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. 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 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). 11. Patients affiliated to the social security system (French specificity).

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. 28. Person deprived of their liberty or under protective custody or guardianship (French specificity).
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