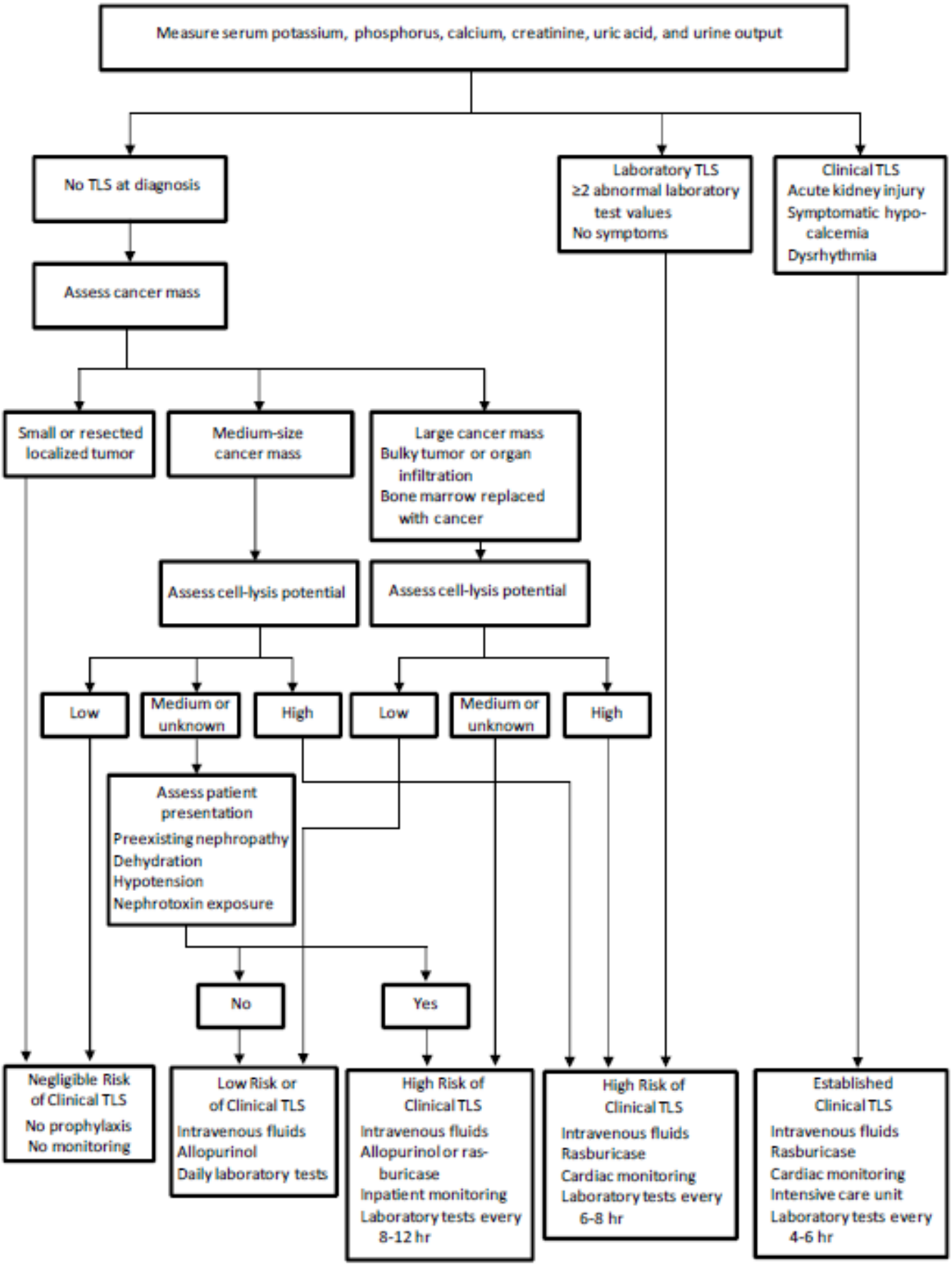
NCI CTCAE Grade	Treatment Modification for Avelumab
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Decrease the avelumab infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours.	• Temporarily discontinue avelumab infusion. • Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity. Monitor closely for any recurrence or worsening.
Grade 3 or Grade 4 – severe or life-threatening • Grade 3: Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae. • Grade 4: Life-threatening consequences; urgent intervention indicated.	• Stop the avelumab infusion immediately and disconnect infusion bag and tubing from the patient. • Subjects have to be withdrawn immediately from avelumab treatment and must not receive any further avelumab treatment.

IV=intravenous, NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events, NSAIDs=nonsteroidal anti-inflammatory drugs.

11.22 Management of Avelumab-Related Tumour Lysis Syndrome

Avelumab can induce antibody-dependent cell-mediated cytotoxicity (ADCC), so there is a potential risk of tumour lysis syndrome. Should this occur, patients should be treated as per local guidelines and the management algorithm (Figure 3) published by Howard et al[42].

Figure 3: Assessment and Initial Management of Tumour Lysis Syndrome (TLS)


Measure serum potassium, phosphorus, calcium, creatinine, uric acid, and urine output
No TLS at diagnosis
Assess cancer mass
Laboratory TLS
≥2 abnormal laboratory test values
No symptoms
Clinical TLS
Acute kidney injury
Symptomatic hypo-calcemia
Dysrhythmia
Small or resected localized tumor
Medium-size cancer mass
Large cancer mass
Bulky tumor or organ infiltration
Bone marrow replaced with cancer
Assess cell-lysis potential
Assess cell-lysis potential
Low
Medium or unknown
High
Low
Medium or unknown
High
Assess patient presentation
Preexisting nephropathy
Dehydration
Hypotension
Nephrotoxin exposure
No
Yes
Negligible Risk of Clinical TLS
No prophylaxis
No monitoring
Low Risk or of Clinical TLS
Intravenous fluids
Allopurinol
Daily laboratory tests
High Risk of Clinical TLS
Intravenous fluids
Allopurinol or ras-buricase
Inpatient monitoring
Laboratory tests every 8-12 hr
High Risk of Clinical TLS
Intravenous fluids
Rasburicase
Cardiac monitoring
Laboratory tests every 6-8 hr
Established Clinical TLS
Intravenous fluids
Rasburicase
Cardiac monitoring
Intensive care unit
Laboratory tests every 4-6 hr

11.23 Recommended concurrent treatment

The following section documents the premedication requirements for avelumab infusions and the recommend supportive care regimens.

Premedication and supportive care for gemcitabine, cisplatin/carboplatin e.g. anti-emetics and hydration will be administered in line with local polices.

11.24 Premedication for avelumab infusions

Premedication to mitigate the risk of avelumab infusion related reactions is detailed in section 11.21. This premedication regimen is mandatory for the first 4 infusions of avelumab. Premedication should be administered for subsequent avelumab infusions based upon clinical judgment and presence/severity of prior infusion reactions. The premedication regimen may be modified based on local treatment standards and guidelines, as appropriate, provided it does not include systemic corticosteroids.

11.25 Recommended supportive care regimens

Supportive care may be administered at the discretion of the site PI, as medically indicated. This includes but not is not limited to the items outlined below:

- **Diarrhoea**: All patients who experience diarrhoea should be advised to drink liberal quantities of clear fluids and administer loperamide. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
- **Nausea/Vomiting:** Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.
- **Anti-infectives:** Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice. Prophylactic administration should be considered for the cases outlined in Table 6 in section 11.19.
- **Anti-inflammatory or narcotic analgesics** may be offered as needed.
- **Acetaminophen/paracetamol** to a maximum total daily dose of 4 g in 24 hours is permitted.
- Patients who need to be on **anticoagulant therapy** during treatment should be treated with low molecular weight heparin. If low molecular weight heparin cannot be administered, coumadin or other coumarin derivatives or other anti-coagulants (including direct factor Xa inhibitors) may be allowed; however, appropriate monitoring of prothrombin time/international normalized ratio (PT/INR) should be performed.

Over the course of this trial, additional medications may be required to manage aspects of the disease state of the patients, including side effects from trial treatment or disease progression. Details of the concomitant medication given, including blood and blood products, must be recorded in the patient's medical records and the eCRF. Supportive care may be administered at the discretion of the site PI, as medically indicated.

11.26 Prohibited medication

Patients must be instructed not to take any medications, including all over-the-counter products such as vitamins, minerals, and other dietary supplements, without first consulting with their site PI or designee.

The following medications are prohibited during the study:

- Concurrent treatment with any other investigational agent or participation in another clinical trials with therapeutic intent within 4 weeks prior to randomisation. Subjects must not have received any prior systemic therapy for locally advanced or metastatic urothelial carcinoma with the following exceptions: subject could have received a platinum containing regimen (cisplatin or carboplatin) in the neoadjuvant or adjuvant setting if more than 6 months since last cycle has occurred.
- Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g. hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g. by local surgery or radiotherapy). In the case of a surgical procedure, avelumab treatment should be withheld. Postoperatively, the decision to reinitiate avelumab treatment should be discussed with the sponsor's medical monitor.
- Immunosuppressive medications, including but not limited to systemic corticosteroids at doses not exceeding 10 mg/day of prednisone or equivalent. The use of inhaled corticosteroids, physiologic replacement doses of glucocorticoids (i.e., for adrenal insufficiency), and mineralocorticoids (e.g., fludrocortisone) is allowed. NOTE: Use of immunosuppressive medications for the management of investigational product-related AEs as per those listed in section 11.19 Table 6 and management of avelumab infusion related reactions as per those listed in section 11.21 are permitted.
- Administration of live attenuated vaccines. Patients must also not have received a live attenuated vaccine within 4 weeks of study enrolment.
- Bisphosphonate or denosumab treatment unless it has been initiated more than 14 days prior to receiving the first administration of avelumab.
- Growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor). Exception: Erythropoietin and darbepoietin alpha may be prescribed at the investigator's discretion).
    - During administration of Gemcitabine + cisplatin/carboplatin growth factors (granulocyte colony stimulating factor or granulocyte macrophage colony stimulating factor) may be prescribed at the investigator's discretion.
- Herbal remedies with immunostimulating properties (eg, mistle toe extract) or known to potentially interfere with major organ function (e.g., hypericin).

11.27 Concomitant Therapies Requiring Caution

- Cisplatin nephrotoxicity may be exacerbated by treatment with other nephrotoxic drugs (e.g. aminoglycoside antibiotics, non-steroidal anti-inflammatory drugs). Caution with use of other nephrotoxic drugs.
- If anticoagulation with warfarin is necessary, frequent monitoring of prothrombin time and the International Normalized Ratio (INR) is recommended.
- Concomitant administration of ototoxic (e.g. aminoglycosides, loop diuretics) medicinal products will potentiate the toxic effect of cisplatin on auditory function.
- Simultaneous use of antihistamines, buclizine, cyclizine, loxapine, meclizine, phenothiazines, thioxathenes or trimethobenzamides may mask ototoxicity symptoms such as dizziness and tinnitus.
- Serum concentrations of anti-convulsive medicines may remain at sub-therapeutic levels during treatment with cisplatin.

11.28 Study restrictions

There are no dietary restrictions for patients taking part in DISCUS.

11.29 Management of overdose

An overdose is defined as the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an adverse event, but it may result in an adverse event. Any overdose or incorrect administration of study drug should be noted on the relevant eCRF and reported as adverse events within 24 hours of awareness by the study site whether or not the event meets adverse event criteria. Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfils seriousness criteria, the event should be reported to the Sponsor immediately (i.e. no more than 24 hours after learning of the event). The CECM DISCUS Coordinating team must be contacted in the event of a study drug overdose.

11.30 Precautions regarding contraception

It is not known what effects avelumab, Gemcitabine or cisplatin/carboplatin has on human pregnancy or development of the embryo or foetus. Patients should use highly effective methods of contraception throughout the study and until 6 months after discontinuing Gemcitabine and cisplatin/carboplatin or 1 month after discontinuing avelumab treatment (whichever is longer). This will apply to both female patients of childbearing potential and for male patients.

Acceptable highly effective methods of contraception for female participants of child bearing potential include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
- Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- True sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of contraception.

Male participants are required to use condoms.

If a patient, or a partner of a male patient, becomes pregnant during the patient's participation in this study and during the 6 months after discontinuing Gemcitabine and cisplatin/carboplatin or 1 month after discontinuing avelumab treatment (whichever is longer), this must be reported to the CECM DISCUS coordinating team immediately. Where deemed appropriate after birth for instance in cases of congenital abnormalities or birth defects further follow up information will be collected. Time of follow-up will be decided on a case-by-case basis

11.31 Arrangements for post-study access to IMP and care

Study treatment will only be provided for a maximum of 2 years post-chemotherapy, no further study IMP or funding for IMP will be provided following this. Due to the stage and type of cancer under investigation it is not projected that treatment beyond 2 years post-chemotherapy will be required.

Upon completion of study treatment, patients will be treated at the discretion of the treating investigator in line with local standard of care polices. Patients deriving benefit on completion of 2 years of treatment with avelumab can be switched to locally supplied avelumab, sourced via the site's local processes at the DISCUS Master Protocol V4.1 dated 25May2023

discretion of the treating investigator. The study sponsor will not cover the cost or provide funding for any further locally sourced avelumab treatment.

Patients will be fully informed of the study design and treatment duration as part of the informed consent process.

Equipment and Devices

No specific equipment or devices used outside of standard practice is required for the DISCUS study.

If patients would like to consent to the optional sub study patients will be given a wearable device. All data from devices is wirelessly consolidated via a MHRA-approved mobile application (app) and uploaded to a secure anonymised database.

12 Pharmacovigilance

12.1 General definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "*response to an investigational medicinal product*" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • Results in death. • Is life-threatening. • Requires inpatient hospitalisation or prolongation of existing hospitalisation • Results in persistent or significant disability/incapacity. • Consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator or medical assessor, believed with reasonable probability to be due to one of the study treatments, based on the information provided.

Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out in the Reference Safety Information (RSI): • In the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product. • In the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the study in question.

12.2 Site investigator assessment

The Principal Investigator is responsible for the care of the participant, or in their absence an authorised medic within the research team is responsible for assessment of any event for:

- **Seriousness:** Assessing whether the event is serious according to the definitions given in section 12.1.
- **Causality:** Assessing the causality of all serious adverse events/reactions in relation to the study treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.
- **Expectedness**: Assessing the expectedness of all SARs according to the definition given. If the SAR is unexpected (as per the RSI), then it is a SUSAR.
- **Severity**: Assessing the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on participant/event endpoint criteria.
    - **Mild**: Some discomfort noted but without disruption of daily life
    - **Moderate**: Discomfort enough to affect/reduce normal activity
    - **Severe**: Complete inability to perform daily activities and lead a normal life

Severity will be assessed using the grading scales found in the NCI CTCAE V 5.0 for all AEs with an assigned NCI-CTCAE term. For those events without assigned NCI-CTCAE grades, the recommendation on page 1 of the NCI-CTCAE that converts mild, moderate and severe into NCI-CTCAE grades should be used. A copy of the NCI-CTCAE V5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

12.3 Reference Safety Information (RSI)

Reference Safety Information (RSI) is the information used for assessing whether an adverse reaction is expected.

- **Avelumab**: The RSI is set out in section 4.8 of the Avelumab SmPC.
- **Gemcitabine:** The RSI is set out in section 4.8 of the Gemcitabine SmPC.
- **Carboplatin:** The RSI is set out in section 4.8 of the Carboplatin SmPC.
- **Cisplatin:** The RSI is set out in section 4.8 of the Cisplatin SmPC.

The SmPCs will be reviewed periodically to ensure that it is up to date and reflects the information currently available about the IMP. SmPCs will be reviewed on a regular basis which will be, at a minimum, once a year.

12.4 Notification and recording of Adverse Events (AEs) or Reactions (ARs)

All AE and AR's are to be documented in the participants' medical notes or other source data documents and the CRF. Once assessed, if the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team.

AEs will be collected from the time the patient signs the informed consent form until the safety visit (83 - 90 days after the last dose of IMP). AEs will be followed up according to local practice until recorded on the eCRF until the event has stabilised or resolved, or the end of treatment visit, whichever is sooner. Any unresolved AEs at the patient's last visit should be followed up for as long as medically indicated, but without further recording in the eCRF. The following details will be collected in the eCRF for each AE: AE term, date of onset, date of resolution, NCI-CTCAE V5.0 grade (maximum intensity), seriousness, Investigator causality rating against the study medication, action taken with regards to study medication and outcome.

12.5 Abnormal Laboratory Test Results

All clinically significant (as assessed by the Principal Investigator) abnormal laboratory test results occurring during the study will be recorded as AEs at the corresponding study visit. The clinically significant abnormal laboratory tests will be repeated at appropriate intervals until they return either to baseline or to a level deemed acceptable by the Investigator or until a diagnosis that explains them is made.

12.6 Notification of AEs of Special Interest (AESIs)

Non-serious adverse events of special interest are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) using the eCRF. AESIs will be collected from the start of avelumab treatment until the safety visit (83 - 90 days after the last dose of IMP) and recorded in the eCRF.

Additional Expedited Reporting Requirements:

The following events must be reported as expedited events as per the reporting requirements in section 12.8:

- Occupation exposure to Avelumab
- Potential drug induced liver injury if they meet the criteria of Hy's Law:

  Criteria for Hy's Law (FDA Guidance 2009)

  - The drug causes hepatocellular injury, generally shown by a higher incidence of 3 fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo
  - Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
  - No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

12.7 Adverse events that do not require reporting

The following situations that fulfil the definition of an SAE are excluded from recording/reporting on an SAE form however they should be recorded on the eCRF and in the medical records.

- AEs meeting the criteria for 'serious' (SAEs) that occur whilst on gemcitabine/cisplatin or gemcitabine/carboplatin chemotherapy only. All SAEs that occur once the subject has moved on to receive avelumab should be recorded and reported to the Sponsor (JRMO or agreed representative) within 24 hours of the PI or co-investigator becoming aware of the event, as per standard SAE reporting guidance.
- Elective hospitalisation and surgery for treatment of urothelial carcinoma or its complications.
- Elective hospitalisation to make treatment or procedures easier. For example, to administer study medication.

- Elective hospitalisation for pre-existing conditions that have not been exacerbated by trial treatment

12.8 Notification and reporting of Serious Adverse Events (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs)

All Serious Adverse Event (SAEs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) will be recorded in the participants' notes, the CRF, the sponsor SAE form and reported to the sponsor (administered by the Joint Research Management Office or agreed representative) within 24 hours of the site becoming aware of the event except those specified in this protocol as not requiring reporting.

Nominated co-investigators (as delegated in the site delegation log) will be authorised to sign the SAE forms in the absence of the PI at the participating sites.

Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur during the study will be reported to the Sponsor (JRMO or agreed representative) within 24 hours of the PI or co-investigator becoming aware of the event.

Receipt of SUSAR by the CECM DISCUS coordinating team is considered to be day 0 for competent authority (CA) reporting. The CECM DISCUS coordinating team are responsible for rapid reporting to the Sponsor. The Sponsor will notify the UK CA in accordance with regulatory timelines and requirements. It is the CI's responsibility to report SUSARs to the REC and to disseminate SUSARs to participating sites. NCCs are delegated reporting responsibility in their country in accordance with local regulatory requirements. Follow up of patients who have experienced a SUSAR should continue until recovery is complete and the condition has stabilised. Day 0 for all SUSARs is when the SAE / SUSAR is received by the CI and / or coordinating team and / or sponsor (whichever is first). Where significant new information on an already reported case is received, the clock starts again at 'day 0' (day 0 is the date the new information is received). This new information is then reported as the follow-up report within the 15 day timeline (or 7 days for fatal or life-threatening events).

If the Investigator becomes aware of safety information that appears to be drug related, involving a subject who participated in the study, even after an individual subject has completed the study, this should also be reported to the Sponsor.

SAE and SUSAR reporting must be performed as per the DISCUS Pharmacovigilance Reporting Instructions. All SAEs and SUSARs must be reported to the CECM DISCUS coordinating team using the DISCUS SAE form via email: BCI-DISCUS@qmul.ac.uk

The CECM Coordinating Team will forward copies of SAEs/SUSARs to Merck.

12.9 Sponsor medical assessment

Sponsor has delegated the responsibility for oversight of IMP safety profile and medical assessment of AEs, ARs, SAEs and SUSARs to the CI as medical assessor. The CI must review all SAEs within 72 hours of receipt. This review should encompass seriousness, relatedness, and expectedness. Day 0 for all SUSARs is when the SAE / SUSAR is received by the CI and / or coordinating team and / or sponsor (whichever is first).

It is noted that the CI cannot downgrade the PI assessment of an event's causality. If there is disagreement between CI and PI assessment, no pressure should be placed on the PI to alter their assessment, but the CI can liaise with the site PI before the CI's final assessment is made. The CI and PI assessment can differ. The expectedness is determined solely by the reference safety information as referred to in 12.3 of this protocol.

12.10 Procedures for reporting blinded SUSARs

The DISCUS study is not a blinded study.

12.11 Urgent safety measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical study participants from any immediate hazard to their health and safety, in accordance with Regulation 30 of the Medicines for Human Use (Clinical Trials) regulations. The measures should be taken immediately. In this instance, the approval of the Competent Authority prior to implementing these safety measures is not required. However, it is the responsibility of the CI to attempt, where possible, to discuss the proposed change with the sponsor and Medical Advisor at the MHRA (via telephone) prior to implementing the change if possible.

The CI has an obligation to inform both the MHRA and Research Ethics Committee in writing **within 3 days** of implementing the Urgent Safety Measure. They must also submit a substantial amendment documenting the changes with 14 days of implementing the urgent safety measure. The JRMO must be sent a copy of the correspondence with regards to this matter as soon as it is sent.

12.12 Pregnancy

If a participant becomes pregnant whilst involved in a CTIMP, it is not considered to be an SAE or an AE. However, it is an event that requires reporting, monitoring and follow up. If a participant or participant's partner becomes pregnant whilst or after taking an IMP, the sponsor should be notified immediately (within 24 hours of site becoming aware of the pregnancy) using the sponsor pregnancy form. The pregnancy reporting procedure will be the same as the SAE reporting route.

The CI (in conjunction with the site PI) should determine if the foetus has been exposed to an IMP. The PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. The initial report should be sent within 24 hours of the PI or co-investigator becoming aware of the event and follow up information submitted as and when it becomes available up to agreed follow up time after birth.

The sponsor will arrange for a review of the pregnancy report by an appropriate expert medic (usually a consultant obstetrician). The study team must follow all instructions provided by the sponsor's expert.

All participant pregnancies, pregnancy of a participant's partner and outcomes of pregnancy should be reported to the CECM DISCUS coordinating. The DISCUS CECM coordinating team will liaise with the sponsor regarding assessment following Sponsor SOPs and additionally inform Merck Healthcare KGaA (for patients exposed to avelumab only) of pregnancies and their outcomes.

12.12.1 Maternal Exposure

If a patient becomes pregnant while on study, treatment must be discontinued immediately. The Investigator must inform the CECM DISCUS coordinating team within 24 hours of becoming aware of the pregnancy using the pregnancy eCRF.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IMP may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/ birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study. Where deemed appropriate after birth for instance in cases of congenital

abnormalities or birth defects further follow up information will be collected. Time of follow-up will be decided on a case-by-case basis dependant on IMP exposure.

12.12.2 Paternal Exposure

Pregnancy of a male patient's partner is not considered to be an AE. Male patients may continue to receive IMP. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 6 months after discontinuing Gemcitabine and cisplatin/carboplatin treatment or 1 month after discontinuing avelumab treatment (whichever is longer) should, if possible, be followed up and documented even if the patient was discontinued from the study.

The Investigator must inform the CECM DISCUS Coordinating Office of any pregnancy in a male participant's female partner within 24 hours of becoming aware of the pregnancy and provide the CECM DISCUS coordinating team with outcome information within 24 hours of becoming aware of the pregnancy outcome. Where deemed appropriate after birth for instance in cases of congenital abnormalities or birth defects further follow up information will be collected. Time of follow-up will be decided on a case-by-case basis.

13 Annual reporting

13.1 Development Safety Update Report (DSUR)

The DSUR will be written by the CI (following Sponsor procedures) and submitted to the sponsor for review prior to submission to the MHRA. The DSUR is due for submission within 60 days of the end of the reporting period. The reporting period is annually from the date on the "*Notice of acceptance letter*" from the MHRA. The sponsor's delegated Medical Assessor, usually the CI, will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the study. REC will be sent a copy of the DSUR.

The Development Safety Update Report (DSUR) will be submitted within 60 days of the end of the reporting period to the UK CA by the CECM DISCUS coordinating team, following JRMO approval, according to current requirements and copies will be forwarded to the JRMO.

NCCs are delegated responsibility for submitting a copy of the DSUR (which will be provided by the Sponsor) in their country in accordance with local regulatory requirements.

13.2 Annual Progress Report (APR)

The APR will be written by the CI (using the HRA's template) and submitted to the sponsor for review prior to submission to the REC. The APR is due within 30 days of the anniversary date of the "favourable opinion" letter from the REC.

Annual progress reports (APR) will be submitted to the main UK Research Ethics Committee (REC) by the CECM DISCUS coordinating team, following JRMO approval, according to current requirements and copies will be forwarded to the JRMO. A copy of the APR and any associated correspondence with the REC will also be sent to relevant participating sites.

NCCs are delegated responsibility for preparing and submitting annual or other reports in their country in accordance with local regulatory requirements

14.0 Statistical and data analysis

14.1 Sample size calculation

The primary endpoint of this two arm phase-II trial is to assess the change in quality of life from baseline to the completion of 6 cycles of treatment. Patients who withdraw from treatment between cycles 4 and 6, will be included in the primary endpoint provided they have completed the EORTC QLQ-C30 assessment completed within 14 days after the date of withdrawal. Comparisons will be made for 3 cycles of platinum-based chemotherapy followed by maintenance avelumab vs 6 cycles of platinum-based chemotherapy only in patients with unresectable locally advanced or metastatic urothelial carcinoma whose disease did not progress on or following completion of first-line platinum-containing chemotherapy.

The difference in EORTC QLQ-C30 GHS/QoL scale scores from baseline to the completion of 6 cycles of treatment l will be used to compare the two arms. The t-test will be used to assess this trial's results and the normal approximation will be used to estimate the sample size required.

As observed in a similar setting by Vaughn et al[43]., a 9 point improvement in the difference in GHS/QoL scale score change from baseline is proposed where the sample standard deviation of this change from baseline is assumed to be 26.9 (a pooled standard deviation calculated using results from the two arms analysed by Vaughn et al.)[43].

To detect a significant result at the 10% level (i.e. α=0.1) with 80% power (i.e. 1-β=0.80) the total sample size required is 224 evaluable patients (112 in each arm). All calculations for sample size were performed using a two-sided two-sample equal variance t-test in the software package PASS version 16.0.1.

In the future this trial may have an expansion phase based on the results of the overall survival analysis. The trial will remain as similar to the current design as possible to facilitate direct comparisons between the original and expansion phase. The TSC, TMG, the Sponsor and funder will need to agree before the expansion phase proceeds. A substantial protocol amendment will be submitted prior to the explansion phase being implemented. For each expansion to the current study design, new sample size calculations will be performed based on the latest literature available.

14.1 Planned recruitment rate

The time to complete recruitment into the DISCUS study is anticipated to take 24 months.

14.2 End of trial (EOT) definition

The end of trial (EOT) is defined as last patient last visit.

The CI is delegated the responsibility of submitting the EOT notification to REC and MHRA once reviewed by the sponsor. The EOT notification must be received by the REC and MHRA within 90 days of the end of the study. If the study is ended prematurely, the Chief Investigator will notify the Sponsor, REC, and MHRA within 15 days, including the reasons for the premature termination.

NCCs are delegated responsibility for submitting a copy of the EOT notification in their country in accordance with local regulatory requirements.

14.3 Statistical Analysis

Full details on the analysis of all endpoints will be outlined in the statistical analysis plan (SAP), which will be finalised prior to any review or analysis of data.

The primary endpoint will be analysed once at least 224 evaluable patients (112 in each arm) have enough EORTC QLQ-C30 data at baseline and on completion of 6 cycles of treatment (or at the assessment

completed within 14 days post the date of withdrawal for those who withdraw from treatment between cycles 4 and 6) for the difference in GHS/QoL scale score change from baseline to be calculated as per the EORTC QLQ-C30 manual[40] (i.e. at least 1 of the 2 questions that make up the GHS/QoL scale score answered at both baseline and the post-baseline assessment used for analysis).

Primary analysis results may be published separately from the other study endpoints and prior to completion of the trial.

14.4 Summary of baseline data and flow of participants

A CONSORT diagram comprising the number of participants who were screened, eligible, randomised, received their allocated treatment, withdrawn from/lost to follow-up along with reasons will be provided.

Demographic and baseline characteristics (including, but not limited to: age; ethnicity; gender; smoking status; number of prior anti-tumour treatments; urothelial cancer diagnosis site; tumour grade; histological type; tumour size; TNM staging) will be summarised using appropriate summary statistics (i.e. mean, standard deviation, median, and range for continuous variables, and number and proportion of patients for categorical variables). Differences between arms for categorical variables will be assessed using the Chi-squared/Fisher's exact tests (as applicable) and continuous variables will be compared using Student's t-tests or Mann-Whitney-U test, depending on the normality of the data.

14.5 Analysis of participant populations

Patient-reported outcome (PRO) analyses (including the primary endpoint) will be performed on the PRO evaluable population, defined as all patients randomised into the trial who have a PRO questionnaire at baseline and also for at least one post-baseline visit. This is regardless of whether they were later found to be ineligible, a protocol violator, or given the wrong treatment allocation. Treatment arms will be compared on the basis of randomised treatment, regardless of the treatment actually received.

Secondary efficacy analyses will be performed on the intention-to-treat (ITT) population, defined as all patients randomised into the trial. This is regardless of whether they were later found to be ineligible, a protocol violator, or given the wrong treatment allocation. Treatment arms will be compared on the basis of randomised treatment, regardless of the treatment actually received.

All safety analyses (including secondary safety analyses) will be performed on the safety set population, defined as all patients randomised into the trial who received at least one dose of study treatment. This is regardless of whether they were later found to be ineligible, a protocol violator, or given the wrong treatment allocation. Treatment arms will be compared on the basis of treatment they actually received, regardless of the treatment randomised to. Therefore, randomised patients who did not receive any doses of study treatment will be excluded from the safety set population.

14.6 Primary endpoint analysis

The primary objective is to evaluate the effect of 3 vs 6 cycles platinum-based, front line chemotherapy followed by maintenance avelumab based on PROs in the study population. The difference in GHS/QoL scale score change from baseline to the completion of 6 cycles of treatment will be used to assess this. Patients who withdraw from treatment between cycles 4 and 6 will be included in the primary analysis provided they complete an EORTC QLQ-C30 assessment within 14 days after the date of withdrawal.

As detailed in the EORTC QLQ-C30 reference values[41], the GHS/QoL scale score is often approximately normally distributed and for this reason the t-test will be used to assess the trial's results.

14.7 Secondary endpoint analysis

14.7.1 Secondary efficacy endpoints

Objective response (OR) is defined as the number of patients with at least one response of complete response (CR) or partial response (PR), according to RECIST v1.1. Patients without a post-baseline tumour assessment will be considered to be non-responders. Objective response rate (ORR) is defined as the number of patients with an OR divided by the number of patients analysed. ORR will be presented at 20 weeks post-randomisation. An estimate of the ORRs for each arm and 95% CIs will be calculated. The odds ratio of responses (treatment: control) will be reported separately along with the associated CIs based on logistic regression. Treatment comparisons will be tested with and without adjustment for the baseline stratification factors.

Progression free survival (PFS) is defined as the time from the date of randomisation to the date of first documented tumour progression (as assessed by the site radiologist and/or investigator, using RECIST v1.1) or death from any cause, whichever occurs first. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST assessment prior to the two missed visits. For patients who have not died or experienced disease progression at the time of analysis, PFS will be censored on the last date the patient was known to be progression-free. Kaplan–Meier (K-M) methodology will be used to estimate the PFS rate at 20 weeks and median PFS for each treatment arm. The PFS rate at 20 weeks and median PFS will be estimated with 95% CIs, and the K-M curve will be plotted. The effect of treatment will be estimated by the HR together with its corresponding CIs and p-value, obtained from the Cox proportional hazards model. Treatment comparisons will be tested with and without adjustment for baseline stratification factors.

Duration of response (**DoR**) is defined, for patients with an OR, as the time from first documentation of CR or PR to disease progression (as assessed by the site radiologist and/or investigator, using RECIST v1.1) or death on study from any cause, whichever occurs first. Methods for handling, censoring, and analysis are the same as those described for PFS. K-M methodology will be used to estimate the median DoR for each treatment arm. The median DoR will be estimated with 95% CI, and the K-M curve will be plotted. The effect of treatment will be estimated by the HR together with its corresponding CIs and p-value, obtained from the Cox proportional hazards model. Treatment comparisons will be tested with and without adjustment for baseline stratification factors.

Overall survival (**OS**) is defined as the time from date of randomisation to the date of death from any cause. All deaths will be included, whether they occur on study or following treatment discontinuation. Patients who are still alive at the time of analysis will be censored at the date of last contact. K-M methodology will be used to estimate the median OS for each treatment arm. The median OS will be estimated with 95% CI, and the K-M curve will be plotted. The effect of treatment will be estimated by the HR together with its corresponding CIs and p-value, obtained from the Cox proportional hazards model. Treatment comparisons will be tested with and without adjustment for baseline stratification factors.

14.7.2 Secondary safety endpoints

Adverse event incidence, nature and severity (graded according to NCI-CTCAE v5.0) through-out treatment as well as on completion of 6 cycles of treatment, and between Cycle 5 Day 1 and the completion of 10 cycles of treatment will be presented. Treatment discontinuation rate due to AEs will also be presented. Differences between arms for instances of AEs will be assessed using Chi-squared/Fisher's exact tests (as applicable).

Performance status as measured by the Karnofsky Scale on completion of 6 cycles of treatment will be presented. Differences between arms on completion of 6 cycles of treatment will be assessed using the Chi-squared/Fisher's exact tests (as applicable).

14.7.3 Secondary patient reported outcome (PRO) endpoints

GHS/QoL scale score change from baseline as per the primary endpoint will be performed with adjustment for any baseline imbalances in GHS/QoL scale scores. Methods for analysis will be similar to those described in section 14.6 for the primary endpoint.

GHS/QoL scale score comparisons between arms at the beginning of cycle 5 to the completion of 10 cycles of treatment will be performed with similar methods for analysis as those described in section 14.6 for the primary endpoint.

GHS/QoL scale score time to deterioration (TTD) comparisons between arms will be performed. For a given baseline score, deterioration in the GHS/QoL scale score will be defined as a decrease by ≥10 points at any time point after baseline with no subsequent observations with a <10 point decrease from baseline. TTD is defined as the time from date of randomisation to the date of first documented ≥10 point decrease from baseline in GHS/QoL scale score (with no subsequent observations with a <10 point decrease from baseline) or death from any cause, whichever occurs first. For patients who have not had a ≥10 point decrease from baseline in GHS/QoL scale score (with no subsequent observations with a <10 point decrease from baseline) and are still alive at the time of analysis, TTD will be censored on the last date the patient was known to be deterioration-free. Patients who die without GHS/QoL scale score deterioration will be considered to have experienced deterioration at the time of death. KM methodology will be used to estimate the median TTD for each treatment arm. The median TTD will be estimated with 95% CI, and the K-M curve will be plotted. The effect of treatment will be estimated by the HR together with its corresponding CIs and p-value, obtained from the Cox proportional hazards model. Treatment comparisons will be tested with and without adjustment for baseline stratification factors.

EORTC QLQ-C30 summary statistics (mean, standard deviation, median, and range) will be presented for items by time point, primarily focusing on completion of 6 cycles of treatment and from the beginning of cycle 5 (to the completion of 10 cycles of treatment. For each arm, to compare changes from baseline (by visit), the paired t-test will be used to assess significance of the mean change for linearly transformed scores. Alternatively, if the paired t-test does not seem appropriate (i.e. if assumptions are not met) the Wilcoxon signed rank test will be used to assess significance of the median change for linearly transformed scores. Previously published minimally important differences (MIDs) will be used to identify meaningful change from baseline within each treatment group and overall on the functional, symptom and GHS/HRQoL scales[44]. An analysis of covariance (ANCOVA) model will be conducted to determine the changes from baseline (to each visit) in the linearly transformed scores with treatment arm as a fixed effect and linearly transformed baseline score as a covariate. Significance of change within each treatment arm and significance of the difference between the treatment arms will be reported. Completion, compliance rates and reasons for missing data will also be summarised at each time point by treatment arm.

14.8 Safety analysis

Summaries of adverse events (including protocol-defined events of special interest and non-serious adverse events), laboratory test results and exposure to IMP will be presented. Drug exposure will be summarised to include treatment duration and dose intensity. Laboratory data will be summarised by NCI CTCAE V5.0 grade.

Verbatim descriptions of adverse events will be mapped to thesaurus terms using the latest available MedDRA dictionary. The CI may wish to group MedDRA codes further into more clinically meaningful groups for analysis and interpretation. Any grouping of toxicity codes will be signed off by the CI.

Events occurring on the day of or after administration of the first dose of treatment will be summarised by thesaurus term, appropriate thesaurus levels, and NCI CTCAE v5.0 grade. Serious adverse events, including deaths, will be summarised and listed separately.

14.9 Exploratory endpoints

Exploratory endpoint analyses will be detailed in the SAP.

14.10 Optional sub study endpoints

Endpoints related to the optional sub study are outlined in Appendix A.

14.10 Subgroup analyses

No subgroup analyses are planned.

14.11 Adjusted analysis

Adjusted analyses as detailed in section 14.7.3 will be detailed in the SAP.

14.12 Interim analysis and criteria for the premature termination of the study

No interim analysis is planned for this study. Any decisions to prematurely discontinue this study would be within the remit of the Trial Steering Committee. Please refer to section 23.2 for further details.

14.13 Procedure(s) to account for missing or spurious data

The process for reporting missing EORTC QLQ-C30 questionnaire data should be documented in the eCRF as per section 8.7.8. Imputations for missing EORTC QLQ-C30 data will follow those detailed in the EORTC QLQ-C30 scoring manual[40].

All other endpoint related missing data will be sought unless confirmed as not available, in which case missing data will be recorded as not available on eCRFs. No further imputations for missing data will be performed unless specified in the SAP.

14.14 Economic evaluation

No economic evaluation is required for this study.

14.15 Other statistical considerations

The DISCUS study SAP details any further statistical considerations in relation to this protocol.

15 Data handling and record keeping

15.1 Source data and source documents

ICH GCP E6 section 1.51 and 1.52, define source data as "All information in original records and certified copies of original records or clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)" and "Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, participants' diaries of evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, participant files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)", respectively.

Source data locations may vary across sites. A source data document will be in place for each site that will detail what will comprise the source data and what will comprise the source documents. This source data document will be created per site at setup prior to site activation.

Sites that use electronic source data should ensure to provide direct access to electronic source systems and database(s) to the DISCUS monitor (and all other authorised personnel as flagged in section 9.1) at onsite visits. It is the site's responsibility to maintain these electronic source databases, to ensure that they are Good Clinical Practice (GCP) and MHRA guidelines compliant (Medicines for Human Use (Clinical Trials) Regulations 2004) and provide a suitable audit trail, and that systems are in place to demonstrate that the PI at site has clinical oversight of electronic source data. Printouts from electronic source data must be documented to be verified copies, dated and signed. This includes data for all assessments as listed in Table 1 and Table 2.

Direct access will be granted to authorised representatives from the sponsor, NCC, host institution, and the regulatory authorities to permit study-related monitoring, audits, and inspections.

15.2 Study Documents

All site level trial related documents should be filed in the ISF and PSF. It should contain essential documents as per the contents page provided to the Investigator by the DISCUS coordinating team. The CECM DISCUS coordinating team will inform the PI, and their staff, of any regulatory updates and forward on any relevant documentation. It is the participating PI's responsibility to maintain this file and keep all records up to date.

15.3 Case Report Forms (CRFs)

This trial uses an eCRF, an Oracle database built and managed by the CECM. The Oracle database is hosted and managed by Barts Cancer Institute and saved on a secure server. Sites will receive training for appropriate eCRF completion. eCRFs will be submitted electronically to the sponsor in a timely manner, and should be handled in accordance with the sponsor's instructions as per the DISCUS eCRF Completion Guidelines. Any data queries arising from initial review will be sent to the relevant centre for resolution. The authorised personnel on site will have access to the data entered on the eCRF at all times.

All eCRFs should be completed by designated, trained site personnel. The eCRF should be reviewed and electronically signed and dated by the investigator on a per-patient basis once all data has been entered, validated, and confirmed by the CECM DISCUS coordinating team. At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records.

The Trial Management Group (TMG) reserves the right to amend or add to the eCRF design as appropriate. Revised or additional forms should be used by centres in accordance with the guidelines provided by the sponsor.

15.4 Sample Transfer Forms (STFs)

The CECM DISCUS coordinating team will be responsible for monitoring transfer and receipt of biological specimens. STFs will be sent by participating sites to the CECM DISCUS coordinating team to monitor the transfer of all biological samples. All data will be handled, computerised and stored in accordance with the General Data Protection Regulation 2018 and Data Protection Act 2018.

15.5 Data capture

Data will be entered onto the electronic CRF (Oracle) by participating sites. Sites will be fully informed of expected data entry timelines as part of the site feasibility and initiation processes. Completed patient questionnaires will be requested from participating sites on a minimum of a quarterly basis. The CECM coordinating team will review data completion rates on a per site basis as part of central monitoring. Further details regarding the frequency and scope of central monitoring processes are documented in the DISCUS study monitoring plan.

The CECM coordinating team will only receive de-identified data and samples from study participants. Please refer to section 6 for further information on how patient data is de-identified for use in the DISCUS study. All patient identifiable information and documentation (for example, PIS/ICFs) will be stored at participating sites and will not be transferred to the CECM coordinating team.

Access to the electronic CRF will be access restricted to delegated individuals only, who have received appropriate training on the use and function of the electronic CRF. Users will be assigned a level of access appropriate to their role in the study. The electronic CRF is hosted on a secure server and is subject to regular data back-ups. An audit trail is maintained as part of the electronic CRF functioning.

15.6 Transferring and transporting data

All data must be handled in accordance with the Data Protection Act (2018). If data is to be transferred outside of the UK or EEA, explicit consent from participants is required as data protection arrangements may not be as robust.

Identifiable information must not be stored or transported on any portable device (e.g. laptops, memory sticks, CD / DVDs) unless it is encrypted. Similarly, data must not be sent electronically if it is not subject to end-to-end encryption.

15.7 Data Management

Further details regarding trial specific data management processes can be found in the DISCUS data management plan.

Source data verification will be utilised throughout the study in order to ensure data is accurate, complete and verifiable. Further details regarding the scope, volume and monitoring procedures used to attain this are documented in the DISCUS study monitoring plan.

Central and remote monitoring activities will also be performed to support source data verification. These activities include, but are not limited to, review of CRF data completion rates, review of manual/automatic data query responses and data consistency checks. Full details regarding centralized monitoring and data cleaning activities can be found in the DISCUS study monitoring plan.

Final database lock will be performed as part of a controlled process as documented in the DISCUS study data management plan. Final database lock will only be performed once all trial data has been received, verified (as required), fully coded and cleaned for analysis with all queries resolved. Access to the final locked database will be restricted to delegated individuals involved in the management and analysis of the study. Procedures for unlocking the database and any pre-planned soft locks will be documented in the DISCUS study data management plan.

16 Confidentiality

The Chief Investigator will be the data custodian for all data generated during the study.

The Chief Investigator and the study team will ensure that all participants' identities are protected at every stage of the study. To ensure this, at time of consent each participant will be allocated a unique screening number (see section 6) by the CECM DISCUS coordinating team before undergoing any screening procedures.

The Principal Investigator is responsible for protecting the identity of participants at their site. Participants will be referred to only by their unique study identifier whenever data is transferred outside of the site, and in all correspondence between the site and the coordinating centre, co-investigators, sponsor, or anyone associated with the study.

No participants will be individually identifiable from any publications resulting from the study.

Information regarding study participants will be kept confidential and managed in accordance with the Data Protection Act (2018), the Research Governance Framework for Health and Social Care and Research Ethics Committee approval. All study data will be stored in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments and the Data Protection Act. Study data will be archived in line with the Medicines for Human Use (Clinical Trials) Regulations 2004 and all subsequent amendments, and as defined in the JRMO SOP 20 Archiving.

All information which is generated in the trial will be kept strictly confidential. As samples are being collected for future use, patient consent forms will be collected and kept in a secure locked cabinet within the tissue bank premises. The researchers conducting the trial will abide by the General Data Protection Regulation 2018 and Data Protection Act 2018, and the rights the patient has under these acts. Parts of the patients' medical records and the data collected for the trial will be looked at by authorised personnel from the sponsor. It may also be looked at by representatives of regulatory authorities and other authorised personnel from the patient's hospital, to check that the trial is being carried out correctly.

All of the above bodies have a duty of confidentiality to the patient as a research participant and nothing that could reveal their identity will be disclosed outside the research site. All data should be stored in a locked and dedicated room only accessed by authorised personnel.

Data collected about participants may be used to support other research (including cancer research) in the futureand may be shared anonymously with other researchers within or outside the UK (including within or outside the EU). This data may be linked to the blood, urine and tissue samples collected during the study. This data may also be combined with other sources of information held about participants within the NHS, for the purposes of health and social care research. Any data sent outside the EEA will be link anonymised, in accordance with the data protection act. Samples which are collected during the study may be transferred within or outside the UK and EU for further ethically approved studies, after being pseudo-anonymised for future research.

16.1 De-identification of participants

A unique participant ID number will be assigned to each participant. This number will serve as the participant's identifier in the trial as well as in the clinical trial database. The participant's data/samples will be stored under this number. Only the investigator will be able to link the participant's trial data to the participant via an identification list kept at the site. The participant's original medical data will be kept strictly confidential. However, medical notes will need to be reviewed by the study monitor or sponsor representative and may be inspected during an audit by the regulatory authorities, sponsors or site R&D staff. Data protection and privacy regulations will be observed in capturing, forwarding, processing and storing participant data. The participant information sheet informs the potential participants about confidentiality and who will have access to their medical notes.

17 Monitoring, Audit, and Inspection

17.1 Monitoring

A Trial Monitoring Plan will be developed and agreed by the sponsor and Chief Investigator based on the sponsor's risk assessment, which will include on site monitoring. Monitoring procedures are detailed in the Trial Monitoring Plan.

Monitoring for the DISCUS study will consist of a combination of activities performed by the sponsor, study team and trial committee members. This includes review of data and progress of the trial by trial oversight committees and on-site monitoring.

Monitoring will involve a compliance review of the ISF and PSF as well as a proportion of Source Data Verification (SDV). This will involve direct access to patient notes at the participating hospital sites which will include the review of consent forms and other relevant investigational reports. Missing data will be sought, unless confirmed as not available.

During these visits the sites' activity will be monitored to verify that:

- Source data transcribed onto eCRFs is authentic accurate and complete.
- Compliance with QoL assessment completion.
- Safety, rights and well-being of the participants are being protected.
- The study is being conducted in accordance with the currently approved protocol.
- Any other study agreements, GCP and all applicable regulatory requirements are met.

Central and remote monitoring may also occur, for sites, pharmacies and the central laboratory. Please refer to the DISCUS Monitoring Plan for full details on monitoring activities for this trial.

17.2 Auditing

The sponsor retains the right to audit any aspect of the study, study sites, or central facilities. In addition, any part of the study may be inspected by the regulatory bodies, and funders where applicable. All sites and vendors are asked to inform the sponsor if notified of any Audit or inspection affecting this study.

The Investigator and institutions will be informed of the audit outcome. Investigators and vendors are obliged to cooperate in any audit allowing the auditor direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor to discuss any findings or issues. Audit may occur at any time during or after completion of the study.

18 Compliance

The CI will ensure that the protocol and study is conducted in compliance with the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, current UK Policy Framework for Social and health care research (2017), GCP guidelines, the World Medical Association Declaration of Helsinki, the Sponsor's and study specific SOPs, and other regulatory requirements. The CI will ensure that the procedures are compliant with the Ionising Radiation (Medical Exposure) Regulations, and appropriate review by a Medical Physics Expert and Clinical Radiation Expert has been undertaken.

In addition, sponsor auditors and CA inspectors will be allowed access to eCRFs, source documents and other trial files to evaluate the trial. Audit reports will be kept confidential.

The study will not commence until sponsor permission to activate sites is received.

Sites will be individually activated by the CI and team; this will not occur until site approval is granted.

18.1 Non-Compliance

Protocol deviations, non-compliances, or breaches are departures from the approved protocol.

Non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of non-compliances to ascertain if there are any trends developing which need to be escalated.

Accidental protocol deviations can happen at any time. The site must adequately document these on the DISCUS eCRF deviation log or ISF/PSF deviation log immediately.

The CI and the coordinating team will assess non-compliances and action a timeframe in which they need to action, including the requirement to escalate to the sponsor GCP manager, if appropriate. Corrective and preventative actions (CAPAs) will be assigned (where applicable), and given a different timeframe dependent on the severity of the non-compliance.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach. Prospective, planned deviations or waivers to the protocol are not allowed under the UK regulations on Clinical Trials and must not be used (i.e. it is not acceptable to enroll a participant if they do not meet the eligibility criteria or restrictions specified in the study protocol).

18.2 Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the patients of the trial; or
- The scientific value of the trial.

The site Principal investigator is responsible for reporting any potential serious breaches to the sponsor BCI-DISCUS@qmul.ac.uk within **24 hours** of becoming aware of the event.

The Chief Investigator is responsible for reporting any potential serious breaches to the JRMO **within 24 hours** of becoming aware of the event.

The sponsor is responsible for determining whether a potential serious breach constitutes a serious breach, and will work with the CI to investigate and notify and report to the MHRA and REC (as applicable) within 7 working days of becoming aware of the serious breach.

The Sponsor is responsible for notifying the CA in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial; or
- The protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

Participating centres should contact the CECM DISCUS coordinating team or CI for further information.

19 Declaration of interests

The Chief Investigator, Principal Investigators at each site and committee members for the overall study management will provide details of:

- All competing interests.
- Ownership interests that may be related to products, services, or interventions considered for use in the study or that may be significantly affected by the study.
- Commercial ties (e.g. pharmaceutical, behaviour modification, and/or technology companies).
- Non-commercial potential conflicts (e.g. professional collaborations that may impact on academic promotion).

These will be held within the Trial Master File. Please address enquiries to BCI-DISCUS@qmul.ac.uk

The sponsor requires that all study committee members complete competing interest declarations.

20 Peer review

The DISCUS study was reviewed by two independent experts in the field as part of the scientific peer review and sponsorship process. Further details can be requested from the CECM DISCUS coordinating team.

21 Public and Patient Involvement (PPI)

The study concept and design has been discussed with urothelial cancer patients PPI groups will be involved in dissemination of information to patients at the end of the study and may also be engaged if a substantial amendment to the study is planned which could affect patient participation in the DISCUS study.

22 Indemnity/ Insurance

The insurance that Queen Mary University of London has in place provides cover for the design and management of the study as well as "No Fault Compensation" for participants, which provides an indemnity to participants for negligent and non-negligent harm.

23 Study committees

23.1 Trial Management Group (TMG)

The TMG will consist of members of the coordinating centre (CI, Country Coordinating Investigator, Trial Coordinator, Project Lead, Senior Research Pharmacist, Statistician). Membership may include Principal Investigators from participating sites. The role of the TMG will be to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet at least twice a year.

23.2 Trial Steering Committee (TSC)

The TSC will consist of an Independent Chair, at least 2 other independent members, CI, the country coordinating investigators, Trial Coordinator, Project Lead and Trial Statistician. The role of the TSC will be to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The TSC will provide advice to the Investigators on all aspects of the trial. Final decisions about continuation or termination of the trial are the responsibility of the Sponsor in conjunction with the TSC. The TSC will meet at least twice a year, but meetings may be more frequent if requested by the TSC.

The three independent members of the TSC will also have IDMC responsibilities in lieu of a separate IDMC. In this capacity their role will be to review the accruing trial data and to assess whether there are any safety issues that should be brought to the participants' attention or any reasons for the trial not to continue. This role and delegation will be clearly laid out in the committee charter.

23.3 Independent data monitoring committee (IDMC)

The TSC has IDMC responsibilities within the DISCUS study.

24 Publication and dissemination policy

24.1 Publication

This is an investigator-led study sponsored by the CI's substantive employer, Queen Mary University of London. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according

to active participation in the statistical design, TMG, accrual of eligible patients and statistical analysis. Contributing centres and participating investigators will be acknowledged in the final manuscript.

All publications will acknowledge the sponsor. The correct designation for the sponsor is Queen Mary University of London. No participant or investigator may present data from his/her centre separately from the rest of the study results unless approved by the TMG and the sponsor.

The sponsor will be notified of any planned outputs of the research such as guidelines, publications, presentation, changes in service delivery etc. prior to external submission or presentation.

All publications will be sent to the JRMO prior to publication.

The full study report will be accessible via EudraCT or other suitable public website within one year of the End of the Trial Notification. Queen Mary University of London shall provide Merck with a copy of the EudraCT report for review and comment as per timelines specified in the contract.

24.2 Dissemination policy

Queen Mary University of London shall provide Merck with a copy of any proposed publication or presentation for review and comment as per timelines specified in the contract.

All study data shall be the property of Queen Mary University of London but may be shared with Merck per the processes and conditions specified in the contract.

In the event that research misconduct or data integrity concerns have been raised, the sponsor, with senior management of the affected organisation in discussion with the CI, reserves the right to review, request a hold on publication submission or to refuse permission to publish.

Responsibility for ensuring accuracy of any publication from this study is delegated to the CI.

24.3 Access to the final study dataset

The final locked dataset will only be accessible to the CECM DISCUS coordinating team, Study Statistician and Chief Investigator. The final study dataset will also be available for review by the Trial Management Group as part of their study oversight responsibilities. The full dataset or any relevant sub-sections will be provided as required.

Any requests to review the final study dataset e.g. external researchers or study investigators, will be made in writing and granted at the discretion of the Trial Steering Committee and sponsor.

25 Archiving

During the course of the research, all records are the responsibility of the Chief Investigator and will be kept in secure conditions. When the research study is complete, it is a requirement of the Queen Mary University of London Policy that the records are kept for 25 years from the End of the study.

Site files from other sites must be archived for 25 years at the external site and will not be stored by the sponsor.

Destruction of essential documents will require written authorisation from the Sponsor

It is the PI and site's responsibility to ensure that at the end of the trial all documentation (as defined by GCP and including source documentation e.g. medical notes, images, results and all related metadata), should be stored by each individual site's archiving facility for at least 25 years or in accordance with

local regulatory requirements, whichever is longer. It is the responsibility of the PI to ensure a full set of records is collated and documented. Records will be retained at each individual site. All records relating to the trial should be stored together, including the ISF, PSF and eCRFs. The location of the archiving facility must be provided to the CECM DISCUS coordinating team.

26 Study Finances

26.1 Funding Sources

This trial is investigator designed and led. It is funded by Merck Healthcare KGaA. Pfizer Inc is a key partner (non-funder).

Merck Healthcare KGaA will also provide the IMP for the study.

26.2 Patient expenses / payments

Participants will receive expenses for those visits which are outside standard of care.

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This protocol is based on JRMO Protocol template for MHRA Regulated Studies; Version 6.0, February 2021.

28 APPENDICES

Appendix A: Optional sub study

Sub study Design	This is a prospective, observational, multicentre research sub-study evaluating the feasibility and efficacy of using digital wearable device data via a commercially available wearable sensor and ePRO device in patients with advanced urothelial carcinoma enrolled into the DISCUS trial (EudraCT Number 2021-001975-17). Patients enrolled on the DISCUS trial can optionally consent to participate in the sub study. Patients will be provided with a set of devices, which together will be referred to as the Home And Locally Observed (HALO) kit. The HALO kit consists of a wrist-worn wearable sensor device (for monitoring biometric data) a mobile application (HALO app), which hosts a PROM questionnaire. The app remotely uploads data to a pseudo anonymised database. Patients will be registered and provided with a trial ID to ensure all transmitted data is pseudo anonymised. This optional study will recruit up to 150 patients (75 in each arm) who will receive treatment as per the DISCUS trial: 3 cycles (Arm A) vs 6 cycles (Arm B) of 3-weekly gemcitabine/platinum- based chemotherapy, followed by 2-weekly maintenance avelumab up to 2 years post-randomisation. All patients who opt into this optional sub study will be given a HALO kit consisting of a wearable sensor and access to the HALO mobile application. The HALO mobile application can be downloaded on their own smart device, or if participants don't have their own smart device, or don't wish to use their own, they will be given a digital ePRO device. Participants who optionally consent to this sub study are required to do wear the wearable tracker device for at least 8 continuous hours per day, at least once per treatment cycle between cycle 1 and cycle 6, and then at one time point 8-12 weeks after C6D1.. Participants data will be included into the primary endpoint analysis providing there are data points in a minimum of 3 separate cycles, one of which must occur during cycle 6*. Patients can wear the tracker for longer durations if they wish to. Participants who optionally consent to this sub study are required to complete the PROM questionnaire at least once per treatment cycle between cycle 1 to cycle 6, and then at one time point 8-12 weeks after C6D1. The PROM questionnaire is hosted on the HALO mobile application on their own smart device or provided ePRO device. The PROM questionnaire consists of 15 scoring questions and should take anywhere between 2 and 5 minutes to complete each day. The questionnaire needs to be completed in a single sitting, and if the patient leaves the app halfway through the questionnaire, they will be required to restart it. The wearable device may collect the following biometric data: • step count, • heart rate, • heart rate variability, • MVPA (moderate-to-vigorous-intensity physical activity) • peripheral oxygen saturation Biometric wearable device data for this sub study will be collected up to 12 weeks after the end of cycle 6 post-randomisation.

	*Patients who withdraw from treatment between Cycles 4 and 6 will be included, provided an EORTC QLQ-C30 questionnaire is completed and there is an evaluable digital biomarker reading within 14 days from the date of withdrawal. At the end of the sub-study duration, participants will be asked to return the wearable device and/or ePRO device. Devices collected from patients will be cleaned in accordance with hospital policy for ambulatory equipment. If any devices are damaged or lost during the study period, participants will not be held responsible for this and it will be fixed or replaced for them. At time of consent, patients will be informed that they should seek medical attention as they normally would if they feel unwell. Collected data from this sub study will not be used to notify physicians to any ill health or form part of adverse event reporting. Patients should seek medical advice as per standard practice.
Schedule of Assessments	During the study period, patients are required to do the following: 1. Wear the wrist worn tracker continuously for a **minimum of 8 consecutive hours** at **least once per treatment cycle** between **cycle 1 to cycle 6* and on a further occasion at least once 8-12 weeks after cycle 6 day 1.** 2. The wearable device **must** be worn for at least 8 consecutive hours at one time point during **cycle 6.** 3. Answer a short **PROM questionnaire** on the mobile application at least once per treatment cycle between **cycle 1 to cycle 6 and on a further occasion at least once 8-12 weeks after cycle 6 day 1** *Patients can wear the device for longer than the above specified time periods if they want to. At the end of the sub-study (approximately 12 weeks after cycle 6), the HALO equipment should be returned back to the research team and the devices will be shipped back to CECM.

	Cycle 1			**Cycle 2**			**Cycle 3**			**Cycle 4**			**Cycle 5**			**Cycle 6**			**Follow up**
	Week1	Week2	Week3	Week4	Week5	Week6	Week7	Week8	Week9	Week10	Week11	Week12	Week13	Week14	Week15	Week16	Week17	Week18	Week 24-28
Wearable device	X *wear for at least 8 consecutive hours at least once per cycle*			X *wear for at least 8 consecutive hours at least once per cycle*			X *wear for at least 8 consecutive hours at least once per cycle*			X *wear for at least 8 consecutive hours at least once per cycle*			X *wear for at least 8 consecutive hours at least once per cycle*			X *wear for at least 8 consecutive hours at least once per cycle*			*X* *Wear for at least 8 consecutive hours at least once 8-12 weeks after cycle 6 day 1*

PROM questionnaire on mobile application	X *Complete at least once per cycle*	X *Complete at least once per cycle*	X *Complete at least once per cycle*	X *Complete at least once per cycle*	X *Complete at least once per cycle*	X *Complete at least once per cycle*	*X* *Complete at least once 8-12 weeks after cycle 6 day 1*

Figure 2: Schedule of assessments

Patients can wear the device and complete the questionnaire at any time point during each treatment cycle providing it is worn for at least 8 consecutive hours at each time point. The device and questionnaire ***must*** *be worn/* completed at least once during cycle 6.

Rationale

Cancer and its treatment such as surgery, chemotherapy or radiotherapy can cause severe toxicities which, if untreated, can lead to poorer quality of life, increased hospital admissions, and worse clinical outcomes[1]. Routine monitoring of patients while under active systemic therapy usually entails regular clinic visits with the acquisition of vital signs, routine laboratory testing, patient-reported outcome surveys, and face-to-face interaction with their physician.

In recent years, commercially available, wearable sensor devices have allowed users to monitor their activity levels. These devices depend on small sensors that can collect high resolution biometric data, including heart rate and activity level (i.e., steps) which are transmitted to a smartphone or computer. Through this system, users can easily track and monitor their health status [2,3].

Given the value of physical function, the majority of current oncological trials involve tools to capture and monitor activity levels and functional performance such as Eastern Cooperative Oncology Group (ECOG) scale or validated self-reported questionnaires such as the EORTC QLQ-C30 questionnaire.

However, such scales are subjective thus leading to the potential for under- or overestimation of a patient's performance status[4]. Similarly, if patients are unable to complete the questionnaire due to an admission to hospital, possibly related to treatment side effects, this data may not be captured in quality-of-life assessments.

Therefore, capturing the fluctuations in physical biomarkers, such as heart rate and step count, could enable objective and real-time monitoring of patients between clinical encounters and allow for earlier detection of significant changes in activity and a more proactive and timely management of toxicities and risks during and after systemic therapy [5,6]. Previous studies in this field have demonstrated that wearable biometric sensors are able to acquire these data in patients undergoing surgery or receiving systemic therapy[7–9]. Compliance with the HALO device has been tested in the DREAMPath study (ISRCTN62293620).

Thus, the aim of this proposal is to evaluate the use of a comprehensive ambulatory monitoring platform that consists of a patient facing mobile application, activity monitor and online dashboard for physicians to assess digital biomarkers and quality of life in patients with advanced urothelial carcinoma, receiving front-line systemic therapy on the DISCUS trial. Data acquired via our monitoring platform combined with routine in office, symptom reporting may be a value method of quality of life assessment for patients on anti-cancer therapy. Continuous assessment of these digital biomarkers may reflect significant variation in quality of life, symptom burden, functional status and risk for readmission or other adverse outcomes.

Primary Objectives	Primary Endpoints
To assess if there is a **difference in physical activity** level between patients on the 2 arms of the DISCUS trial, obtained using a wearable activity tracker.	• Difference in average step count* at data point collected during cycle 6**, collected via wearable device. * The sub-study will meet its primary data efficacy endpoint if ≥ 20% of difference in average daily step is observed between the treatment arms. **To be eligible for primary endpoint analysis patient must have worn the device for 8 continuous hours per day, at least once per treatment cycle, in a minimum of 3 cycles, between cycle 1 and cycle 6. One of these data points must be within cycle 6.
Secondary Objectives	**Secondary Endpoints**
To determine the **feasibility of using a wearable sensor device** to obtain objectively measured biometric data in patients receiving treatment on the DISCUS trial.	• The number of participants who were able to wear the device for 8 continuous hours per day, at least once per treatment cycle between cycle 1 to cycle 6. This will be measured by continuous heart rate monitoring.
To assess if there is a **difference in objectively measured biometric data** between patients on the 2 arms of the DISCUS trial, obtained using a wearable activity tracker.	Biometric data to be compare may include but is not limited to: • **Average number of steps** per treatment at collected timepoints of data collection** • **Average resting heart rate** per treatment cycle** • **Heart rate variability** per treatment cycle** • **Maximum heart rate** per treatment cycle** • **Time spent in moderate to vigorous physical activity (MVPA)** per treatment cycle 6** • **Sleep metrics** per treatment cycle** **Patients who withdraw from treatment prior to cycle 6 will be excluded from primary endpoint analysis but can be included in secondary analyses, provided an EORTC QLQ-C30 questionnaire is completed between cycle 4-6 and there is biometric data obtained within 14 days from the date of withdrawal.
To evaluate the relationship between objectively measured in **biometric data** (collected via a wearable activity tracker) and **patient-reported functional outcomes** (measured via EORTC-QLQ-C30 questionnaire).	• Correlation between **biometric data collected from wearable device and score from EORTC-QLQ-C30 questionnaire**.
To evaluate the relationship between objectively measured **biometric data** collected via a wearable activity tracker and **toxicity**	• Correlation between **biometric data collected from wearable device and patient-reported symptom** as measured by Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) collected via **smartphone-based** and occurrence of **physician reported adverse events as measured by** Common Terminology Criteria for Adverse Events **(CTCAE v.5),** collected by the physician during patient visits.
To assess if there is a difference in **Patient Reported Outcomes** (PROs) between patients when assessed at home via **ePRO on a**	• Differences in patient-reported symptom as measured by Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (**PRO-CTCAE**) collected via ePRO on a smartphone-based application,

smartphone-based application vs	between cycle 1 and cycle 6 **compared to patient-**

EORTC-QLQ-C30 questionnaire.	**reported QoL as per EORTC-QLQ-C30 questionnaire** collected during DISCUS trial assessments.
To evaluate the relationship between objectively measured **biometric data** collected via a wearable activity tracker and **efficacy outcomes**	• Correlation between **biometric data collected from wearable device** and **efficacy outcomes** including **Progression Free Survival** (PFS), **Overall Survival** (OS), **Overall Response Rate** (ORR).
Sample size	As this is an optional sub study, up to 150 patients will be included into this sub study.
Statistical analysis	An interim analysis for this sub-study will be carried out after the first 15 patients recruited and if < 50% of patients meet the monitoring criteria, the measurement criteria of the primary data collection endpoint will be reassessed. The sub-study will meet its primary data efficacy endpoint if ≥ 20% of difference in average daily step is observed between the treatment arms.
Eligibility criteria	**Inclusion Criteria** 1. All participants successfully enrolled in the DISCUS study will be considered eligible for participation in the DISCUS sub-study. Refer to the DISCUS Protocol for a full list of inclusion and exclusion criteria. 2. Willing and able to provide written informed consent to the DISCUS sub-study 3. Willingness to wear sensors to track physical activity and provide symptom ratings via an ePRO device/mobile application. 4. Able to operate a tablet and wearable wristband 5. Patient is able to complete QoL assessments. 6. Ambulatory (use of walking aids, such as cane and rollator, is acceptable) 7. Able to demonstrate basic digital literacy **Exclusion Criteria** 1. Physical conditions that preclude daily walking 2. Inability to give informed consent. 3. Local skin diseases prohibiting wearing of the device. 4. Medical or psychiatric condition which in the investigator's opinion would affect the successful completion of the study. 5. Using a pacemaker, implantable cardiac defibrillator, neurostimulator, implantable hearing aids, cochlear implants, or other electronic medical equipment. However, removable hearing aids are permitted. 6. No Wifi/internet access at home.
Study Intervention	**Device:** comprehensive ambulatory monitoring platform A wearable wrist worn sensor combined with a mobile application hosted on an electronic patient-reported outcome (ePRO) device (HALO kit).

Trial governance and recruitment plan	The sub study will recruit across open DISCUS sites in the UK, Spain and France. The trial recruitment will take approximately 24 months but can continue up to LPLV on DISCUS trial. Patients already established on the DISCUS trial cannot retrospectively consent to participate in the wearable device sub study. Queen Mary University of London are the sponsor of the DISCUS trial. All digital data acquired from the wearable and the ePRO devices will be stored via remote web server. Analysis of the digital biometric data and its correlation with safety and efficacy data will occur alongside the analysis of the primary endpoint of the DISCUS study. The existing DISCUS Trial Steering Committee is established with representation from UK Investigators and will oversee the scientific integrity of the trial and the DISCUS wearable device sub study.
Data collection, storage and sharing	Data from the HALO device and mobile application will be automatically uploaded to a pseudo-anonymised web server. After informed consent is obtained, participants will be registered and provided with a trial ID to ensure all transmitted data is pseudo-anonymised. Electronic data will be stored behind a firewall in a permission-controlled area over and above the use of passwords. The manufacturer of the device (Ethera Health Limited) will not be able to access, or otherwise obtain any personal data. Any information accessed or otherwise obtained by Ethera shall be anonymised. Ethera owns all Intellectual Property Rights in the wearable device and its mobile application, but not the data. QMUL owns all rights in the Data. Access to the data generated by the mobile application will be restricted to authorised users within the DISCUS study team only. All data generated as part of the sub-study will be transferred to QMUL DISCUS study team for analysis on a 6 monthly basis and at the end of the study. No data will be kept by Ethera after the substudy has completed.

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