Non-Interventional Study Protocol
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A multi-centre non-interventional study to describe the early clinical experience of avelumab used as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma who are progression-free following platinum-based chemotherapy

Statistical Analysis Plan
(SAP)

Version: 2.0

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SAP Approval and Sign-off

I confirm that I have read the contents of this SAP and its attachments. I approve the SAP in its current form.

Client			
	Print name here	Signature	Date
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	Print name here	Signature	Date
Statistician			
	Print name here	Signature	Date
Author			
(if different from the Statistician)	Print name here	Signature	Date

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1 LIST OF ABBREVIATIONS

Abbreviation	Definition
AE(s)	Adverse event(s)
BSC	Best supportive care
CAG	Confidentiality Advisory Group
EAMS	Early Access to Medicines Scheme
EC	European Commission
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EHR	Electronic Health Record
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
IgG1	Immunoglobulin G1
IQR	Inter-quartile range
JB100	JAVELIN Bladder 100
NHS	National Health Service
NIS	Non-interventional study
PD-L1	Programmed death-ligand 1
QMS	Quality management system
rwTTNT	Real-world time to next treatment
rwOS	Real-world overall survival
rwPFS	Real-world progression-free survival
rwTTD	Real-world time to discontinuation
R&D	Research and Development
SDV	Source data verification
SACT	Systematic anti-cancer therapy
SAP	Statistical analysis plan
SOP	Standard operating procedure
TCC	Transitional cell carcinoma
UC	Urothelial carcinoma
UK	United Kingdom
USA	United States of America
1L	First-line
2L	Second-line

2 ABSTRACT

Title	A multi-centre non-interventional study (NIS) to describe the early clinical experience of avelumab used as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (UC) who are progression-free following platinum-based chemotherapy.
Rationale and Background	Bladder cancer is the 11th most common cancer in the United Kingdom (UK). Patients with advanced or metastatic UC are usually offered a platinum-based chemotherapy. Avelumab is a human monoclonal antibody which, as demonstrated in the JAVELIN Bladder 100 (JB100) trial, is associated with a median overall survival gain of 7.1 months when used as maintenance therapy in combination with best supportive care (BSC) compared with BSC only. The drug has been approved by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) as monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy. Access to the drug has initially been facilitated by the Early Access to Medicines Scheme (EAMS) programme in the UK since September 2020. There is now a need for UK-specific early clinical and outcome data in patients treated with avelumab for this indication in routine clinical care.
Research Question and Objectives	The primary objective of this study is to estimate real-world overall survival (rwOS) in a real-world cohort of patients treated with avelumab monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy. The secondary objectives are: 1. To describe the clinical and demographic characteristics of the study population 2. To estimate real-world progression-free survival (rwPFS) 3. To describe treatment characteristics of 1L anti-cancer therapies received prior to the initiation of avelumab as 1Lmaintenance therapy 4. To describe treatment patterns after initiation of avelumab as 1L maintenance therapy

	5. To describe the adverse events (AEs) explicitly attributed to avelumab in a real-world population 6. To describe real-world all-cause associated healthcare resource burden associated with avelumab therapy
Study Design	A multi-centre NIS with both a retrospective chart review and prospective follow-up of patients conducted in selected secondary/tertiary care centres of the UK National Health Service (NHS). The study will be entirely conducted using records obtained in routine clinical care and will not involve contact with patients. Confidential Advisory Group (CAG) and appropriate ethics permission will be obtained before commencing the study.
Population	Patients must meet all the following criteria to be eligible for inclusion in the study: 1. Patients with a diagnosis of locally advanced or metastatic UC, either de novo or relapsed 2. Patients received 1L platinum-based chemotherapy and had stable disease, partial response, or complete response to this treatment 3. Patients received avelumab as indicated as a monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy 4. Patients aged ≥18 years on the date that they commenced avelumab Patients meeting any of the following criteria will be excluded from the study: 1. Patients whose hospital records are not available for review 2. Patients who are receiving an investigational medicinal product as part of a clinical trial at the time of maintenance therapy with avelumab
Variables	Variables to be collected include: Demographic and clinical characteristics of the study population, at selected time points, including: • Age at diagnosis and at avelumab initiation

	• Diagnostic details on UC
	• Eastern Cooperative Oncology Group (ECOG) performance status
	• Cigarette smoking history
	
	Treatment characteristics prior to avelumab initiation, including:
	• Systemic anti-cancer therapy (SACT) regimen received
	• Number of platinum-based chemotherapy cycles received since initial diagnosis
	• Number of distinct platinum-based chemotherapies received
	• Time from completion of 1L SACT to avelumab initiation
	• Response to 1L therapy
	
	Treatment characteristics from avelumab initiation, including:
	• Duration of avelumab treatment
	• Time to second-line (2L) therapy
	• SACT regimen received as 2L therapy
	• Number of cycles received as 2L therapy
	• High dose systemic steroid treatment following initiation of avelumab
	
	AEs explicitly attributed to avelumab treatment:
	• AE diagnosis
	• Outcome of AE
	• Classification as either serious or non-serious AE
	  o Results in hospitalisation or prolongation of hospitalisation
	  o Is life threatening
	  o Resulted in death
	  o Persistent or significant incapacity
	  o Congenital anomaly/birth defect in any offspring
	  o Other important medical event that may require medical or surgical intervention to avoid any of the above criteria
	• AEs leading to administration adjustments or discontinuation of avelumab

	• AEs leading to systemic steroid treatment All-cause associated healthcare resource burden: • Accident and emergency visits • Hospitalisations • Duration of hospitalisation
Data Sources	A total of 8-12 NHS centres will be selected for this study and each of them will be required to identify a minimum of 6 patients identified in sequential order from the first eligible patient treated at the site according to prespecified criteria. Data on patient and treatment characteristics as well as events and outcomes will be extracted from patient medical records and hospital charts from participating NHS sites using electronic case report forms (eCRF).
Study Size	We aim to include approximately 100 patients into the study and follow them up for treatment patterns, events and endpoints in the study for up to 24 months per patient.
Data Analysis	Clinical and demographic characteristics, treatment characteristics, toxicity and AEs will be analysed descriptively, where continuous variables will be described using the mean (with standard deviation) and/or the median (with inter-quartile range, IQR) and categorical variables will be described using number and percentage. rwOS, rwPFS, time to next treatment (rwTTNT) and time to discontinuation (rwTTD) will be analysed using time to event analysis. Survival curves and median survival times will be estimated using Kaplan-Meier methods.
Milestones	Study commencement: August 2021 Study completion: December 2023 Final study report: June 2024

3 AMENDMENTS FROM PREVIOUS VERSION(S)

This is the final version (v2.0) of the document. The major changes from the previous versions are as follows:

Version number	Amendment
1.0	The eCRF question numbers were updated to reflect the updated CRF
2.0	N/A

4 RATIONALE AND BACKGROUND

Note: in this section, text taken directly from the non-interventional study (NIS) protocol is ***italicised***.

Urothelial carcinoma, also known as transitional cell carcinoma (TCC) arises from the transitional epithelium in the urinary system and is the most commonly occurring bladder cancer (1). Risk factors for UC include cigarette smoking, older age, being of male sex, being Caucasian, genetic susceptibility, having a family history, chronic bladder infections as well as arsenic and chemical exposure (2). Patients usually present with haematuria, difficulty urinating, pelvic pain, bone pain and unintentional weight loss (3).

There were 10,233 new incident cases of invasive bladder cancer (ICD-10 code C67) annually in the UK 2015-2017, with 5,485 deaths annually between 2016-2018. Bladder cancer is the 11th most common cancer in UK, and the 10th most common cause of cancer death in the UK. When diagnosed at its earliest stage, more than 9 in 10 (95%) people with bladder cancer will survive their disease for one year or more, compared with more than 1 in 3 (36%) people when the disease is diagnosed at the latest stage (4). Five-year age-standardised survival is 53% for all patients, ranging from 79% for stage I to 41% for stage III patient (5). Five-year survival data for stage IV patients in the UK are not available but data from the United States of America (USA) report that 5-year relative survival decreases to 37% if it has spread to regional lymph nodes, and to 6% if it has spread to a more distant site (6).

Treatment success depends on how early the patient is diagnosed and treated. In early stage UC, surgical resection is the course of action, while advanced or metastatic UC is treated with chemotherapy. In the UK, cisplatin-based chemotherapy is offered. If cisplatin-based chemotherapy is unsuitable, carboplatin in combination with gemcitabine is offered among Programmed death-ligand 1 (PD-L1) negative patients, and atezolizumab or carboplatin in combination with gemcitabine is offered for PD-L1 positive patients. 2L treatment depends on prior treatment and includes platinum-based chemotherapy, checkpoint inhibitors or BSC (7,8).

In June 2020, the FDA approved avelumab for maintenance treatment in patients with locally advanced or metastatic UC that have not progressed with 1L platinum-containing chemotherapy (9). In January 2021, the European Commission (EC) approved avelumab as a monotherapy for the 1L maintenance treatment of adult patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy (10). Avelumab is a human monoclonal Immunoglobulin G1 (IgG1) antibody that targets the immunomodulatory cell surface ligand protein, PD-L1. The JB100 trial was designed to be a randomized, multicentre and open label study conducted to understand the efficacy of maintenance avelumab. Maintenance therapy with avelumab in addition to BSC showed improved overall survival compared to BSC alone in patients with advanced UC whose cancer had not progressed following 1L

platinum-based chemotherapy (11,12). Overall survival at 1 year was 71% in the avelumab group and 58% in the control group, with a hazard ratio for death reported at 0.69 (95% confidence interval, CI, 0.56 – 0.86, p=0.001). Median overall survival was 21.4 months in the avelumab group vs. 14.3 months in the control group and median progression-free survival was 3.7 months vs. 2.0 months, respectively. Patients received avelumab following a treatment-free interval of four to ten weeks after receipt of four to six cycles of chemotherapy with gemcitabine plus cisplatin or carboplatin. AEs of any grade occurred in 98.0% of patients in the avelumab group and 77.7% in the control group (13).

This NIS aims to understand clinical outcomes of patients treated with avelumab as monotherapy for the 1L maintenance treatment of locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy, in a real-world setting in the UK.

5 STUDY OBJECTIVES

Note: in this section, text taken directly from the non-interventional study (NIS) protocol is ***italicised***.

The purpose of this NIS is to describe the early clinical real-world outcomes of patients treated with avelumab as monotherapy for the 1L maintenance treatment of locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy. As from September 2020, patients in the UK meeting the UC indication have been provided access to avelumab via EAMS. This study aims to investigate patients who received avelumab in secondary/tertiary care in the UK through either the EAMS or through NHS commissioning. The primary objective of this study is to compare overall real-world survival with overall survival reported by the JB100 clinical trial (13). Detailed objectives have been ratified by three NHS medical oncologists with an academic interest in UC to ensure feasibility in the real-world setting.

5.1 PRIMARY OBJECTIVE:

1. To describe real-world overall survival (rwOS) in a real-world cohort of UC patients who were treated with avelumab as maintenance therapy for locally advanced or metastatic cancer, who are progression-free following platinum-based chemotherapy

5.2 SECONDARY OBJECTIVES:

1. To describe the clinical and demographic characteristics of the study population at first diagnosis of UC, diagnosis of locally advanced or metastatic disease and at avelumab treatment initiation.

2. To describe real-world progression-free survival (rwPFS) in the study population

3. To describe treatment characteristics of 1L anti-cancer therapies received prior to the initiation of avelumab as 1L maintenance therapy in the study population

4. To describe treatment patterns after initiation of avelumab as 1L maintenance therapy in the study population

5. To describe the AEs explicitly attributed to avelumab in the study population

6. To describe real-world all-cause healthcare resource burden associated with avelumab therapy in the study population

6 RESEARCH METHODS

Note: in this section, text taken directly from the non-interventional study (NIS) protocol is ***italicised***.

6.1 STUDY DESIGN

This is a multi-centre, UK-based, NIS, with both a retrospective chart review and prospective follow-up of patients. Data collected as part of routine care entered into electronic patient records and paper-based charts will be extracted from records of adult patients with locally advanced or metastatic UC whose disease has not progressed following 1L platinum-based chemotherapy, and are treated with avelumab as a 1L maintenance therapy. Detailed information on the setting, the inclusion and exclusion criteria of patients, the study period and follow-up are described below.

This is a NIS because there will be no patient contact and only clinical data collected in routine clinical care will be collected and analysed as part of this study. No study visits, examinations, laboratory tests or procedures will be mandated. No changes to routine patient management are expected to occur as a result of a patient's inclusion in the study.

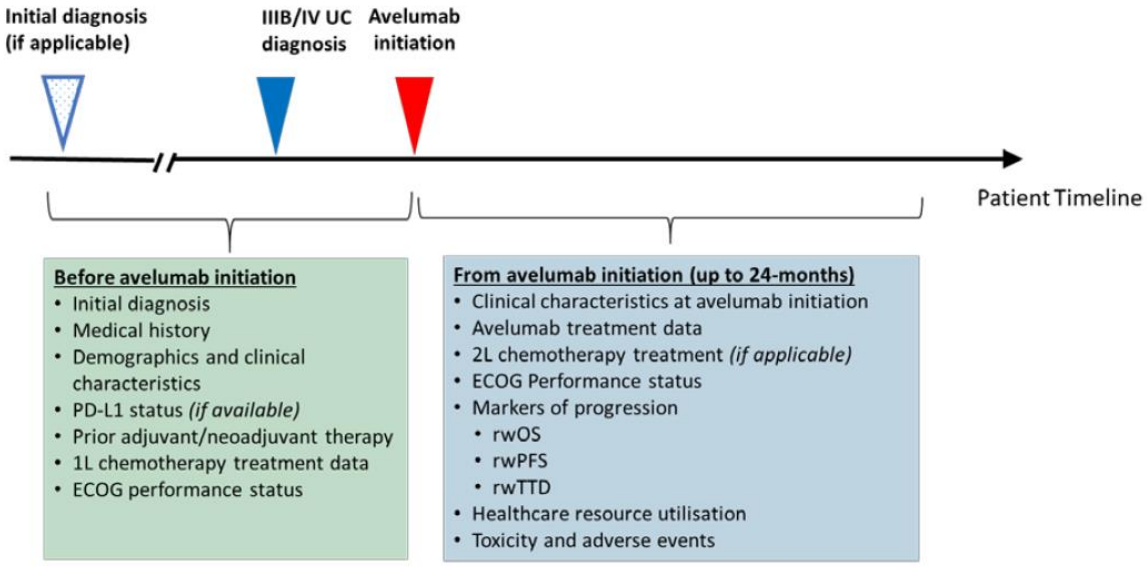

Figure 1. Schematic of the study design

6.2 STUDY SETTING

This study is to be conducted in secondary/tertiary care centres of the UK NHS. In the UK, avelumab is indicated as monotherapy for the 1L maintenance treatment of adult

patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy.

The study aims to recruit approximately 100 patients treated with avelumab with follow-up for up to 24 months after avelumab initiation. Among all centres who have registered patients as treated with avelumab, we will select 8-12 centres for participation ensuring a good geographical spread and instruct centres to extract data from 6-12 patients per centre. Potential participating hospitals will be subject to a site feasibility assessment to ensure eligible sites have the required number of patients, access to data and capacity to take part in this study. Data collection will commence after the appropriate ethics and research and development (R&D) approvals have been obtained and the site is fully initiated.

Centres will be provided with clear instructions on how to identify patients and extract their data. They will be instructed to extract patients in chronological order of avelumab initiation (earliest first) to avoid selection bias and to ensure consistency in the recruitment methodology across the participating research sites. Centres will be requested to recruit 6-12 patients each so that the geographical spread of patients across centres is maintained.

Sample Size

It is planned to include 100 patients in the study, with up to 24 months follow-up period per patient. Sample size calculations were not carried out as the planned analyses do not include formal statistical comparisons. However, data from the previous JB100 clinical trial of avelumab (13) suggests a median overall survival of 21.4 months for avelumab patients, therefore the planned follow-up period of 24 months is expected to include >50 deaths in the analysis of overall survival for the primary research objective.

Inclusion Criteria

Each inclusion criterion is indicated explicitly on the eCRF as a yes/no indicator variable. Patients must meet all the following inclusion criteria to be eligible for inclusion in the study:

- Patients with a diagnosis of locally advanced or metastatic UC, either de novo or relapsed, prior to or on the date of avelumab treatment initiation
- Patients received 1L platinum-based chemotherapy and had stable disease, partial response, or complete response to this treatment recorded prior to the date of avelumab treatment initiation
- Patients received avelumab as indicated as a monotherapy for the first-line maintenance treatment of adult patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy
- Patients aged ≥18 years on the date that they commenced avelumab
- Patients whose hospital records are available for review

Exclusion Criteria

Each exclusion criterion is indicated explicitly on the eCRF as a yes/no indicator variable. Patients meeting any of the following exclusion criteria will not be eligible for inclusion in the study:

- Patients who have a record of receiving an investigational medicinal product as part of a clinical trial at any date during the period of maintenance therapy with avelumab (inclusive of avelumab start and stop dates)

Study Time Period

Data collection is planned to begin in November 2021, with retrospective identification of patients first treated with avelumab from September 2020 onwards. Given that avelumab was only recently introduced to the UK, it is anticipated that there will be fewer than the required sample size of 100 patients treated with avelumab in the NHS sites participating in the study prior to the data collection period. The patient identification window is therefore planned to be extended beyond November 2021 to allow prospective patient identification up until the time that the 100th participant is entered into the study. *After identification of all patients, periodic data collection of treatment and outcome data for all identified patients will run until 24 months has elapsed since the avelumab initiation date for each patient, with the data collection component of the study being completed shortly after 24 months since the latest initiation date in the study.*

Index Date

The index date will be defined as the initiation date of avelumab, reported on the eCRF as the 'first ever date of avelumab treatment' in Q25.

Follow-up and Censoring

The follow-up period for participants will be from the index date to the earliest date of:

- Death (as recorded in eCRF Q35)
- Loss to follow up (as recorded in eCRF Q36)
- 24 months after the index date

For each participant, the censoring date used for the time-to-event analyses will be the earliest date of loss to follow up or 24 months after the index date, as recorded on the eCRF. Note that death is treated as an event in the time-to-event analyses, therefore not used as a censor point. For the time-to-progression variable only, the start date of 2L SACT will be used as an additional censoring point. Specific definitions of events and

censoring for each time-to-event variable individually are provided in the relevant section of the table in **Section 8**.

For a subset of the variables, data will be collected from medical records prior to the index date and recorded retrospectively in the eCRF. This look-back period will cover the period for each patient from the date (inclusive) of their first UC diagnosis (relating to diagnosis at any stage; as recorded on the eCRF Q5) to the day before the index date (inclusive). This look-back period applies to some clinical and demographic characteristics to be described for Objective 2, as well as some pre-avelumab treatment patterns to be analysed for Objective 4 (see **Section 8** for full details of each variable and the time period to be used for data collection).

Case Definition

The study population is UC patients with a diagnosis of locally advanced or metastatic cancer either diagnosed during the patient identification window or identified retrospectively through electronic medical records and charts.

7 DATA SOURCES

Note: in this section, text taken directly from the non-interventional study (NIS) protocol is ***italicised***.

Data will be extracted from patient medical records and hospital charts from participating NHS sites using eCRF. A study information pack will be shared with R&D departments in the hospital. Only after each site has been initiated will data be collected by the study teams directly from patient medical records (paper and/or electronic) and hospital charts. Centres will be provided with clear instructions on how to identify patients and extract their data. Centres will be requested to recruit 6-12 patients each so that the geographical spread of patients across centres is maintained. They will be instructed to extract these patients in chronological order of avelumab initiation (earliest first) to avoid selection bias and to ensure consistency in the recruitment methodology across the participating research sites.

eCRFs will be developed for use in this study using an electronic data capture (EDC) system called INES with the help of three therapy areas experts. INES is a fit-for-purpose EDC system that has been used in over 2,000 studies and survey-based projects. The web-based system can be accessed by the NHS using a multitude of internet browsers. In addition to the eCRF, a data management plan will be constructed.

8 VARIABLES

Note that in this table, study objectives are linked to the relevant table and figure shells presented in the associated table shells document.

Variable	Role	Time of measurement	Operational definition
Primary objective			
Objective 1: to describe rwOS (table shell Table 1 and Figure 1)			
Real-world overall survival (rwOS)	Effectiveness endpoint	From index date to date of death by any cause, or date of censoring (whichever is first)	Time (in months) from the start date of avelumab treatment (eCRF Q25) to the earliest of date of death (eCRF Q35) or date of censoring, inclusive of start and end date. Full details of follow-up and censoring are described in **Section 6.2**.
Secondary objectives			
Objective 2: to describe clinical and demographic characteristics (table shell Table 2.1.1 and 2.1.2)			
Age at date of first diagnosis of UC	Demographic characteristic	At date of first diagnosis of UC	Age (in years) at date of first diagnosis of UC (eCRF Q5). Calculated as the number of years between date of birth (eCRF Q2) and date of first diagnosis (eCRF Q5), rounded down to the nearest whole year of age.
Stage at first diagnosis	Clinical characteristic	At date of first diagnosis of UC	As recorded in eCRF Q6 as: • Stage 0a • Stage 0is • Stage I • Stage II • Stage IIIA • Stage IIIB • Stage IVA • Stage IVB
Primary tumour site	Clinical characteristic	At date of first diagnosis of UC	As recorded in eCRF Q7 and summarised as:

			• Bladder • Renal pelvis • Ureter • Other • Not recorded
Sex	Demographic characteristic	At date of first diagnosis of UC	As recorded in eCRF Q1: • Male • Female • Not stated
Age at date of locally advanced or metastatic cancer diagnosis	Demographic characteristic	At date of locally advanced or metastatic cancer diagnosis	Age (in years) at date of locally advanced or metastatic cancer diagnosis (eCRF Q11). Calculated as the number of years between date of birth (eCRF Q2) and date of locally advanced or metastatic diagnosis (eCRF Q10), rounded down to the nearest whole year of age.
Stage at locally advanced or metastatic diagnosis	Clinical characteristic	At date of locally advanced or metastatic cancer diagnosis	As recorded in eCRF Q13: • Stage IIIA • Stage IIIB • Stage IVA • Stage IVB
Histology at locally advanced or metastatic diagnosis	Clinical characteristic	At date of locally advanced or metastatic cancer diagnosis (or if not available, at date of first diagnosis)	As recorded in eCRF Q14 (or eCRF Q8 for histology at date of first diagnosis): • Pure urothelial cancer (transitional cell carcinoma) • Mixed urothelial with component of another pathology • Other • Not recorded
PD-L1 tumour assessment immune cell (IC) test result	Clinical characteristic	At date of locally advanced or metastatic cancer diagnosis (or if	Test result as recorded in eCRF Q23 (values range from 0-100; 'not recorded' will be treated as missing)

		not available, at closest timepoint available)	
PD-L1 combined positive cells (CPC) test result	Clinical characteristic	At date of locally advanced or metastatic cancer diagnosis (or if not available, at closest timepoint available)	Test result as recorded in eCRF Q24 (values range from 0-100; 'not recorded' will be treated as missing)
ECOG performance status at locally advanced or metastatic diagnosis	Clinical characteristic	At date of locally advanced or metastatic cancer diagnosis (or if not available, at date of first diagnosis)	As recorded in eCRF Q19: • 0 = Fully active, able to carry on all pre-disease performance without restriction • 1 = Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work • 2 = Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours • 3 = Capable of only limited self-care, confined to bed or chair more than 50% of waking hours • 4 = Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair • Not recorded
De novo or newly relapsed	Clinical characteristic	At date of locally advanced or	As recorded in eCRF Q15: • De novo disease

		metastatic cancer diagnosis	• Newly relapsed disease
Site of metastases at locally advanced or metastatic diagnosis	Clinical characteristic	At date of locally advanced or metastatic cancer diagnosis	As recorded in eCRF Q16: • Lymph nodes • Bone • Lung • Liver • Peritoneum • Other • Not recorded Note that free text responses can be recorded under the 'other' option on the eCRF; these patients will be counted within the patient totals for 'other'. More than one site of metastases can be selected per patient, therefore percentage of total patients reporting each site will be shown, but percentages across all categories combined will not necessarily sum to 100%.
Time from first diagnosis to locally advanced or metastatic diagnosis	Clinical characteristic	At date of locally advanced or metastatic cancer diagnosis	Time (in months) between date of first diagnosis (eCRF Q5) and date of locally advanced or metastatic diagnosis (eCRF Q10), inclusive of both dates.
Prior radical treatment of primary urothelial carcinoma (including radiotherapy and surgical resection)	Clinical characteristic	From date of first diagnosis to date of locally advanced or metastatic cancer diagnosis	As recorded in eCRF Q17: • Yes • No • Not recorded
Prior adjuvant or neoadjuvant systemic therapy	Clinical characteristic	From date of first diagnosis to date of locally advanced or	As recorded in eCRF Q18: • Yes • No • Not recorded

		metastatic cancer diagnosis	
Cigarette smoking history	Demographic characteristic	From index date to date of locally advanced or metastatic cancer diagnosis	As recorded in eCRF Q3: • Current smoker • Former smoker (if stopped prior to index) • Never smoked • Not recorded
Age at start date of avelumab treatment	Demographic characteristic	At start date of avelumab treatment	Age (in years) at avelumab treatment initiation (eCRF Q26). Calculated as the number of years between date of birth (eCRF Q2) and start date of avelumab (eCRF Q25), rounded down to the nearest whole year of age.
Objective 3: to describe rwPFS (table shell Table 2.2 and Figure 2.1)			
Real-world progression-free survival (rwPFS)	Effectiveness endpoint	From index date to date of progression, or date of censoring (whichever is first)	Time (in months) from the start date of avelumab treatment (eCRF Q25) to the first date of either: any evidence of progression (eCRF Q30); or date of death (eCRF Q35). Both evidence of disease progression and death will be treated as types of progression event. Patients will be censored without a progression or death event at the earliest date of: loss to follow-up; 24 months after the index date; or date of starting 2L SACT (eCRF Q31). Time to event or censoring will be calculated inclusive of start and end dates.
Objective 4: to describe treatment characteristics prior to avelumab			

(table shell Table 2.3)			
Type of SACT regimen received as 1L therapy before avelumab start date	Treatment patterns	From date of locally advanced or metastatic diagnosis to index date	Type of 1L SACT regimen received after date of locally advanced or metastatic diagnosis date until index date, inclusive, as recorded in eCRF Q28: • Cisplatin/gemcitabine • MVAC (Methotrexate, vinblastine, doxorubicin and cisplatin) in combination with granulocyte-colony stimulating factor (G-CSF) • Carboplatin/gemcitabine • Other cisplatin regimen • Other carboplatin regimen
Number of SACT cycles received as 1L therapy before avelumab start date	Treatment patterns	From date of locally advanced or metastatic diagnosis to index date	Number of SACT cycles received as 1L therapy before avelumab start date, as recorded in eCRF Q28 (1-8 cycles)
Number of patients switching between different platinum-based chemotherapies	Treatment patterns	From date of locally advanced or metastatic diagnosis to index date	If there is any evidence of patients changing regimens during 1L therapy prior to avelumab, as reported in eCRF Q29 (yes/no/not recorded)
Time duration between completion date of 1L SACT and start date of avelumab	Treatment patterns	From date of the last record of 1L SACT to avelumab initiation date	Calculated as the number of days from the end date of the last 1L SACT cycle (eCRF Q28) to the start date of avelumab (eCRF Q25), inclusive of the start and end dates of this period.
Response to 1L SACT before avelumab start date	Treatment patterns	From date of 1L SACT initiation to date of avelumab initiation	Response to 1L SACT as reported in eCRF Q29: • Complete response • Partial response

			• Stable disease
Response to 1L SACT based on CT scan after 1L SACT and before avelumab	Treatment patterns	From date of 1L SACT initiation to date of avelumab initiation	If response to 1L SACT was judged based on CT scan evidence after the last cycle of 1L SACT, as reported in eCRF Q29 (yes/no)
Objective 5: to describe treatment patterns after avelumab initiation (table shell Table 2.4.1 and 2.4.2 and Figure 2.2)			
Duration of avelumab treatment	Treatment patterns	From index date to end date of avelumab, or date of censoring (whichever is first)	Calculated as the number of days from the start date of avelumab treatment (eCRF Q25) to the latest date avelumab treatment was interrupted (eCRF Q27), inclusive of start and end dates. If the patient is censored before a stop date is recorded, the censor date will be used as a stop date. The eCRF allows for avelumab treatment pauses to be recorded; for the purposes of this variable, the pauses will be disregarded and the full duration will end on the most recent stop date recorded for eCRF Q27.
Time interval between start date of avelumab and start date of 2L therapy	Treatment patterns	From index date to start date of 2L therapy	Calculated as the number of days from the start date of avelumab treatment (eCRF Q25) to the start date of the first regimen of 2L therapy (eCRF Q31), inclusive of the start and end dates of this period. This will only be calculated for patients who report receiving 2L therapy after avelumab start date (in eCRF Q31).

Number of patients who receive 2L therapy after avelumab start date	Treatment patterns	From index date to date of censoring	If any 2L therapy received after the start date of avelumab is reported in eCRF Q31 (any regimens reported vs. none reported)
Type of SACT regimen received as 2L therapy after avelumab treatment	Treatment patterns	From index date to date of censoring	Type of 2L SACT regimen received after avelumab start date, as recorded in eCRF Q31: • Cisplatin/gemcitabine • MVAC (Methotrexate, vinblastine, doxorubicin and cisplatin) in combination with granulocyte-colony stimulating factor (G-CSF) • Carboplatin/gemcitabine • Gemcitabine/paclitaxel • Paclitaxel • Docetaxel • Vinflunine • Enfortumab vedotin • Sacituzumab govitecan • Clinical trial • Other • None reported Note that patients who do not report starting any 2L SACT therapy after avelumab will be counted as 'none reported'. More than one type of 2L SACT regimen can be reported per patient, therefore percentage of total patients reporting each type will be shown, but percentages across all categories combined will not necessarily sum to 100%.

Real-world time to treatment discontinuation (rwTTD) of avelumab	Treatment patterns	From index date to date of censoring	Time (in months) from the start date of avelumab treatment (eCRF Q25) to the earliest date of: date of avelumab discontinuation (eCRF Q27); date of start of 2L SACT after avelumab (eCRF Q31); or date of death (eCRF Q35). Each of these will be treated as events of evidence of treatment discontinuation. Patients will be censored without any event at the earliest date of loss to follow-up (eCRF Q36), or 24 months after index date. Time to event or censoring will be calculated inclusive of start and end dates.
Systemic steroid use	Treatment patterns	From index date to date of censoring	If systemic steroid use is reported in eCRF Q32 (yes/no)
Objective 6: to describe AEs attributed to avelumab (table shell Table 2.5)			
Patients with adverse events	Patient outcome	From index date to date of censoring	If any AEs are recorded for the patient in eCRF Q39 (yes/no)
Adverse events	Patient outcome	From index date to date of censoring	The number of separate AEs recorded per patient (with explicit linkage in the medical notes to avelumab) will be calculated using data from eCRF Q39 (each reported event on the eCRF counts as a separate AE). This will be used to calculate the rate of events per patient per year of follow-up time
Objective 7: to describe healthcare resource burden associated with avelumab (table shell Table 2.6)			

Accident and Emergency visits	Healthcare resource burden indicator variable	From index date to date of censoring	The number of accident and emergency visits recorded per patient (each reported visit on the eCRF Q37 counts as a separate visit) will be used to calculate the rate of events per patient per year of follow-up time
Hospitalisations	Healthcare resource burden indicator variable	From index date to date of censoring	The number of hospital admissions recorded per patient (each reported visit on the eCRF Q38 counts as a separate visit) will be used to calculate the rate of events per patient per year of follow-up time
Duration of hospitalisation	Healthcare resource burden indicator variable	From index date to date of censoring	The total number of days duration of hospitalisation recorded per patient will be calculated as the sum of the duration of all separate hospitalisations reported per patient in eCRF Q38 (where the duration of each event is the number of days between the reported start and end date, inclusive of the start and end dates). This will then be used to calculate the number of days of hospitalisation per patient per year of follow-up time

9 HANDLING OF MISSING VALUES

No imputation of missing values will be carried out and the analyses will use a complete-case approach. The eCRF setup allows missing information for a number of variables to be included as 'not recorded' or 'not stated' options, and numbers of patients in these categories will be reported in descriptive statistics where appropriate. Descriptive statistics reported for continuous variables will include the numbers of patients with non-missing data per variable. For time-to-event analyses, the numbers of uncensored (at-risk) individuals will be reported at each timepoint.

For eCRF Q2 ('Patient's month and year of birth'), date of the month will not be recorded, and for eCRF Q10 ('Date of locally advanced or metastatic UC diagnosis'), date of the month can be entered as unknown. For both of these variables, the 15th date of the month will be used to complete the full date as needed.

For eCRF Q4 ('Date of initial diagnosis of urothelial carcinoma'), partial dates are allowed to be recorded where either date only is missing, or where date and month are both missing. Where only month and year are recorded, the date will be analysed as the 15th date of that month. Where only year is recorded, the date will be analysed as the 30th June of that year. Since this data is only used to calculate (i) age (in years) at first diagnosis, and (ii) time between initial diagnosis and locally advanced/metastatic diagnosis, this level of precision is expected to be sufficient.

10 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

10.1 ANALYSIS SETS

All patients who meet all the inclusion criteria and none of the exclusion criteria will be included in the Full Analysis Set (FAS). All research objectives will be addressed via analysis of the FAS.

10.2 PRIMARY OBJECTIVE

Overall survival of all participants in the FAS will be tabulated at timepoints 6, 12, 18 and 24 months since the date of avelumab treatment initiation. Kaplan-Meier methods will be used to estimate rwOS, and survival curves will also be shown graphically for the 24-month duration of the follow-up time. The median and first and third quartiles of rwOS will be presented as the number of months, along with the 2-sided 95% confidence intervals calculated based on the Brookmeyer-Crowley method. The number of at-risk patients (ie, surviving and uncensored) will be shown at each timepoint under the survival curve. The estimated survival probability will also be presented at each timepoint, with confidence intervals generated using the log(-log) method with back-transformation to present results on an untransformed scale. The presentation of these results is illustrated in the table shells document (Table 1 and Figure 1).

10.3 SECONDARY OBJECTIVES

The secondary research objectives each involve descriptive analysis of the variables described in **Section 8**, which includes clinical and demographic variables (objective 2), rwPFS (objective 3), treatment characteristics (objective 4), avelumab treatment patterns (objective 5), AEs attributed to avelumab (objective 6), and healthcare resource burden associated with avelumab (objective 7).

Analysis of time-to-event variables

Both secondary objective time-to-event endpoints will be analysed and reported following the same methods described above for the primary endpoint (rwOS) in **Section 10.2**. This includes the analysis of time to progression (Objective 3; table shells Table 2.2 and Figure 2.1) and time to treatment discontinuation (Objective 5; table shells Table 2.4.2 and Figure 2.2).

Analysis of continuous variables

All continuous variables will be described using the following statistics: number of observations, mean, standard deviation, median, minimum, and maximum values, first and third quartile (Q1 and Q3). The mean, median, Q1 and Q3 will be displayed to one decimal place. The standard deviation will be displayed to two decimal places.

The number of AEs, number of hospitalisations, duration of hospitalisation, and number of Accident & Emergency visits will each be used to calculate a rate per patient per year of follow-up time. This will be calculated as the total number of incident events (or total number of days hospitalisation) recorded per patient during the follow-up time divided by the total follow-up time (time at risk) per patient in years. All rate variables will be presented in the same way as for the other continuous variables.

Analysis of categorical variables

Categorical variables will be described using frequency counts and percentages. Calculation of percentages will include a category for missing values where applicable for a given variable, therefore counts of missing observations will be included in the denominator and presented as a separate category. All percentages will be reported to one decimal place.

10.4 QUALITY CONTROL

All aspects of study design and management, from protocol to ongoing site management, will be conducted within the framework of the IQVIA Quality Management System (QMS) and in accordance to IQVIA and/or Pfizer's Standard Operating Procedures.

10.5 STUDY LIMITATIONS

Selection bias

Selection bias could be introduced to the study via patient selection methods, since the study population is small and only includes participants from EAMS and EAMS extension NHS sites, which could differ demographically from NHS sites more generally. These patient selection methods are necessary to find sufficient numbers of patients using avelumab therapy. Given that the date for the EMA license for avelumab is 30th June 2020, low numbers of patients are expected to be using it, therefore the sample size for this study is limited to the first 100 eligible patients.

Information bias

Most participants will be assessed retrospectively, although a minority will be identified after the study has started (ie, assessed prospectively). The data for the patients who are prospectively assessed is expected to be of a higher quality in comparison to the data for patients who are retrospectively assessed, although this will depend on the accuracy of the medical records.

The proposed data source to be used is eCRF, and so not all variables are expected to be recorded consistently in the available electronic medical records and charts, especially for patients who are assessed retrospectively. However, the primary endpoint (rwOS) is expected to be well-recorded in hospital system. This potential limitation will be

particularly important for variables which involve, for example, computing time windows or complex definitions of staging, at the point of eCRF data collection. This risk will be minimised by providing hospital staff with appropriate information and training in the information packs provided with the study materials. Site monitoring, and where required, source data verification (SDV) will also be carried out to aim to reduce and minimise the risk of missing data or data errors.

Further limitations

All analyses are carried out on the FAS which includes all patients irrespective of the duration of avelumab treatment. As such, duration of avelumab treatment could confound the interpretation of some results, especially the efficacy endpoints (rwOS and rwPFS) and AEs, by inclusion of patients who may have started avelumab therapy but discontinued treatment after a short period. To account for this, the results will include descriptive statistics of treatment duration in the study population.

Research Objective 6 includes the descriptive analysis of AEs which are explicitly attributed to avelumab treatment, based on AEs being directly linked to avelumab in medical notes. Given that the data for analysis will be extracted from the standard medical records via eCRF and largely based on retrospective assessment of participants, it is unlikely that explicit linkage between AEs and avelumab will be consistently recorded. This means that descriptive statistics of AEs are likely to underestimate the numbers of AEs that are attributed to avelumab in a real-world setting.

The follow-up period for this study has been defined as 24 months from the date of avelumab treatment initiation, based on previous clinical trial data that median overall survival for patients receiving avelumab as 1L maintenance therapy in locally advanced or metastatic UC is 21.4 months (13). However, it is possible that this focus on a relatively short follow-up period will overlook longer-term outcomes (including, but not limited to, efficacy endpoints and safety events).

11 LIST OF TABLES AND TABLE SHELLS

List of tables and table shells are available in a separate document.

12 REFERENCES

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