Sponsor : Pfizer (SAS)

This study is being conducted as part of a joint development programme for Bavencio® between Pfizer and Merck.

NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	AVENANCE - A non-interventional study to provide real-world data on the use of **avelumab** as a maint**enance** treatment for patients with advanced or metastatic Urothelial Carcinoma
Protocol number	B9991045
Protocol version identifier	6.0
Date	November 21st 2022
Active substance	Avelumab
Medicinal product	BAVENCIO®
Research question and objectives	<u>To generate clinical evidence on:</u> • The characteristics of adv/mUC patients treated with avelumab as maintenance treatment in the real-world setting. • The effectiveness and safety of avelumab in the real-world setting. To describe patients' characteristics and effectiveness of avelumab in different subgroups of interest. The main subgroup of interest will be the patients with adv/mUC with histological variants.
Mains authors	PPD Institut Cancerologie Strasbourg Europe, Strasbourg (ICANS). PPD Pfizer France.

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
adv/Muc	Locally advanced or metastatic urothelial carcinoma
AE	Adverse Event
AEC	Angiotensin-converting enzyme (ACE)
AIS	Anti-inflammatory steroids
ATU	Temporary Authorization for Use
BSC	Best Supportive Care
ChT	Chemotherapy
CNIL	French Data Protection Agency (Commission Nationale de l'Informatique et des Libertés)
CNOM	French National Medical Association (Conseil National de l'Ordre des Médecins)
CPP	Committee for the Protection of Persons (Comité de Protection des Personnes)
CR	Complete response
DOR	Duration Of Response
DOT	Duration Of Treatment
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
ePRO	Electronic Patient Reported Outcomes
EQ-5D-5L	EuroQoL – 5 dimensions 5 level
FACT FBlSI-18	Functional Assessment of Cancer Therapy - Bladder Symptom Index-18
IRR	Infusion related reaction
NCCN	National Comprehensive Cancer Network
NSAIDs	Non-steroidal anti-inflammatory drugs
OS	Overall Survival
ORR	Overall Response Rate
PFS	Progression Free Survival
PD-L1	Programmed death ligand1
PPI	Proton pump inhibitors
PR	Partial response
Q	Quadrimester
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable disease
UC	Urothelial Cancer
VAS	Visual analogue scale

3. RESPONSIBLE PARTIES

Scientific Committee

Name	Title	Affiliation
PPD		Institut Cancerologie Strasbourg Europe, Strasbourg (ICANS)
		Institut Jean Godinot, Reims
		Centre Léon Bérard, Lyon
		Gustave Roussy, Villejuif
		CHU, Bordeaux
		HEGP, Paris
		Clinique Victor Hugo, Le Mans

Scientific Committee coordinator

Nom	Title	Affiliation
PPD		Institut Cancerologie Strasbourg Europe, Strasbourg (ICANS)

Study team

Name	Role
PPD	Medical Team Leader Oncology - Pfizer
	Medical Advisor Oncology - Pfizer
	Medical Director Oncology - Merck
	Medical Advisor Oncology - Merck
	Real World Data Medical Manager - Pfizer
	NIS Project manager - Pfizer
	NIS Lead - Pfizer
	Health economics manager - Pfizer
	Data management - Pfizer
	Statistical Lead - Pfizer

4. ABSTRACT

Title	AVENANCE - A non-interventional study to provide real world data on the use of **avelumab** as a maint**enance** treatment for patients with advanced or metastatic Urothelial Carcinoma
Main author	PPD Institut Cancerologie Strasbourg Europe, Strasbourg (ICANS). PPD Pfizer France.
Rationale	On December 11th, 2020 the CHMP has adopted a positive opinion for avelumab as first line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma (adv/mUC) whose disease has not progressed with platinum-based induction chemotherapy. Marketing authorization for avelumab use in adv/mUC was issued on January 21st, 2021 by European Medicine Agency. The early use in France of avelumab in maintenance treatment for adv/mUC patients in the setting of the ATU (since July 2020) is an opportunity to early collect real-world data of avelumab in this indication. In addition to confirm the effectiveness and safety data provided by JAVELIN Bladder 100 study in routine clinical practice, this non-interventional study is an opportunity to generate effectiveness and safety data on different subgroups of interest. The main subgroup of interest will be the adv/mUC patients with histological variants. Few data are available on the efficacy of immunotherapy in histology variants of adv/mUC.
Objectives	Primary objective: to estimate Overall Survival (OS) of adv/mUC patients treated with avelumab in the real-world setting. Secondary objectives : • To describe patients' characteristics: ECOG (0-4) at chemotherapy (ChT) 1st and avelumab initiation, sex, age, ChT regimens received in 1st line (Cis/Gem, Carbo/Gem, Cis/Carbo/Gem, MVAC regimens, others), median number of ChT cycles received in 1st line, median time between the end of ChT 1st line and the start of avelumab, best response to 1st line chemotherapy (CR, PR, SD; CR-RP, SD), site and histology of the primary tumor (bladder, urethra or upper tract), site of baseline metastasis before ChT and avelumab (visceral vs non visceral), biological abnormalities (neutropenia, lymphopenia, impaired renal function, anemia), PD-L1 status and FGFR abnormality, Bajorin risk classification (0, 1, 2) evaluated before the start of

	ChT 1st line, use of concomitant treatments (corticosteroids/anti-inflammatory steroids (AIS)/non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-II-receptor antagonists (sartans)/angiotensin-converting enzyme (ACE) inhibitors, antibiotics, proton pump inhibitors (PPI)) at avelumab initiation, type of neoadjuvant and adjuvant treatments. • To estimate: Overall Survival from the start of ChT in 1st line, Progression Free Survival one and two (PFS1 and PFS2). Overall Response Rate (ORR), Duration Of Response (DOR) and Duration Of Treatment (DOT) while receiving avelumab. • To describe the pattern of progression while receiving avelumab. • To describe subsequent treatments and response to these treatments. • To describe the safety profile of avelumab. • To describe use of premedication (acetaminophen and antihistamine). • To describe Patient-Reported Outcomes (PROs) related to symptoms via the NCCN/FACT FBlSI-18 questionnaire and related to global health via the EQ-5D-5L questionnaire. This objective will be evaluated only among patients initiating avelumab after the start of the study. The primary and secondary objectives will be evaluated on the overall population and for prespecified subgroups.
Design	Multicenter ambispective (retrospective and prospective) non-interventional study of adv/mUC patients treated with avelumab, not impacting the treatment decision made by the treating physician and the medical management of treated patients. • All patients who initiated avelumab before the start of the study in the site will be included retrospectively. All patients are eligible: those under avelumab at inclusion, those who died before the start of the study, and those no longer treated with avelumab at the time of the study start. • Patients initiating the drug after the start of the study in the site will be prospectively included. <u>Follow-up</u>: The last patient prospectively included will be followed during 2 years. All other patients will be followed until death or until the end of the follow-up of the last patient prospectively included.
Population	**Inclusion criteria**

	1. Patient ≥ 18 years of age 2. Patient with locally advanced or metastatic urothelial carcinoma (irrespective of tumor histology) whose disease has not progressed (ongoing stable disease, partial response or complete response) following completion of first-line platinum-based chemotherapy and who has been (restrospective), is (retrospective and prospective), will be (prospective) treated with avelumab. 3 For a patient alive at the moment of the inclusion in the study: the patient must be informed of the study, he/she must be given an information letter signed by the investigator and must not be opposed to the collection of his/her data For a patient who died before the inclusion in the study: the patient (during his lifetime) must not be opposed in writing to the collection of his data. 4. Patient benefiting from a social security scheme according to local regulations **Exclusion criteria** 5. For a patient alive at the moment of the inclusion in the study: patient without liberty, under tutelage, or unable to give oral consent. 6. Patient enrolled in a prospective interventional clinical trial assessing an investigational product.
Variables	The following types of information will be collected: . Characteristics of patients and their cancer before avelumab initiation and previous treatments . Initiation of avelumab (date, premedication, biological exams) . Follow-up data (collect at inclusion and every 3 months until end of follow-up): avelumab administrations, tumoral responses, discontinuation, subsequent treatments, death . Patient reported outcome (PRO) : NCCN/FACT FBlSI-18 and EQ-5D-5L (at the time of avelumab initiation, at different time points after initiation if the patient is still treated with avelumab (6 weeks, 3 months, and every three months for up to 2 years, tumor progression if so), and at avelumab discontinuation).
Data sources	The data of interest will be reported in electronic case report forms (eCRF) by the investigator site for each selected patient, at inclusion and regularly during follow-up, on the basis of the data available in the patients' medical records. In addition, two questionnaires will be completed by participants.
Study size	Target sample size is 600 patients.

Data analysis	A detailed statistical analysis plan will be available before the database lock. The primary end point is the Overall Survival (OS). OS is defined as the time from the date of first injection of avelumab to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact. OS will be summarized using the Kaplan-Meier method and displayed graphically. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles will be reported. A first interim analysis (IA) will be performed 6 months after the inclusion of the 1st patient and then every year for publication purposes. The data collected in the present study may also be analyzed together with data from other countries, to increase sample size to address with a higher precision for some of the study objectives. The details of this pooled analysis will be described in a separate analysis plan.
Milestones	Selection of investigating centers: Q1 2021 CPP submission: January 2021 Start of data collection (First patient First Visit): Q2 2021 End of data collection (Last Patient Last Visit): Q4 2024 Interim analysis 1: Q2 2022 Interim analysis 2: Q4 2022 Interim analysis 3: Q4 2023 Interim analysis 4: Q4 2024 Final analysis and study report: Q1 2025

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1 / Protocol V3.0	07-JUN-2021	- Cover page - 9.6.1 - 10.6	Pfizer is jointly responsible of the processing of the personal data with Merck.	This study is being conducted as part of a joint development programme for Bavencio® between Pfizer and Merck.
		- 9.6.2 - 9.10.1	Data storage period	Clarification added
		- 10.6	The study comes within the scope of MR003 but also of MR004.	Due to the retrospective part of the study.
2 / Protocol V4.0	25-NOV-2021	-4 – ABSTRACT (inclusion criteria n° 3)	- information to person of trust not mandatory - the patient must not be opposed in writing	According to MR004
		9.2.1	- information to person of trust not mandatory - the patient must not be opposed in writing	According to MR004
3 / Protocol V5.0	29-NOV-2021	11.2 (reporting period)	Non serious AE reporting period is reduced to 90 days after the last avelumab administration	Exception request validated by Pfizer Pharmacovigilance Policy Committee
4 / Protocol V6.0	21-NOV-2022	-4 – ABSTRACT (Study size) And 9.5 Study Size	Target sample size is increased to 600 patients	Obtain the number of patients with variant initially planned

		9.3 Variables And 9.4 Data Sources	* In order to validate the type of variants, anonymized anatomical pathology reports of the patients concerned will be collected and reviewed by the steering committee. For the patients presenting an UC with variant, anonymized anatomical pathology reports will be collected and stored in a dedicated directory in the eCRF.	In order to confirm the histological type of the urothelial tumors of the patients included in the Avenance study, the scientific committee of the study wishes to review the anatomical pathology reports of these patients

6. MILESTONES

Table 1: study scheduled planning

Milestone	Planned date
Selection of investigating centers	Q1 2021
CPP submission	January 2021
Start of data collection (First patient First Visit)	Q2 2021
End of data collection (Last Patient Last Visit)	Q4 2024
Interim analysis 1	Q2 2022
Interim analysis 2	Q4 2022
Interim analysis 3	Q4 2023
Interim analysis 4	Q4 2024
Final analysis and study report	Q1 2025

7. RATIONALE AND BACKGROUND

Urothelial Cancer (UC) accounts for approximately 90% of all cancer of urinary tract (bladder, upper urinary tract, urethra). About 11 000 patients are newly diagnosed with an urinary tract cancer each year in France[1]. Patients with metastatic UC have a dismal prognosis with a five-year survival rate of only 5%. Platinum-based polychemotherapy regimen is currently the first-line standard of care for patients with advanced/metastatic disease, but despite high initial response rates, durable and complete responses following first-line chemotherapy (ChT) are uncommon, and most patients will ultimately experience disease progression within nine months after initiation of treatment.

Avelumab (MSB0010718C, BAVENCIO®) is a human Immunoglobulin G1 monoclonal antibody directed against the programmed death ligand1 (PD-L1).

Avelumab in combination with Best Supportive Care (BSC) as a maintenance treatment had been evaluated versus BSC alone in a phase III randomized trial (JAVELIN Bladder 100) for locally advanced or metastatic Urothelial Carcinoma (adv/mUC) patients who have not progressed with first-line platinum-based chemotherapy[2]. The JAVELIN Bladder 100 study has demonstrated a significant 7.1-months improvement in median Overall Survival with Avelumab+BSC as first-line maintenance versus BSC alone, with a 31% reduction of the death risk in the overall population (hazard ratio = 0.69 (95% CI, 0.56, 0.86), p<0.001). The results of the JAVELIN Bladder 100 had been presented at ASCO 2020 and published in the New England Journal of Medicine on September 18th, 2020.

On June 30th, 2020, U.S. Food and Drug Administration approved avelumab for maintenance treatment of patients with locally advanced or metastatic Urothelial Carcinoma who have not progressed with first-line platinum-containing chemotherapy.

On July 3rd, 2020 the French National Agency for Medicines and Health Products issued a cohort Temporary Authorization for Use (ATU) extension for avelumab in the first-line maintenance treatment of adult patients with locally advanced or metastatic Urothelial Carcinoma who have not progressed with first-line platinum-based chemotherapy and presenting an ECOG performance status of 0 or 1.

On December 11th , 2020 the CHMP has adopted a positive opinion for avelumab as first line maintenance treatment of adult patients with locally advanced or metastatic urothelial carcinoma whose disease has not progressed with platinum-based induction chemotherapy. Marketing authorization for avelumab use in adv/mUC was issued on January 21st, 2021 by European Medicine Agency[3].

The early use in France of avelumab in maintenance treatment for adv/mUC patients in the setting of the the ATU is an opportunity to early collect real world data of avelumab in this indication.

In addition to confirm the effectiveness and safety data provided by JAVELIN Bladder 100 study in routine clinical practice this non-interventional study is an opportunity to generate effectiveness and safety data on different subgroups of interest. The main subgroup of interest will be the adv/mUC patients with histological variants. Few data are available on the efficacy of immunotherapy in histology variants of adv/mUC.

8. RESEARCH QUESTION AND OBJECTIVES

The study will generate clinical data on the characteristics of adv/mUC patients treated with avelumab and on the effectiveness and safety of avelumab in the real-world setting.

Primary objective: to estimate Overall Survival (OS) of adv/mUC patients treated with avelumab in the real-world setting.

Secondary objectives :

- To describe patients' characteristics: ECOG (0-4) at ChT 1st and avelumab initiation, sex, age, ChT regimens received in 1st line (Cis/Gem, Carbo/Gem, Cis/Carbo/Gem, MVAC regimens, others), median number of ChT cycles received in 1st line, median time between the end of ChT 1st line and the start of avelumab, best response to 1st line chemotherapy (CR, PR, SD; CR-RP, SD), site and histology of the primary tumor (bladder, urethra or upper tract), site of baseline metastasis before ChT and avelumab (visceral vs non visceral), biological abnormalities (neutropenia, lymphopenia, impaired renal function, anemia), PD-L1 status and FGFR abnormality, Bajorin risk classification (0, 1, 2) evaluated before the start of ChT 1st line, use of concomitant

treatments (corticosteroids/anti-inflammatory steroids (AIS)/non-steroidal anti-inflammatory drugs (NSAIDs), angiotensin-II-receptor antagonists (sartans)/angiotensin-converting enzyme (ACE) inhibitors , antibiotics, proton pump inhibitors (PPI)) at avelumab initiation, type of neoadjuvant and adjuvant treatments.

- To estimate: Overall Survival from the start of ChT in 1st line, Progression Free Survival one and two (PFS1 and PFS2). Overall Response Rate (ORR), Duration Of Response (DOR) and Duration Of Treatment (DOT) while receiving avelumab.
- To describe the pattern of progression while receiving avelumab.
- To describe subsequent treatments and response to these treatments.
- To describe the safety profile of avelumab.
- To describe use of premedication (acetaminophen and antihistamine).
- To describe Patient-Reported Outcomes (PROs) related to symptoms via the NCCN/FACT FBlSI-18 questionnaire and related to global health via the EQ-5D-5L questionnaire. This objective will be evaluated only among patients initiating avelumab after the start of the study.

The primary and secondary objectives will be evaluated on the overall population and for prespecified subgroups.

- Main subgroup of interest: histology (UC with variant; UC without variant).
- Other subgroups of interest: ECOG at avelumab initiation (PS 0-1; PS ≥2), locally advanced urothelial carcinoma versus metastatic urothelial carcinoma, previous ChT regimens (Cis/Gem, Carbo/Gem, Cis/Carbo/Gem, MVAC regimens, others), best response to 1st line chemotherapy (CR, PR, SD; CR+PR, SD), number of ChT cycles received in 1st line (< 4 cycles; ≥ 4 cycles and ≤ 6; > 6 cycles), site of baseline metastases before ChT (visceral vs non-visceral), patients with an early relapse on avelumab (progression at the first tumoral assessment) and patients with a long-term response to avelumab (4th quartile), delay between the end of ChT and the start of avelumab (< 4 weeks; between 4 and 10 weeks; >10 weeks), ATU patients versus non ATU patients, site for the primary tumor (bladder, urethra, upper tract), PD-L1 status, FGFR abnormality, Bajorin risk classification evaluated before ChT 1st line (0, 1, 2), presence of biological anomalies (neutropenia, lymphopenia, impaired renal function, anemia), use of concomitant treatments (corticosteroids/AIS/NSAIDs, sartans/ACE inhibitors, antibiotics, PPI) at avelumab initiation.

9. RESEARCH METHODS

9.1. Study design

Multicenter ambispective (retrospective and prospective) non-interventional study of adv/mUC patients treated with avelumab, not impacting the treatment decision made by the treating physician and the medical management of treated patients (Figure 1).

Inclusion period: expected 18 months to reach sample size.
Target sample size is 600 patients.

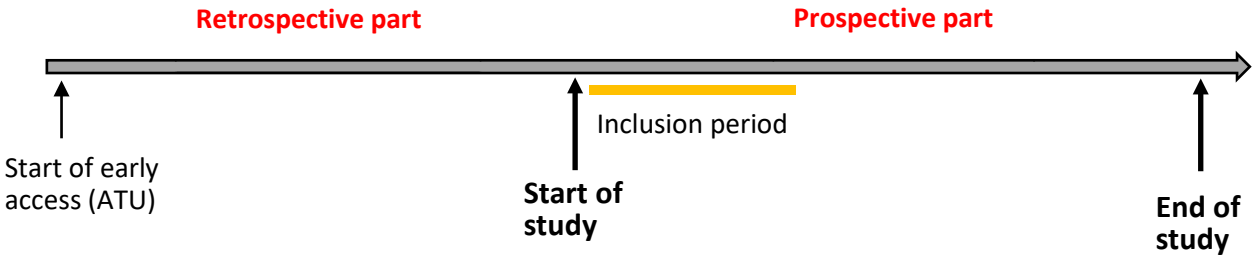
- All patients who initiated avelumab before the start of the study in the site will be included retrospectively. All patients are eligible: those under avelumab at inclusion, those who died before the start of the study, and those no longer treated with avelumab at the time of the study start.
- Patients initiating the drug after the start of the study in the site will be prospectively included.

Follow-up:
The last patient prospectively included will be followed for 2 years. All other patients will be followed until death or until the end of the follow-up of the last patient prospectively included.

Patients who started avelumab before the start of the study will be followed retrospectively, but also prospectively for those still alive at the beginning of the study.
Follow-up visits will be made during the course of regular visits and/or hospitalisations. No additional visits or examinations are required by the protocol, as the study is observational: follow-up and treatment modalities will be at the sole discretion of the participating physician. Clinical data will be collected every three months after the inclusion in the study and until death or the end of the study: 24 months after the inclusion of the last prospective patient. Patients initiating avelumab after the start of the study (prospective part of the study) will complete PRO questionnaires : 1) at the time of avelumab initiation, 2) at different time points after initiation if the patient is still treated with avelumab (6 weeks, 3 months, and every three months for up to 2 years, tumor progression if so), 3) and at avelumab discontinuation.

Number of sites: the study will be proposed to all sites participating to the ATU program, plus some additional centers expected to treat patients after the ATU period. Approximately 100 sites are expected to participate to the study.

Figure 1. Study design



9.1.1. Primary endpoint

OS: time between the first injection of avelumab and the date of death from any cause.

9.1.2. Secondary endpoints

- OS from the start of the chemotherapy used in 1st line: time between the first injection of the chemotherapy used in 1st line and the date of death from any cause.
- PFS1: time between the first injection of avelumab and the date of progression or death from any cause. Progression status will be defined according to RECIST 1.1.
- PFS2: time between the first injection of avelumab and the date of progression or death from any cause during the 2nd line of treatment post-avelumab. Progression status will be defined according to RECIST 1.1.
- ORR: proportion of patients with a Complete Response or Partial Response as a best response during the avelumab treatment. Responses to treatment will be defined according to RECIST 1.1.
- DOR: time between the beginning of the response and progression or death from any cause.
- DOT: time between the first and last dose of avelumab.
- Patterns of progression under avelumab: metastatic sites and type of progression (new lesion(s)/progression of known lesion(s)).
- Subsequent treatments and response to these treatments: DOT, PFS, ORR and OS.
- Safety: AEs of any type, grade 3-4 AEs, AEs leading to interruption or discontinuation, AEs leading to death.

- Premedications (acetaminophen and antihistamine): Proportion of patients who received a premedication at each injection of avelumab. Median number of cycles with premedication. To evaluate the correlation between infusion-related reactions and premedication.

- Evolution of PROs NCCN/FACT FBlSI-18 and EQ-5D-5L scores during avelumab treatment.

9.2. Setting

The study will be proposed to all French centers where patients have been treated with avelumab in the setting of the ATU, plus some additional centers suitable to treat patients after the ATU period.

All the eligible patients from the participating centers will be proposed to be included in the study. Regarding the ATU patients who died before the start of the study, families will be informed.

9.2.1. Inclusion criteria

Patients must meet all of the following inclusion criteria to be eligible to the study:

1. Patient ≥ 18 years of age

2. Patient with locally advanced or metastatic urothelial carcinoma (irrespective of tumor histology) whose disease has not progressed (ongoing stable disease, partial response or complete response) following completion of first-line platinum-based chemotherapy and who has been (restrospective), is (retropsectifve and prospective), will be (prospective) treated with avelumab.

3. For a patient alive at the moment of the inclusion in the study : the patient must be informed of the study, he/she must be given an information letter signed by the investigator and must not be opposed to the collection of his/her data

For a patient who died before the inclusion in the study : the patient (during his lifetime) must not be opposed in writing to the collection of his data. 4. Patient benefiting from a social security scheme according to local regulations

9.2.2. Exclusion criteria

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

5. For a patient alive at the moment of the inclusion in the study: patient without liberty, under tutelage, or unable to give oral consent.

6. Patient enrolled in a prospective interventional clinical trial assessing an investigational product.

9.3. Variables

Table 2 shows the information which will be collected in the study.

Table 2. Information collected in the study and timing of data collection

Data elements	**Variables**	**Timing of data collection**		
		Inclusion	**6 weeks**	**3 months, then every three months until end of follow-up**
Inclusion	• Type of center • Eligibility criteria (inclusion/exclusion) • Date of provision of information letter	X		X
Characteristics of patients and their cancer before avelumab initiation	• Demographics : month and year of birth, sex • Patient and Cancer characteristics: . Localisation: upper/lower (bladder, urethra) urinary tract . Cancer characteristics: histological subtype including type of variant*, PD-L1 status and FGFR alteration with type of test and CPS score. • Localized cancer: date of diagnosis, type of treatment (adjuvant/neoadjuvant), regimen, dates of start and end, number of ChT cycles, complete response if neoadjuvant. • Adv/mUC: date of diagnosis, stage at ChT initiation, metastatic sites at ChT initiation, Karnowski index and ECOG at ChT initiation, type of ChT regimen, dates of start and end, number of ChT	X		X

	cycles, response at the end of ChT, date of start of partial or complete response if so.			
Initiation of avelumab	• Patients characteristics : ECOG at initiation • Biological exam: neutrophil, lymphocyte, haemoglobin, creatinine clearance • Metastatic sites • Date of first administration, dose • Use of premedication (acetaminophen and antihistamine)	X		X
Clinical Follow-up data	• Avelumab administration . Date of each infusion, dose . Use of premedication (acetaminophen and antihistamine) • Tumoral response under avelumab . At inclusion (for retrospective data collection): tumoral evaluation (yes/no), best response since avelumab initiation, date of partial or complete response if so, date of progression if so with site(s) of progression and type (new or preexisting lesions). . Tumoral evaluation since last visit (yes/no, date), response (partial remission, complete remission, progression, stable disease, not evaluable), site(s) of progression if so and type (new or preexisting lesions). • ECOG if the patient is still on avelumab • Avelumab discontinuation	X		X

	. Temporary interruption(s) with reason and dates . Permanent discontinuation with reason and date • Subsequent treatments after avelumab discontinuation . Regimen and dates start/discontinuation . Best response, progression with date, • Death with date and cause • Lost to follow-up if so and date • Date of withdrawal if so			
Safety	Adverse events (see section 11)	X		X
Concomitant treatments	Corticosteroids/AIS/NSAIDs, sartans/ACE inhibitors, antibiotics, PPI, **if the patient is still on avelumab**	X		X
Patient reported outcome (PRO)	Patients initiating avelumab after the start of the study will complete NCCN/FACT FBlSI-18 and EQ-5D-5L questionnaires: 1) at the time of avelumab initiation (baseline) 2) at different time points after initiation **if the patient is still treated with avelumab** : 6 weeks, 3 months, every three months for up to 2 years, tumor progression if so 3) at avelumab discontinuation (whatever the reason is)	X	X	X

* In order to validate the type of variants, anonymized anatomical pathology reports of the patients concerned will be collected and reviewed by the steering committee.

9.4. Data sources

The data of interest will be reported in an electronic case report forms (eCRF) by the investigator for each included patient, at inclusion and regularly during follow-up, on the basis of the data available in the patients' medical records. A clinical study technician may help the investigator to enter the patient's data in the eCRF.

For the patients presenting an UC with variant, anonymized anatomical pathology reports will be collected and stored in a dedicated directory in the eCRF.

Pfizer and Exystat, in charge of study data management, are responsible for the creation and maintenance of the eCRFs.

No directly nominative data will be collected. During the individual set up of the investigator site, Pfizer will assign a 4-digit code to each site: this code corresponds to the site number.

The patient number will comprise the site number (4 digits) followed by a 3-digit code assigned in ascending order of inclusion: for example, patient number 0009-002 corresponds to the second patient at site 9. The collected data will be confidential and covered by medical secrecy.

In addition, two questionnaires (ePRO or paper) will be completed by participants who initiated avelumab after the beginning of the study:

- NCCN/FACT FBlSI-18 (Functional Assessment of Cancer Therapy – Bladder Cancer Symptom Inventory) : The FBlSI-18 is a self-administered questionnaire to assess patient bladder cancer-specific symptoms using a 'core' set of questions a cancer site-specific bladder subscale. Higher scores indicate a higher degree of bladder symptoms.

- EQ-5D-5L (EuroQoL – 5 dimensions 5 level) : The EuroQol EQ-5D-5L is patient-completed generic questionnaire consisting of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) :

  - The questionnaire (descriptive system) is designed to assess health status in terms of a single index value or utility score. It comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). For each dimension, respondents select the statement that best describes their health on that day from five possible options of increasing levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems).

  - The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement.

9.5. Study size

The primary endpoint is the Overall Survival (OS). In this non-interventional study, the objective is only descriptive and the sample size will rely on the precision of the estimate.

The expected precision of the median survival time can be calculated using following assumptions:

- Expected median Overall Survival time: 20 months.
- Two-sided 95% Confidence Interval (CI).
- Exponential Lifetime Percentile distribution ($S(t)=e^{-t/29}$) with a median survival time of 20 months and a mean survival of 29 months.
- Assuming the absence of right-censoring before the median survival and the occurrence of a single event for each event time.

The different accuracies and CI for the median overall survival time can therefore be calculated as a function of sample sizes. Below accuracy and 95%CI for a median survival time of 20 months:

Total Sample size	Accuracy (total patients)	Lower CI	Upper CI
400	4,0	18,3	22,2
433	3,8	18,3	22,1
467	3,7	18,4	22,1
500	**3,5**	**18,4**	**22,0**
533	3,4	18,5	21,9
567	3,3	18,5	21,9
600	**3,2**	**18,6**	**21,8**
667	3,1	18,7	21,7
800	2,8	18,8	21,6
1000	2,5	18,9	21,4

With 600 patients, the CI of OS is expected to be [18.6; 21.8] for a 3.2 months accuracy.

A total of 47 variant patients for a total sample size of 600 patients will produce a two-sided 95% confidence interval for the median survival time with a width equal to 12 months (PASS® version 15.0 validated with Nquery® version 8.3.1 - reference Mathews, Paul. 2010. Sample Size Calculations: Practical Methods for Engineers and Scientists. Mathews Malnar and Bailey, Inc.).

With a total of 47 patients, the two-sided 95% CI associated to a median survival time of 20 months will be [15.4 ; 27.4]. Of note the two-sided 95% CI for the whole sample (600 patients) will be [18.6 ; 21.8].

9.6. Data management

The data will be collected thanks to the software Cleanweb (from Telemedicine SA) and stored in a secured file storage server. The eCRF and the PROs data will be merged in the Cleanweb database.

Only dedicated study personnel will have access to the database.

A Data Management Plan will be drawn up to describe all of the Data Management activities carried out during the study, together with a Data Validation Plan, which will describe all of the coherence tests and listings of inconsistencies found during the study together with request messages for corrections sent to the participating investigator. This Data Management Plan must be approved by the sponsor before inclusions begin.

The use of the e-CRF enables the pre-tests to be carried out (coherence tests performed online that enable an immediate correction of inconsistencies from the participating doctors), which will help to reduce the number of requests for correction.

On a regular basis during the conduct of the study, the Data Manager will trigger the planned coherence tests. Incoherencies will be resolved online by the participating investigators or his delegates.

Once all corrections have been made to the database and all the eCRFs signed by the investigators, the data manager will lock the database making the data available for the final statistical analysis.

All the data management decisions will be documented in the data management issue log.

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

The data of interest will be recorded in electronic format in a case report form (e-CRF).

A e-CRF is required and should be completed for each included patient. The completed original e-CRFs will b*e* sole property of Pfizer and Merck and should not be made available in any form to third parties, except for authorised representatives of Pfizer or Merck or appropriate regulatory authorities, without written permission from Pfizer and/or Merck. The investigator shall ensure that the e-CRFs are securely stored at the study site in encrypted electronic or paper format and are protected by a password or kept securely in a locked room in order 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 e-CRFs and any other data collection supports (source documents) and for ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The e-CRFs must be signed by the investigator or by an authorised member of the

research team in order to guarantee that the data contained on the e-CRFs are correct and complete. Any corrections to entries made in the e-CRF source documents must be dated, initialled by the author, and explained (if necessary) and should not obscure the original entry.

In most cases the source documents are the hospital or the physician's record. In these cases, data collected on the e-CRFs must match these records.

In some cases, the e-CRF/e-PRO may also serve as the source document. In these cases, a document should be available at the investigator site or at Pfizer that clearly identifies those data that will be recorded on the e-CRF, and for which the e-CRF will stand as the source document.

The e-PRO will be completed by those participants who chose to use this method to fill in data.

Participants not wanting to use the e-PRO method may fill in the data concerning them using the same data collection forms in paper format. These paper forms will be entered in the study database by data entry operators appointed by the sponsor.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, e.g., CRFs/e-CRFs and hospital records), all original signed information letters, copies of all CRFs/e-CRF*s*, pharmacovigilance notification forms, source documents, detailed records of treatment dispensing, 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. 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), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

Investigator records must be kept for up to 2 years after the last publication of the results of the study or, failing any publication, up to the signature of the final report of the study and must then be archived for up to 20 years maximum or a duration in accordance with the existing regulations.

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

Patient self-questionnaires may be directly completed in electronic format by the patients on the study ePRO.

Otherwise, hard copies of the completed patient self-questionnaires will be sent to Pfizer by the investigator site using secure follow-up envelopes. They will then be sent electronically by Pfizer via a secure site to the data management company for entry.

9.7. Data analysis

A detailed statistical analysis plan will be available before the database lock.

All effectiveness analyses (except PRO analysis) will be performed on a Full Analysis Set (FAS) defined as all enrolled patients who received at least one injection of avelumab. “Enrolled" means a participant's, or his or her legally authorized representative’s, agreement to participate in a clinical study following completion of the informed consent/assent process and who meet all eligibility criteria. Potential participants who are screened for the purpose of determining eligibility for the study, but do not participate in the study, are not considered enrolled.

The primary end point is the Overall Survival (OS). OS is defined as the time from the date of first injection of avelumab to the date of death due to any cause. Patients last known to be alive will be censored at date of last contact. OS will be summarized using the Kaplan-Meier method and displayed graphically. Confidence intervals (CIs) for the 25th, 50th (median) and 75th percentiles will be reported. In particular, six-months and one-year survival rate will be assessed with a 95%CI.

A first interim analysis (IA) will be performed 6 months after the inclusion of the 1st patient and then every year for publication purposes.

The data collected in the present study may also be analyzed together with data from other countries, to increase sample size to address with a higher precision some of the study objectives. The details of this pooled analysis will be described in a separate analysis plan.

9.8. Quality control

The quality of the data collected during the study will be ensured by:

- The training of investigator teams during study set-up meeting (objectives and conduct of the study, protocol and e-CRF, logistics, pharmacovigilance procedures etc.)
- Regular follow-up of investigators during the study (by telephone calls, emails and on-site visits)
- Control of data captured in the e-CRF (automated on-line control for key data and additional correction requests). All of these controls will be described in the Data Management Plan.

Monitoring of participating centres

The investigators will be contacted throughout the study to ensure that they understand and follow the protocol and electronic questionnaire. All the contacts will be documented.

Depending on the progress of e-CRF completion, the CRA will carry out site monitoring visits. During these visits, the CRA will check the quality of data collected. The CRA will also ensure that the investigator and the team responsible for the study in the centre have understood and followed the protocol, the existence of patients who have been included, that the data listed in the e-CRF are identical to the original data, checking that the site master file (SMF) is correctly maintained and confirming declaration of AEs to the Pfizer Pharmacovigilance Department.

In order to do this, he/she will need to refer to the patients' medical record. The investigators will therefore need to ensure that the CRA has access to the patients' records. The CRA involved in the monitoring procedures will not be involved in data collection. The frequency of on-site visits will depend on the number of patients included in each centre.

Key indicators of the good conduct of the study (number of active sites, number of included patients, number of follow-ups performed, number of queries, etc…) will be generated from the study database. This database can be used to edit study progress reports in order to manage site reminder letters.

9.9. Limitations of the research methods

9.9.1. Selection bias

Centers selection

Both specialized centers in adv/mUC management and non-specialized public and private centers have included patients in the avelumab ATU and will therefore be contacted to participate in the study. If the representativeness of the sample in relation to all patients treated with avelumab for adv/mUC in France over the study period cannot be guaranteed, this multicenter selection will make it possible to minimize this bias.

In addition, the characteristics of participating centers and contacted centers will be compared (i.e local public hospitals, private centers, expert centers, university hospitals), and in case of difference, adjustment on the type of centers could be done to provide corrected estimates of primary and secondary endpoints as sensitivity analysis.

Patients selection

In order to limit the selection bias of study patients, participating centers will be asked to include retrospectively all eligible patients from their center who had already initiated a treatment with avelumab for adv/mUC, and for the prospective part of the study, to consecutively enroll all eligible patients after study set-up, until the planned number of patients have been included in the study. All patients who died before study set-up will be included, to avoid survival bias.

9.9.2. Measures taken to reduce patients lost to follow-up and missing data

Data will be collected from medical chart, which may lead to incomplete or missing information. As this study will not influence or modify usual practices, investigators will have

the possibility to note "not done", "not known" or "not applicable" in the e-CRF, facilitating the quantification of missing data. In the event of missing data without one of these references being made, the CRA will endeavour to collect the corresponding information with the assistance of the investigator. However, if the data remain missing at the time of the analysis, they will not be replaced and will be treated as such.

In addition, the use of an e-CRF will limit data entry errors through automated online checks. Finally, training of the investigation teams to the e-CRF, as well as monitoring of data collection, will guarantee the quality of the information collected.

If patients are lost to follow-up, the investigators will agree to call patients, one of their family circles or their general practitioner, in order to recover enough data in order to close the file.

If any patients die, the doctor will investigate the cause of death.

9.10. Other aspects

9.10.1. Archiving

The investigators will store the questionnaires for up to 2 years after the last publication of the results of the study or, failing any publication, up to the signature of the final report of the study and will then archive the questionnaires for up to 20 years maximum or a duration in accordance with the existing regulations.

The study management centre will store and then archive all study-related documents for the same periods of time.

After this period, all the documents will be returned to the study sponsor.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational 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 authorized study staff have access. The study site will implement appropriate technical and organizational 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 Pfizer and other authorized parties, patient

names will be removed and will be replaced by a single, specific, numerical code, based on a numbering system defined by Pfizer. All other identifiable data transferred to Pfizer or other authorized parties will be identified 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, Pfizer and other authorized parties will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient consent

The informed consent documents and any patient recruitment materials must be in compliance with local regulatory requirements and legal requirements, including applicable privacy laws.

In the present French study, no signed consent is required. An information note signed by investigator is provided to the patient.

The informed consent documents used during the informed consent process and any patient recruitment materials must be reviewed and approved by Pfizer, approved by the institutional review board (IRB)/independent ethics committee (IEC) before use, and available for inspection.

The investigator must ensure that each study patient or his or her legally acceptable representative, is fully informed about the nature and objectives of the study, the sharing of data relating to the study and possible risks associated with participation, including the risks associated with the processing of the patient's personal data. The investigator further must ensure that each study patient or his or her legally acceptable representative, is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

Whenever consent is obtained from a patient's legally acceptable representative, the patient's assent (affirmative agreement) must subsequently be obtained when the patient has the capacity to provide assent, as determined by the IRB/IEC. If the investigator determines that a patient's decisional capacity is so limited that he or she cannot reasonably be consulted, then, as permitted by the IRB/IEC and consistent with local regulatory and legal requirements, the patient's assent may be waived with source documentation of the reason assent was not obtained. If the study patient does not provide his or her own consent, the source documents must record why the patient did not provide consent (e.g., minor, decisionally impaired adult), how the investigator determined that the person signing the consent was the patient's legally acceptable representative, the consent signer's relationship to the study patient (e.g., parent, spouse), and that the patient's assent was obtained or waived. If assent is obtained verbally, it must be documented in the source documents.

10.3. Patient withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document patient

outcome, if applicable. The investigator would inquire about the reason for withdrawal and follow-up with the patient regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent pursuant to applicable local regulations.

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

This is a non-interventional study that does not modify in any way the usual medical management of the persons entering the study or compromise their physical or mental integrity or require any particular follow-up visit for the persons entering the study. All procedures are performed, and all products used in a usual way, without any additional or unusual diagnostic or monitoring procedure.

Under these conditions, this study comes within the scope of application of Ordinance No. 2016-800 of 16 June 2016 for research, article L1121-1, and the project must therefore be declared to the French National Agency for Medicines and Health Products Safety (Agence nationale de sécurité du medicament), and a submission made to the Committee for the Protection of Persons (CPP).

The sponsor must obtain prior authorization for the study protocol, protocol amendments and patient information sheets, and all other significant documents (for example, advert to obtain recruits), where necessary, from the CPP.

All correspondence with the CPP must be kept by the investigator.

10.5. French National Medical Association (Conseil National de l'Ordre des Médecins, CNOM)

In the context of article L.1453-7 et seq., in particular articles L.1453-10 and L.1453-11 of the Public Health Code (CSP), it is Pfizer's responsibility to submit the study for authorization to the CNOM.

Indeed, the sponsor of the study must inform the CNOM of all financial aspects between the sponsor, the members of the scientific committee and the physicians participating in the study.

In accordance with article L.4113-9 of the Public Health Code, it is the responsibility of each participating doctor to take the same steps with the Departmental Council of the Order to which he or she belongs.

10.6. Data protection: French Data Protection Agency (Commission Nationale de l'Informatique et des Libertés [CNIL])

In accordance with law No. 78-17 of 6 January 1978 on Data Processing, Data Files and Civil Liberties as amended concerning the protection of individuals with regard to the

processing of personal data, this protocol will be subject to a declaration of compliance with a reference method to the French Data Protection Agency (CNIL).

Taking into account the fact that the study comes within the scope of MR003 and MR004, the compliance commitments of Pfizer and Merck allows us to start without the opinion of the French Data Protection Agency (CNIL).

10.7. 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

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2016; 25:2-10.

https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891

- Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR)

http://www.ispor.org/workpaper/practices_index.asp

- Good practices for real-world data studies of treatment and/or comparative effectiveness: Recommendations from the joint ISPOR-ISPE Special Task Force on real-world evidence in health care decision making

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5639372/

- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS)

https://cioms.ch/shop/product/international-ethical-guidelines-for-epidemiological-studies/

- European Medicines Agency (EMA) European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology

http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

- The ENCePP Code of Conduct for scientific independence and transparency in the conduct of pharmacoepidemiological and pharmacovigilance studies

http://www.encepp.eu/code_of_conduct/

- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment

https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071696.pdf

- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM243537.pdf

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Single reference safety document

The current French Summary of Product Characteristics (SPC), will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The single reference safety document should be used by the investigator for prescribing purposes and guidance.

11.2. Pharmacovigilance requirements

PRIMARY DATA COLLECTION REQUIREMENTS (prospective part of the study)

The table below summarizes the requirements for recording safety events on the e-CRF and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Safety event	**Recorded on the** e-CRF	**Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness**
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) Note: Any associated AE is reported together with the exposure scenario.

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a SAE (refer to section "Serious Adverse Events" below).

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to** avelumab. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the e-CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period
For each patient, the serious adverse event reporting period begins at the time of the patient's first dose of avelumab or the time of the patient's informed consent if s/he is being treated with avelumab at study start, and lasts through the end of the observation period of the study, or at least 90 calendar days following the last administration of a drug under study (whichever is longer); a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of serious adverse events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 90 calendar days following the end of observation.

For each patient, the non-serious AE collection period begins at the time of the patient's first dose of avelumab or the time of the patient's informed consent if s/he is being treated with avelumab at study start, and lasts through 90 calendar days following the last administration of a drug under study. After the completion of the active study collection/reporting period of 90-calendar days post-last administration of avelumab, through to the end of the observation period of two years, non-serious AEs are not collected on the e-CRF.

Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient

changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to avelumab, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each AE. For AEs with a causal relationship to avelumab, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that avelumab caused or contributed to an AE. If the investigator's final determination of causality is "unknown" and s/he cannot determine avelumab caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that avelumab did not cause the event, this should be clearly documented on the e-CRF and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE);
- Clinically significant signs and symptoms;
- Changes in physical examination findings;
- Hypersensitivity;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Serious adverse events

A SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;

- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute AEs);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as a SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as a SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as a SAE with severity Grade 5.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance (PV) personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) avelumab, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to avelumab (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to avelumab prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with avelumab, this information must be submitted to Pfizer, irrespective of whether an AE has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to avelumab in a pregnant woman (e.g., a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP Supplemental Form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

<u>Exposure during breastfeeding</u>

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
  - An identifiable reporter;
  - A suspect product;
  - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

SECONDARY DATA SAFETY REPORTING REQUIREMENTS (retrospective part of the study)

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 adverse events (AEs) with explicit attribution to any Pfizer 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 non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the e-CRF and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- 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 Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer 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 research staff members must complete the following Pfizer training requirements:

- *"YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)*".

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 Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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 Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

13. REFERENCES

1. Estimations nationales de l'incidence et de la mortalité par cancer en France métropolitaine entre 1990 et 2018. Synthèse. Saint-Maurice : Santé publique France, 2019. 20 p. http://www.santepubliquefrance.fr/ ; https://geodes.santepubliquefrance.fr/ #c=home ; http://lesdonnees.e-cancer.fr/ ; https://www.e-cancer.fr/.
2. Powles T, Park SH, Voog E, et al. Avelumab Maintenance Therapy for Advanced or Metastatic Urothelial Carcinoma. N Engl J Med. 2020;383(13):1218-1230. doi:10.1056/NEJMoa2002788
3. https://www.pfizer.com/news/press-release/press-release-detail/european-commission-approves-bavencior-avelumab-first-line

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

Number	Title

1	CRF V 2.0 du 25 MAR 2021
2	Information letter V3.0 du 07 JUN 2021
3	Questionnaire EQ-5D-5L
4	Questionnaire FACT FBlSI-18
5	Pregnancy form

ANNEX 2. ADDITIONAL INFORMATION

Not applicable