NON-INTERVENTIONAL (NI) STUDY PROTOCOL

CCI

Study information

Title	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
Protocol number	B9991047
Protocol version identifier	Version 1.0
Date	21st July 2021
Active substance	LO1XC31
Medicinal product	Avelumab
Research question and objectives	To understand the early clinical experience of using avelumab as monotherapy for first line (1L) maintenance treatment of adult patients with locally advanced or metastatic Urothelial Carcinoma (UC) including describing the real-world overall survival (rwOS) in patients who are progression-free following platinum-based chemotherapy.
Author(s)	PPD

1. TABLE OF CONTENTS

1. TABLE OF CONTENTS 2
2. LIST OF ABBREVIATIONS 5
3. RESPONSIBLE PARTIES 8
4. ABSTRACT 8
5. AMENDMENTS AND UPDATES 13
6. MILESTONES 15

7. RATIONALE AND BACKGROUND 16
8. RESEARCH QUESTION AND OBJECTIVES 17
9. RESEARCH METHODS 18
9.1. Study design 18
9.1.1. Setting 19
9.1.2. Inclusion criteria 19
9.1.3. Exclusion criteria 20
9.1.4. Study period 20
9.1.5. Study follow-up time 20
9.2. Variables 21
9.2.1. Demographic and clinical characteristics 23
9.2.2. Treatment-related variables 29
9.2.3. Outcomes 31
9.3. Data sources 35
9.4. Study size 35
9.5. Data management 36
9.5.1. Case report forms (CRFs)/Electronic data record 36
9.5.2. Record retention 36
9.6. Data analysis 37
9.6.1. Descriptive analysis 37
9.6.2. Overall and progression-free survival 37
9.6.3. Treatment patterns 37
9.7. Quality control 38
9.8. Limitations of the research methods 38
9.8.1. Selection bias and study representativeness 38
9.8.2. Missing or erroneous data 38
10. PROTECTION OF HUMAN SUBJECTS 39
10.1. Patient information 39
10.2. Patient consent 39
10.3. Institutional review board (IRB)/Independent ethics committee (IEC) 40
10.4. Ethical conduct of the study 40
11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 40
12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 41
13. REFERENCES 43
14. LIST OF TABLES 44
ANNEX 1. LIST OF STAND ALONE DOCUMENTS 44
ANNEX 2. ADDITIONAL INFORMATION 45

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE(s)	Adverse event(s)
AEM	Adverse event monitoring
BSC	Best supportive care
CAG	Confidentiality Advisory Group
CSA	Clinical study agreement
CSR	Clinical study report
CPS	Combined positive score
CRF	Case report form
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
HRA	Health Research Authority
IEC	Independent ethics committee
IgG1	Immunoglobulin G1

IRB	Institutional review board

IRAS	Integrated research application system
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
REC	Research ethics committee
R&D	Research and Development
SDV	Source data verification
SACT	Systemic 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
YRR	Your reporting responsibilities
1L	First-line
2L	Second-line

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
PPD			

Sponsor Protocol Authors

PPD

4. 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 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) for 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 1L maintenance 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: o Age at diagnosis and at avelumab initiation o Diagnostic details on UC o Eastern Cooperative Oncology Group (ECOG) performance status o Cigarette smoking history Treatment characteristics prior to avelumab initiation, including: o 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 ○ Time from initiation of avelumab to treatment discontinuation ○ High dose systemic steroid treatment following initiation of avelumab Adverse events explicitly attributed to avelumab treatment: ○ AE diagnosis ○ Outcome of AE ○ Classification as either serious or non-serious AE ○ Results in hospitalisation or prolongation of hospitalisation ○ Is life threatening ○ Resulted in death ○ Persistent or significant incapacity ○ Congenital anomaly/birth defect in any offspring ○ 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 2024 Final study report: January 2025

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1	30/06/2023	All sections	Changes of mentions of Pfizer to Merck Serono, change in authroship, pharmacovigilance reporting	Change of sponsor to Merck Serono because of the Merck -Pfizer Alliance termination on Avelumab
2	30/06/2023	Section 3 – Responsible authors	Removal of Pfizer author and replacing the previous Merck Serono author with the current study lead PPD	Change of sponsor to Merck Serono because of the Merck Serono-Pfizer Alliance termination on Avelumab
3	30/06/2023	Section 4 & 6 - Milestone	Update to the data collection end date from November 2023 to June 2024 Update of report date from June 2024 until January 2025	We expect the last patient enrolled to complete 24 months follow up by end of June 2024, this will push the final study report till January 2025
4	30/06/2023	Section 10.4 – Ethical conduct	Replacing mentions of 'controlled document pertaining to Pfizer' with Merck Serono controlled documents	We will be using Merck Serono controlled documents
5	30/06/2023	Section 11	Replacing the Pfizer specific document name 'NIS Adverse Event Monitoring (AEM) Report Form'	We will be using Merck Serono's Adverse Event Report From.

			with 'NIS Adverse Event (AE) Report Form Replacing '*Your Reporting Responsibilities Training'* by *'Merck PV Responsibilities Training'* or similar Merck Serono local training	Training reference updated to a Merck Serono one

6. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	August 2021
Ethics approval	August 2021
Start of data collection	November 2021
End of data collection	June 2024
Interim report 1	November 2022
Study progress report 1	On the 1-year anniversary of receiving ethical approval in the UK
Final study report	January 2025

7. RATIONALE AND BACKGROUND

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 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.

8. RESEARCH QUESTION AND OBJECTIVES

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, are as follows:

Among all adult patients with locally advanced or metastatic UC who are progression-free following platinum-based chemotherapy and are treated with avelumab as a 1L maintenance therapy:

Primary Objective

1. To estimate rwOS in a real-world cohort of patients treated with maintenance avelumab for locally advanced or metastatic UC

Secondary objectives

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

2. To estimate real-world rwPFS from initiation of avelumab

3. To describe treatment characteristics of the anti-cancer therapies received for locally advanced or metastatic UC **prior** to the initiation of avelumab as a 1L maintenance therapy

4. To describe treatment patterns **after** initiation of avelumab as a 1L maintenance therapy

5. To describe the 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

9. RESEARCH METHODS

9.1. 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.

The primary outcome of interest is rwOS and secondary outcomes include rwPFS and rwTTD. Other variables of interest include demographic, clinical and treatment characteristics. Outcome and variable definitions are described in detail in section 9.

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.

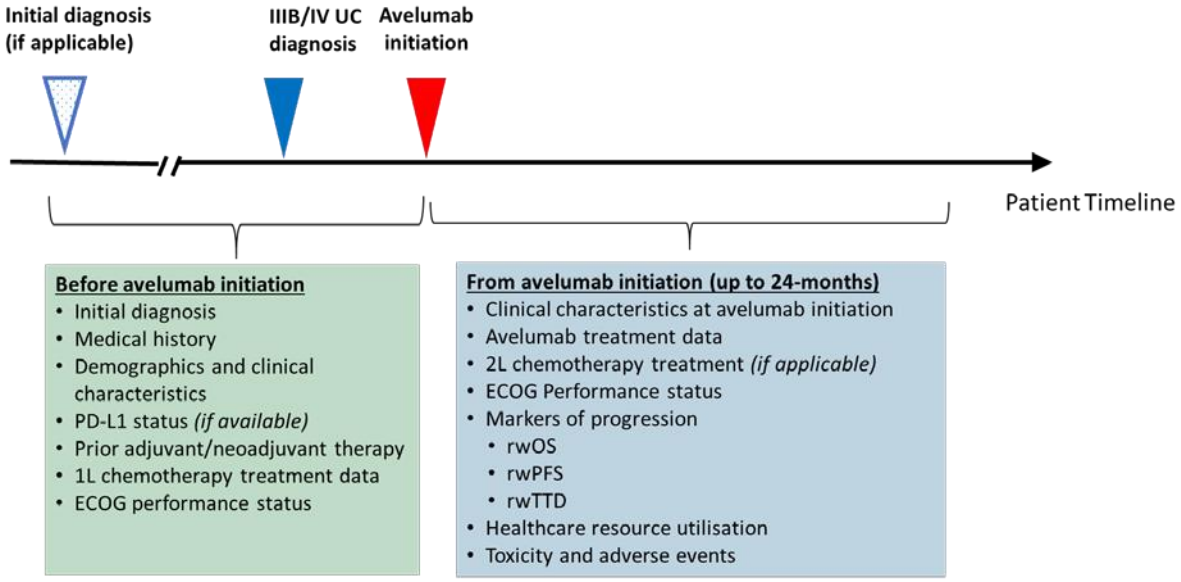

Figure 1. Schematic of the study design

9.1.1. 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.

9.1.2. Inclusion criteria

Patients must meet all the following inclusion 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

9.1.3. Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patients whose hospital records are not available for review

2. Patients who are part of a clinical trial testing an investigational medicinal product at the time of maintenance therapy with avelumab

9.1.4. Study period

The data collection period will start November 2021 with retrospective identification of patients first treated with avelumab since September 2020. It is anticipated that by July 2021 fewer than 100 patients will have been treated with avelumab in the UK across NHS sites participating in this study. Therefore, the patient identification window and subsequent follow up window would need to be extended by prospective identification of patients up to the time point the 100th patient is entered. 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.

9.1.5. Study follow-up time

Follow-up time will be defined as the time from avelumab initiation date (the 'index date') until the end of follow-up (defined as the earliest of; death, being lost to follow up, 24 months post avelumab-initiation, end of study period or censoring as defined per each objective, see below Table 1).

Reasons for loss to follow-up would include emigration and transition into private healthcare settings. For patients who are identified as lost to follow-up, records will be censored at the last available record or end of study, whichever is earlier.

Follow-up time for the primary and secondary outcomes is defined below.

Table 1. Follow-up time for outcomes

Outcome	**Follow-up start date**	**Follow-up end date until event defined as below, or censoring at the earliest of the following outcomes:**
rwOS	Date of avelumab initiation	Endpoint of interest: survival Censoring of follow-up at the earliest of: • Death • Lost to follow-up • 24 months after avelumab initiation
rwPFS	Date of avelumab initiation	Endpoint of interest: the earliest of progression or death Censoring of follow-up at the earliest of: • Progression* • Death • Lost to follow-up • 24 months after avelumab initiation
rwTTNT	Date of last dose of 1L SACT treatment	Endpoint of interest: initiation of avelumab Given that only patients who initiated avelumab in this study are included, no other censoring endpoints need to be defined.
rwTTD	Date of avelumab initiation	Endpoint of interest: earliest of discontinuation of avelumab or death Censoring of follow-up at the earliest of: • Discontinuation of avelumab • Death • Lost to follow-up • 24 months after avelumab initiation
*Progression is defined as any event identified either through radiological scans or other assessment judged by a clinician to be progression		

9.2. Variables

Variables and their operational definitions are defined in the tables below. Further definitions of variables will be included in the statistical analysis plan (SAP). The operational definitions,

e.g. the definition of progression, might be updated in the SAP to reflect the availability of routinely collected data in patient records.

9.2.1. Demographic and clinical characteristics

Table 2. Variable definitions for demographic and clinical characteristics

Variable	Role	Time of measurement	Operational definition
Objective 1: demographic and clinical characteristics at first diagnosis of UC			
Age at initial diagnosis	Demographic and clinical characteristics	First diagnosis of UC	Derived using date of birth and date of initial UC diagnosis
Date of initial diagnosis	Demographic and clinical characteristics	First diagnosis of UC	As recorded: • Day/Month/Year of diagnosis
Stage at initial diagnosis	Demographic and clinical characteristics	First diagnosis of UC	As recorded: • Stage 0a • Stage 0is • Stage I • Stage II • Stage IIIA • Stage IIIB • Stage IVA • Stage IVB
Primary tumour site	Demographic and clinical characteristics	First diagnosis of UC	As recorded: • Bladder • Not-bladder

Sex	Demographic and clinical characteristics	First diagnosis of UC	As recorded: • Male • Female

Variable	Role	Time of measurement	Operational definition
			• Not known
Objective 1 (continued): demographic and clinical characteristics at diagnosis of locally advanced or metastatic UC			
Age at diagnosis	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis	Derived from date of birth and date of stage IV UC diagnosis
Date of locally advance or metastatic UC diagnosis	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis	As recorded: • Day/Month/Year of diagnosis
Stage of UC	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis	As recorded • Stage III • Stage IVA • Stage IVB
Histology	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis (or if not available, at initial diagnosis, where applicable)	As recorded: • Benign • Papillary urothelial neoplasm of low malignant potential • Malignant • Undifferentiated carcinoma

PD-L1 status	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis (or if not available, at initial diagnosis, where applicable)	• PD-L1 test (present or not recorded) • Type of antibody testing used or not recorded • PD-L1 positive or negative or not recorded
ECOG performance status	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis	As recorded (0-5)

Variable	**Role**	**Time of measurement**	**Operational definition**

			• 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 • 5 = Dead
De novo/newly relapsed	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis (and look-back period from initial diagnosis)	As recorded: at locally advance or metastatic UC diagnosis: • De novo disease • Newly relapsed • Unknown When patients are classified as newly relapsed stage IV; the following details will be described: • Previous stage

Variable	Role	Time of measurement	Operational definition
			• Histological subtype Time from previous diagnosis to relapse
Site of metastases	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis	Sites of metastases as recorded in the records: • lymph nodes • bone • lung • liver • peritoneum • other, as specified • Unknown
Time from first diagnosis	Demographic and clinical characteristics	At locally advanced or metastatic UC diagnosis	Time between date of initial diagnosis and diagnosis of locally advanced or metastatic UC diagnosis
Prior surgical resection of primary UC	Demographic and clinical characteristics	Look-back window (between initial diagnosis and at locally advanced or metastatic UC diagnosis)	As recorded
Prior adjuvant/neoadjuvant systemic therapy	Demographic and clinical characteristics	Look-back window (between initial diagnosis and at locally advanced or metastatic UC diagnosis)	• Yes • No

Cigarette smoking history	Demographic and clinical characteristics	Look-back window (at locally advanced or metastatic UC diagnosis)	As recorded • Current smoker • Former smoker • Never smoker • Unknown
Variable	**Role**	**Time of measurement**	**Operational definition**
Previous history of non muscle invasive bladder cancer	Demographic and clinical characteristics	Look-back window (prior to locally advanced or metastatic UC diagnosis)	As recorded • Yes • No
Objective 1 (continued): demographic and clinical characteristics at avelumab treatment initiation			
Age at avelumab initiation	Demographic and clinical characteristics	At avelumab treatment initiation	Derived from date of birth and date of avelumab initiation
ECOG performance status	Demographic and clinical characteristics	At avelumab treatment initiation	As recorded (0-5). For definitions of each category, see above

9.2.2. Treatment-related variables

Table 3. Variable definitions of treatment-related variables

Variable	Role	Time of measurement	Operational definition
Number of patients switching between different platinum-based chemotherapies	Treatment pattern prior to avelumab initiation	Look-back window (between locally advanced or metastatic UC diagnosis and avelumab initiation)	Patients will be described as switching treatment if they receive a different therapy in comparison to their initial treatment during the period between initial treatment and avelumab initiation (avelumab not included). The number of patients switching from initial platinum-based chemotherapy initiated after locally advanced or metastatic UC diagnosis will be described for each different therapy after switch

Variable	Role	Time of measurement	Operational definition
Objective 3: Treatment characteristics of anti-cancer therapies received for locally advanced or metastatic UC prior to initiation of avelumab			
SACT regimen received	Treatment pattern prior to avelumab initiation	Look-back window (between locally advanced or metastatic UC diagnosis and avelumab initiation)	Unique SACT regimen reported as initial therapy after locally advanced or metastatic UC diagnosis (inclusive)
Number of cycles of platinum-based chemotherapy received	Treatment pattern prior to avelumab initiation	Look-back window (between locally advanced or metastatic UC diagnosis and avelumab initiation)	Number of cycles of platinum-based chemotherapy received since locally advanced or metastatic UC diagnosis

rwTTNT from completion of 1L SACT	Treatment pattern prior to avelumab initiation	Look-back window (between locally advanced or metastatic UC diagnosis and avelumab initiation)	Time between completion of 1L SACT (derived from date of last SACT cycle) and date of initiation of avelumab See also Table 1.
Response to 1L therapy	Treatment pattern prior to avelumab initiation	Look-back window (between locally advanced or metastatic UC diagnosis and avelumab initiation)	Response to 1L therapy as reported by the clinician will be described at the end of 1L therapy according to the following categories: • Complete response • Partial response • Stable disease
Objective 4: Treatment patterns after initiation of avelumab as 1L maintenance therapy:			
Duration of treatment with avelumab	Treatment pattern from avelumab initiation	Between avelumab initiation and end of follow-up	Will be derived based on the date of avelumab initiation (index date) and the last date of avelumab treatment. The last day of avelumab treatment will be calculated based on the last recorded date of avelumab treatment received + 14 days. A gap of 30 consecutive days of no treatment with avelumab will be used to establish the last recorded date of avelumab treatment received.

Variable	**Role**	**Time of measurement**	**Operational definition**
Time interval between start of avelumab and start of 2L therapy	Treatment pattern from avelumab initiation	Between avelumab initiation and end of follow-up	Time interval will be derived using the dates of avelumab initiation and initiation of first regimen of 2L therapy. This parameter will be calculated only among patients who go on to receive 2L therapy after avelumab initiation

Number of patients who receive 2L therapy	Treatment pattern from avelumab initiation	Between avelumab initiation and end of follow-up	Number of patients who received 2L therapy after initiating avelumab
Number of patients who discontinue avelumab and start 2L therapy	Treatment pattern from avelumab initiation	Between avelumab initiation and end of follow-up	Number of patients who discontinue avelumab and subsequently receive 2L therapy
SACT regimen received as 2L therapy	Treatment pattern from avelumab initiation	Between avelumab initiation and end of follow-up	Among the number of patients receiving 2L therapy, unique SACT regimen reported as 2L therapy after avelumab initiation any time during follow-up
Number of SACT cycles received as 2L therapy	Treatment pattern from avelumab initiation	Between avelumab initiation and end of follow-up	Number of cycles received as 2L therapy after avelumab initiation
rwTTD from initiation of avelumab	Treatment pattern from avelumab initiation	Between avelumab initiation and end of follow-up	Time between avelumab initiation until the earliest of: • Date of discontinuation (a gap of 30 days without treatment with avelumab will be used to establish a patient as having discontinued avelumab) • Having a subsequent systemic therapy regimen • Date of death from any cause See Table 1 for other censoring points
High dose systemic steroid use	Treatment from avelumab initiation	Between avelumab initiation and end of follow-up	Name of systemic steroid used Dose of systemic steroid Start and stop dates Reason for treatment (if recorded)

9.2.3. Outcomes

Table 4. Outcome variables definitions

Variable	Role	Time of measurement	Operational definition

Primary objective: Estimation of overall survival			
rwOS	Patient outcome	From avelumab initiation to end of follow-up	Time between avelumab initiation until date of death from any cause See table 1 for other censor endpoints rwOS will be reported at 6-monthly intervals and at the end of the study.
Objective 2: Estimation of progression-free survival			
rwPFS	Patient outcome	From avelumab initiation to end of follow-up	Time between avelumab initiation until earliest of: • Date of first progression • Date of death from any cause See Table 1 for other censor endpoints rwPFS will be reported at 6-monthly intervals and at the end of the study. Progression will be determined based on progression being referenced in a clinician and/or radiology report, as described by an electronic health record (EHR) study (14). A proxy for progression could also be established as the earliest of death or start of new SACT after avelumab initiation

Variable	**Role**	**Time of measurement**	**Operational definition**
Objective 5: To describe the adverse events attributed to avelumab in a real-world population			

Adverse events explicitly attributed to avelumab	Patient outcome	From avelumab initiation to end of follow-up	Any AE with explicit attribution to avelumab as noted in the clinical records. Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE. • 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 discontinuation of avelumab • AEs leading to systemic steroid treatment
Objective 6: To describe real-world all-cause associated healthcare resource burden associated with avelumab therapy			
Variable	**Role**	**Time of measurement**	**Operational definition**

All-cause healthcare resource burden	Health care resource outcomes	From avelumab initiation to end of follow-up	Mean and median number, per patient, of the following: • Accident and emergency visits • Hospitalisations • Duration of hospitalisation (days)

9.3. Data sources

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.

9.4. Study size

We aim to enter 100 patients into the study with a maximum follow-up of 24 months per patient. Based on the JB100 trial, 1-year overall survival in the avelumab-treated group was 71% and median overall survival was 21.4 months (13). In our anticipated study population of 100 patients we would therefore expect 29 deaths by 12 months and >50 deaths by 24 months of follow-up. We have estimated the number of survivors by 12 and 24 months of follow-up, with the corresponding overall survival estimate and its 95% CI, based on 80, 100 and 120 patients included in the study in the table below.

Table 5. Estimated overall survival with 95% CI at 12 and 24 months of follow-up from avelumab initiation

	At 12 months			At 24 months		
Number of patients in the study	Number of survivors	Estimate of OS(a)	95% CI (c)	Number of survivors	Estimate of OS(b)	95% CI(c)
80	57	71%	60-81%	38	48%	36-59%
100	71	71%	61-80%	48	48%	38-58%
120	85	71%	62-79%	58	48%	39-58%

(a) Based on 1-year survival of 71.3% from trial
(b) Based on 2-year survival of 48.0% (estimated from (13)) (c)
Based on Clopper-Pearson exact method for binomial probability

9.5. Data management

9.5.1. Case report forms (CRFs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to an online, eCRF that will be built in the INES EDC system.

An eCRF is required and should be completed for each included patient. The completed original eCRFs are the sole property of Merck Serono and should not be made available in any form to third parties, except for authorised representatives of Merck Serono or appropriate regulatory authorities, without written permission from Merck Serono. The investigator shall ensure that the eCRFs will only be accessible to authorised staff members to prevent access by unauthorised third parties.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The eCRFs must be signed by the investigator or by an authorised staff member to attest that the data contained on the eCRFs are true and accurate. Any corrections to entries made in the eCRFs or source documents must be dated, initialised, and explained (if necessary) and should not obscure the original entry.

In this study, the source documents are the hospital or the physician's charts. In these cases, data collected on the eCRFs must match those source documents.

9.5.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Merck Serono or its agents, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), copies of all CRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, relocation), Merck Serono should be prospectively notified. The study records must be transferred to a designee acceptable to Merck Serono, such as another investigator, another institution, or to an independent third party arranged by Merck Serono.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Merck Serono have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

The investigator must obtain Merck Serono's written permission before disposing of any records, even if retention requirements have been met.

9.6. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a SAP, which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

The SAP will include detailed tables shells and example data visualisation of the analysis. A brief overview of the planned analysis is below.

9.6.1. Descriptive analysis

Clinical and demographic characteristics, treatment characteristics and toxicity and AEs will be analysed descriptively, where continuous variables will be described using the mean (with standard deviation) and/or the median (with IQR) and categorical variables will be described using number and percentage.

9.6.2. Overall and progression-free survival

Real-world OS and PFS will be analysed using time to event analysis. The definitions of these outcomes are provided in Table 1. Survival curves will be estimated using Kaplan-Meier methods and median (and IQR) time to event will be estimated with rwOS and rwPFS as endpoints. The number of patients who have not experienced the outcome and estimated survival probability (with 95% CI) will also be described at 6-monthly intervals post diagnosis until the end of follow-up. Censoring in analysing each individual outcome will be described in detail in the SAP.

9.6.3. Treatment patterns

In addition to the description of treatment characteristics, rwTTD and rwTTNT will be analysed using time to event analysis. Survival curves will be estimated using Kaplan-Meier methods and median (and IQR) time to event will be estimated with rwTTD and rwTTNT as endpoints. Table 1 describes the censoring endpoints. Healthcare resource utilisation

Healthcare resource burden (specifically number of all- cause hospitalisations, and duration of hospital stay, A&E admissions) will be reported. As reason for hospitalisation is harder to extract and subject to misclassification, only all-cause hospitalisation will be analysed.

9.7. Quality control

At the study level, all aspects of the study design and management from study document preparation (protocol, Questionnaire, SAP, reports) to ongoing site management will be conducted within the framework of the IQVIA Quality Management System (QMS) and in accordance to IQVIA and/or Merck Serono's SOPs.

According to these policies and procedures, a Data Management and Data Monitoring plan for the study will be developed and executed, which will include quality control on study management and centre management.

9.8. Limitations of the research methods

9.8.1. Selection bias and study representativeness

The study aims to collect information on patients treated with avelumab, initially as part of the EAMS, and further to include other NHS sites treating patients with avelumab through NHS commissioning. The EAMS closed on 21st January 2021 once the marketing authorisation from the European Medicines Agency was granted and the EAMS extension was put in place in the interim until a funding decision was made.

There is a potential selection bias that could be introduced by only including the participating EAMS and EAMS extension NHS sites, as they might differ compared to other NHS sites (e.g. being centres of excellence), this is a limitation of this study. Additionally, the geographies of the participating NHS sites are spread throughout the UK, aimed at maximising representativeness of the study population.

It is anticipated that most patients to be included in the study will already have initiated avelumab by the time the study is started and that only a minority of patients will be identified after the study has started at the centre. For most patients, therefore, demographic and treatment characteristics will be retrospectively assessed based on existing records and for a minority, prospectively. There is a potential for prospectively assessed data to be of different (higher) quality and/or completeness if a centre being aware that the avelumab-treated patients are part of a study changes medical record keeping practices or if the centre extracts data in real-time. While this is difficult to assess, it can be partially circumvented by extracting patient records retrospectively at periodic intervals, even if they are created after initiation of the study.

9.8.2. Missing or erroneous data

Due to variability in hospital record keeping practices, not all variables are expected to be available in the electronic medication records and medical charts. Whilst the primary objective (rwOS) is based on vital status which we expect to be well-captured within the hospital system,

some other variables are more likely to be missing than others. Site monitoring, and where required, source data verification (SDV) will also aim to reduce and minimise the collection of erroneous data.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organisational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

The personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorised study staff have access. The study site will implement appropriate technical and organisational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Merck Serono and other authorised parties, patient names will be removed and will be replaced by a single, specific, study numerical code, based on a numbering system defined by the study sponsor. All other data transferred to Merck Serono or other authorised parties will be non-identifiable by this single, patient-specific code. The investigator site will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Merck Seronowill maintain high standards of confidentiality and protection of patients' personal data consistent with the CSA and applicable privacy laws.

10.2. Patient consent

At the time of entry of patients into the study, it is likely that some patients may have died or be receiving end of life care. Therefore, to avoid the potential of biasing the study cohort towards that of a survivor cohort, and to avoid causing any unnecessary distress to the family and next of kin of deceased patients or patients receiving end of life care, no consent will be sought as part of this study.

An application to the CAG has been made to waive the need for seeking informed consent from all patients on the grounds of the abovementioned concerns. Therefore, no patients or their next of kin will be informed about the use of their data or consent sought as part of this study.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Merck Serono

An application for ethical review by the Health Research Authority (HRA) Research Ethics Committee (REC) using the Integrated Research Application System (IRAS) platform will be made for this study. HRA approval is the process by which the NHS will assess aspects of governance and legal compliance, as well as the independent REC opinion, provided through the UK research ethics service. It replaces the need for local checks of legal compliance and related matters by each participating organisation in England.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Merck Serono's controlled medical documents.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report AEs with explicit attribution to any Merck Serono drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the NIS Adverse Events (AE) Report Form to Merck Serono Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Merck Serono drug** that appear in the reviewed information must be recorded on the CRF and reported, within 24 hours of awareness, to Merck Serono Safety using the NIS AE Report Form.
    - This is inclusive of any adverse events or known toxicities that is explicitly attributed to any first-line chemotherapy regimen observed where a component of that chemotherapy regimen is marketed by Merck Serono.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Merck Serono product

must be reported, within 24 hours of awareness, to Safety using the NIS AE Report Form.

- This is inclusive of any off-label prescribing of any Merck Serono marketed medicinal products.

For these AEs with an explicit attribution or scenarios involving exposure to a Merck Serono product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AE Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AE Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female..." or "An elderly male..." Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness", "Study Drug", and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month/year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Merck Serono training requirements:

- *"Merck PV Responsibilities Training*" or similar a Merck Serono local training.

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Merck Serono.

Re-training must be completed on an annual basis using the most current Merck PV Responsibilities Training.*"* All certificates of training completion must be stored in the study master file (SMF) .

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Upon completion of this study, the aggregated results will be interpreted and discussed in a clinical study report (CSR) within 12 months after the completion of the last patient's follow up period. This CSR will contain a description of the objectives of the study, the methodology, results, and conclusions. The completed eCRFs, the final study output and CSR will remain

the confidential property of Merck Serono and may not be released to unauthorized people in any form (publication or presentations) without express written approval from Merck Serono.

An annual study progress report will be submitted to the IEC on a yearly basis following the initial ethical approval of the study.

We will publish the summary details and results of the NIS as per guidance within the Association of the British Pharmaceutical Industry's Code of Practice and Merck Serono's SOP. Further dissemination of the study findings may also be made, including abstracts and posters to scientific and medical conferences, as well as other scientific publications as decided by Merck Serono .

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Merck Serono product, Merck Serono should be informed immediately.

13. REFERENCES

1. What Is Bladder Cancer? [Internet]. [cited 2021 Jun 16]. Available from: https://www.cancer.org/cancer/bladder-cancer/about/what-is-bladder-cancer.html

2. Bladder Cancer Risk Factors [Internet]. [cited 2021 Jun 16]. Available from: https://www.cancer.org/cancer/bladder-cancer/causes-risks-prevention/risk-factors.html

3. Bladder cancer - Symptoms [Internet]. nhs.uk. 2018 [cited 2021 Jun 17]. Available from: https://www.nhs.uk/conditions/bladder-cancer/symptoms/

4. Bladder cancer statistics [Internet]. Cancer Research UK. 2015 [cited 2021 Jun 16]. Available from: https://www.cancerresearchuk.org/health-professional/cancerstatistics/statistics-by-cancer-type/bladder-cancer

5. Cancer survival in England - adults diagnosed - Office for National Statistics [Internet]. [cited 2021 Jun 16]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancersurvivalratescancersurvivalinenglandadultsdiagnosed

6. Survival Rates for Bladder Cancer [Internet]. [cited 2021 Jun 17]. Available from: https://www.cancer.org/cancer/bladder-cancer/detection-diagnosis-staging/survivalrates.html

7. Overview | Atezolizumab for untreated PD-L1-positive locally advanced or metastatic urothelial cancer when cisplatin is unsuitable | Guidance | NICE [Internet]. NICE; [cited 2021 Jun 16]. Available from: https://www.nice.org.uk/guidance/ta492

8. 1 Recommendations | Bladder cancer: diagnosis and management | Guidance | NICE [Internet]. NICE; [cited 2021 Jun 22]. Available from: https://www.nice.org.uk/guidance/ng2/chapter/1-Recommendations

9. Research C for DE and. FDA approves avelumab for urothelial carcinoma maintenance treatment. FDA [Internet]. 2020 Jul 1 [cited 2021 Jan 29]; Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/fda-approves-avelumaburothelial-carcinoma-maintenance-treatment

10. Bavencio - News | Merck global [Internet]. [cited 2021 Feb 24]. Available from: https://www.merckgroup.com/en/news/bavencio-1l-uc-eu-approval-25-01-2021.html

11. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma | NEJM [Internet]. [cited 2021 Jun 16]. Available from: https://www.nejm.org/doi/full/10.1056/NEJMoa2002788

12. Pfizer. A phase 3, multicenter, multinational, randomized, open-label, parallel-arm study of avelumab (msb0010718c) plus best supportive care versus best supportive care alone as a maintenance treatment in patients with locally advanced or metastatic urothelial cancer whose disease did not progress after completion of first-line platinum containing chemotherapy [Internet]. clinicaltrials.gov; 2021 Apr [cited 2021 Jun 14]. Report No.: NCT02603432. Available from: https://clinicaltrials.gov/ct2/show/NCT02603432

13. Powles T, Park SH, Voog E, Caserta C, Valderrama BP, Gurney H, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med [Internet]. 2020 Sep 24 [cited 2021 Jan 29];383(13):1218–30. Available from: https://doi.org/10.1056/NEJMoa2002788

14. Griffith SD, Tucker M, Bowser B, Calkins G, Chang C (Joe), Guardino E, et al. Generating Real-World Tumor Burden Endpoints from Electronic Health Record Data: Comparison of RECIST, Radiology-Anchored, and Clinician-Anchored Approaches for Abstracting Real-World Progression in Non-Small Cell Lung Cancer. Adv Ther [Internet]. 2019 Aug 1 [cited 2021 Feb 5];36(8):2122–36. Available from: https://doi.org/10.1007/s12325-019-00970-1

14. LIST OF TABLES

Table 1. Follow-up time for outcomes 20
Table 2. Variable definitions for demographic and clinical characteristics.....21
Table 3. Variable definitions of treatment-related variables 25
Table 4. Outcome variables definitions 28
Table 5. Estimated overall survival with 95% CI at 12 and 24 months of follow-up from avelumab initiation 31

LIST OF FIGURES

Figure 1. Schematic of the study design 18

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.