Non-Interventional Study Protocol
B9991045

AVENANCE - A non-interventional study to provide real-world data on the use of avelumab as a maintenance treatment for patients with advanced or metastatic Urothelial Carcinoma

Statistical Analysis Plan
(SAP)

Version: 1

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ABBREVIATIONS

Abbreviation	Term
ACE	Angiotensin-Converting Anzyme
ADC	Antibody-Drug Conjugate
AE	Adverse Event
AIS	Anti-Inflammatory Steroids
ATU	Autorisation Temporaire d'Utilisation (Temporary Use Authorization)
BSC	Best Supportive Care
ChT	Chemotherapy
CI	Confidence Interval
CR	Complete Response
CRF/eCRF	(electronic) Case Report Form
DOR	Duration Of Response
DOT	Duration Of Treatment
ECOG	Eastern Cooperative Oncology Group
FAS	Full Analysis Set
FU	Follow-Up
HR	Hazard Ratio
IA	Interim Analysis
MAR	Missing At Random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model for Repeated Measures
NE	Not Estimable
NI/NIS	Non-Interventional (Study)
NSAID	Non-Steroidal Anti-Inflammatory Drugs
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease

Abbreviation	Term
PD-L1	Programmed Death Ligand1
PFS	Progression-Free Survival
PPI	Proton Pump Inhibitors
PR	Partial Response
PRO/ePRO	(electronic) Patient-Reported Outcomes
PT	Preferred Term
Q1/Q3	First/Third Quartile
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SD	Stable Disease
SOC	System Organ Class
UC	Urothelial Cancer

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Issue Date	Change Type (New, Revise, Admin)	Summary of Changes
1	02-Dec-2022	New	

2 INTRODUCTION

Note: in this document, any text taken directly from the non-interventional (NI) study protocol is ***italicized***.

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 a 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 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.

2.1 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: Study design).

Inclusion period: expected 18 months to reach sample size.
Target sample size is 500 patients.

1. *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.*
2. *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 hospitalizations. 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.

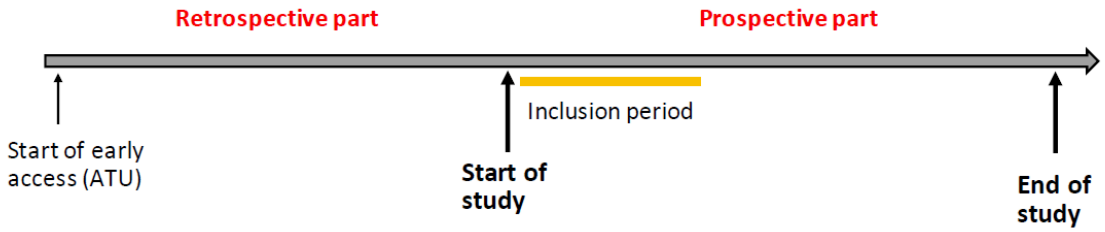

Figure 1: Study design

Study 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 (retrospective), 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 person of trust of the patient must be informed and the patient (during his lifetime) must not be opposed 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.*

Data source:

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.

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.*

2.2 STUDY 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 from the end of ChT 1st line to 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.*

3 INTERIM ANALYSES

A first interim analysis (IA1) will be performed for the population of participants who begun avelumab at least 6 months before the cut-off date of 31 January 2022 (Abstract for ESMO 2022 with associated publication) and then every year for publication purposes.
For the IA1, all efficacy and safety analyses will be presented for this population (8.2) and depending on the maturity of the data at least demographic/baseline characteristics data (8.2.4), time-to-event analyses and safety data (8.2.3) on the whole population (SAF population for safety analyses and FAS population otherwise). Subgroup analyses may be performed depending on the maturity of data and medical interest.

4 HYPOTHESES AND DECISION RULES

4.1 STATISTICAL HYPOTHESES

There are no formal statistical hypotheses for this study.

4.2 STATISTICAL DECISION RULES

All the analyses will be purely descriptive. Two-sided 95% confidence interval will be provided for estimates of primary interest.

5 ANALYSIS SETS/POPULATIONS

5.1 FULL ANALYSIS SET

The full analysis set (FAS) is defined as all enrolled participants who received at least one injection of avelumab. “Enrolled" means a participant, 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.

5.2 SAFETY ANALYSIS SET

The safety analysis set (SAF) is defined as all participants who received at least one injection of avelumab.

5.3 SUBGROUPS

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

- *Main subgroup of interest: histology (UC with variant; UC without variant).*
- *Other subgroups of interest:*
  - Histology (Pure UC; UC with variant, Pure adenocarcinoma, Other, Missing)
  - *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)*
  - *Regrouped best response to 1st line chemotherapy (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),*
  - *Participants with an early relapse on avelumab and participants with a long-term response to avelumab.* Patient is considered as early progressor if PFS is less than 3 months and if progression is observed. Patient is considered as long responder if PFS is equal or higher than 12 months, whatever the outcome.
    This subgroup of interest will be used only for Overall Survival and progression free survival analyses, and baseline characteristics.
  - *Delay between the end of ChT and the start of avelumab (< 4 weeks; between 4 and 10 weeks; >10 weeks),*
  - *Delay between the end of ChT and the start of avelumab (< 4 weeks; ≥ 4 weeks),*
  - *ATU participants versus non ATU participants, 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,*
  - Type of subsequent treatment: Antibody-Drug Conjugate (ADC) treatment, chemotherapy, immunotherapy, targeted therapy, other. This classification will be made thanks to a medical review from Pfizer team.
  - Type of subsequent treatment: ADC versus Other.

Analysis in subgroups will be discussed in function of the number of participants in each subgroup. If too few people are in each subgroup (less than 10 participants), no analysis will be conducted for the corresponding subgroups.

6 ENDPOINTS AND COVARIATES

6.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

6.1.1 Time-to-event endpoints

Variable	Role	Data source(s)	Operational definition
Overall Survival (OS)	Time to Event Outcome (primary endpoint)	Patient medical records and CRF	*Time (month) from the first injection of avelumab to death, whatever the reason +1*
Overall Survival 2	Time to Event Outcome (secondary endpoint)	Patient medical records and CRF	*Time (month) from the first injection of the chemotherapy used in 1st line to death, whatever the reason +1*
Progression Free Survival (PFS)	Time to Event Outcome (secondary endpoint)	Patient medical records and CRF	*Time (month) from the first injection of avelumab to the date of progression or death from any cause +1.*
Progression Free Survival (PFS) 2	Time to Event Outcome (secondary endpoint)	Patient medical records and CRF	*Time (month) from the first injection of avelumab to the date of progression or death from any cause during the 2nd line of treatment post-avelumab +1.*
Objective Response Rate (ORR)	Outcome (secondary endpoint)	Patient medical records and CRF	*Proportion of patients with a Complete Response (CR) or Partial Response (PR) as a best response during the avelumab treatment.*
Duration Of Response uber avelumab (DOR)	Time to Event Outcome (secondary endpoint)	Patient medical records and CRF	*Time (month) from the beginning of the response to progression or death from any cause + 1.*
Duration Of	Time to Event	Patient medical	*Time (month) from the first to last dose of avelumab + 1.*

Treatment (DOT)	Exposure	records and CRF	
Patterns of progression under avelumab	Outcome (secondary endpoint)	Patient medical records and CRF	*Description of metastatic sites and type of progression (new lesion(s)/progression of known lesion(s)).*
OS of subsequent treatment	Time to Event Outcome (secondary endpoint)	Patient medical records and CRF	*Time (month) from the first injection of avelumab-subsequent treatment to death, whatever the reason +1*
PFS of subsequent treatment	Time to Event Outcome (secondary endpoint)	Patient medical records and CRF	*Time (month) from the first injection of avelumab-subsequent treatment to the date of progression or death from any cause +1.*
ORR of subsequent treatment	Outcome (secondary endpoint)	Patient medical records and CRF	*Proportion of participants with a Complete Response or Partial Response as a best response during the avelumab-subsequent treatment.*
DOT of subsequent treatment	Time to Event Exposure	Patient medical records and CRF	*Time (month) from the first to last dose of avelumab-subsequent treatment + 1.*
FBlSI-18 score evolution	Outcome (secondary endpoint)	NCCN/FACT FBlSI-18	*Absolute value and relative change from baseline of PRO evaluation at available timepoints*
EQ-5D-5L score evolution	Outcome (secondary endpoint)	EQ-5D-5L	*Absolute value and relative change from baseline of EQ-5D-5L scores at available timepoints*
EQ VAS evolution	Outcome (secondary endpoint)	EQ-5D-5L	*Absolute value and relative change from baseline of EQ VAS at available timepoints*
Premedication's (acetaminophen and antihistamine)	Outcome (secondary endpoint)	Patient medical records and CRF	*Proportion of participants who received a premedication at each injection of avelumab*

6.1.2 Objective response rate (ORR)

Best response will be calculated with all available response assessments, from study treatment initiation to treatment discontinuation (included) or end of study if no discontinuation.

For best response, the following order will be used (from better outcome to worst) Complete Response (CR) > Partial Response (PR) > Stable Disease (SD) > Not Estimable (NE) > Progressive Disease (PD).

6.1.3 FBlSI-18 score

NCCN-FACT FBlSI-18 is an 18-item questionnaire filled by the participant.
The response to each of the 18 questions is evaluated using a 5-point scale ranging from 0='Not at all' to 4='Very much'. For items negatively framed, scores will be reversed for analysis so that higher scores translate a good quality of life.

6.1.4 EQ-5D-5L score

A participant's score at a specific timepoint will then go from 0 (0=severely symptomatic) to 72 (asymptomatic).
For each participant, a unique Health state score will be created by combining the answer given to each of the 5 dimensions. This score will thus be ranging from 11111 (no problems in any domain) to 55555 (severe problems). This score will be after converted into EQ-5D single utility index values anchored at 0 for death and 1 for perfect health, by applying a formula download from the EQ-5D official website, that essentially attaches values (also called weights) to each of the levels in each dimension.

6.2 SAFETY ENDPOINTS

Adverse events (AE) reported during the study will be coded using the MedDRA terminology (SOC and PT) with the most recent version of MedDRA.

6.3 COVARIATES

Refer to 5.3.

7 HANDLING OF MISSING VALUES

Unless otherwise specified, all data will be evaluated as observed, and missing data will not be imputed.

- The objective response will be the only endpoint with a formal imputation of missing data. Participants who do not have a post-baseline radiographic tumour assessment due to early progression, who receive anti-tumour therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: no OR; 1: OR).
- Time-to-event endpoints will include the observation period before an event of interest or till the censoring date and therefore will be analysed on all participants included in the analysis set.

- Continuous longitudinal data will be analysed using a mixed model for repeated measures. Maximum likelihood estimates will be provided on all participants included in the analysis set without any imputation.

Missing dates or partially missing dates will be imputed conservatively for adverse events and prior/concomitant medications/procedures. Specific rules for handling of missing or partially missing dates for date of birth, adverse events, prior/concomitant medications/procedures, and diagnosis of urothelial carcinoma are provided in 11.1

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

Unless otherwise specified, the following conventions will be applied to all analyses:

- Mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3) values will be formatted to 1 more decimal place than the measured value. Minimum and maximum values will be presented with the same number of decimal places as the measured value.
- Percentages will be rounded to 1 decimal place. Number and percentage values will be presented as xx (xx.x%).
- P-values will be rounded to 4 decimal places. P-values that round to 0.000 will be presented as '< 0.001' and p-values that round to 1.000 will be presented as '> 0.999'.

8.1.1 Analysis of continuous data

Summary statistics will be presented for continuous variables, by way of n, n missing (if any), mean, standard deviation (SD), median, first and third quartiles (Q1 and Q3), minimum and maximum.

8.1.2 Analysis of categorical data

Qualitative/Categorical parameters will be presented in terms of number and percentage of each modality and number of missing and non-missing observations.

Results recorded as "not done" or "unknown" will be considered as missing data and will not be considered in percentage calculation.

8.1.3 Analysis of time-to-event data

Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median survival time with 2-sided 95% CIs. In particular, the survival rate at 3, 6, 9, 12, 15, 18 and 24 months will be estimated with corresponding 2-sided 95% CIs. The CIs for the median will be calculated according

to Brookmeyer and Crowley (Brookmeyer R, 1982) and the CIs for the survival function estimates at the time points defined above will be derived using the log-log transformation according to Kalbfleisch and Prentice (Kalbfleisch JD, 2002) (conftype=loglog default option in SAS Proc LIFETEST) with back transformation to a CI on the untransformed scale. The estimate of the standard error will be computed using Greenwood's formula.
Frequency (number and percentage) of participants with each event type and censoring reasons will be presented.

For each subgroup analysis, comparison of the different modalities to a reference level will be performed using univariate Cox proportional hazard models. Ties will be handled using the Exact option in SAS (Ties=Exact option in SAS PROC PHREG). Results will be expressed in terms of hazard ratios (HR) and a 2-sided 95% CI will be associated to each HR. A HR of 1 equals a lack of association, a HR greater than 1 suggests an increased risk compared to the reference level, and a HR below 1 suggests a decreased risk.

Time of follow-up for each event (OS and PFS)
A Kaplan-Meier estimation for follow-up duration will also be generated to assess the follow-up time reversing the censoring and event indicators.

Handling of left truncation and right censoring:
The overall survival from the first injection of the chemotherapy used in 1st line will cover
a retrospective and/or prospective data collection period. The time to event of interest ("survival" time) or censoring if no event occurs (right censoring) will be based on the 1st line of chemotherapy start date at a time-point preceding the study entry (avelumab start date). As a result, only participants who are still alive are included in the study. Therefore, the time from 1st line of chemotherapy start date to avelumab start date is called immortal time and corresponds to a left truncation in survival analyses.
The distribution of an estimator which is both left-truncated and right censored can be estimated using the estimator of Kaplan and Meier (Klein, 1997). The likelihood of conditional survival will be estimated as $Sa(t) = Pr[X > t \mid X \geq a]$. Occurrence of an event will be studied over time t (the time since the start date) conditional on being free of this event at study entry where a represents the time from the start date to inclusion into the study. This is estimated as follows:

$$\widehat{S_a}(t) = \prod_{a \leq t_i \leq t} \left\{1 - \frac{d_i}{Y_i}\right\}, t \geq a$$

where d represents the number of events and Y represents the risk set.

In addition, the Kaplan-Meier estimator does not work well when the size of the risk set is extremely small. This may occur at the end of the curve when right censorings are

present and also at the start of the curve if left truncation of data occurs. This latter situation confers early instability in the point estimator of the survival function which may propagate throughout the entire curve. Lai and Ying (Lai, 1991) suggested a solution to this problem by a slight modification of the Kaplan-Meier estimator where events are ignored when the risk set is small:

$$\widehat{S_a}(t) = \prod_{a \leq t_i \leq t} \left\{1 - \frac{d_i}{Y_i} I[Y_i \geq cn^{\alpha}]\right\}, t \geq a$$

where I represents an indicator, n represents the population size and c and α represent constant values. These constant values are used to define a minimum risk set size below which the events are not counted. This minimum risk set size is usually defined in terms of the size n of the study population but for study B9991045, the constants will be set arbitrarily to ensure that the minimum risk set size is equal to 5. The method proposed by Lai and Ying therefore will only be effective for portions of the Kaplan-Meier curve in which the risk set does not exceed 5 participants. This analysis will be performed using the SAS® PROC HPSEVERITY procedure.

8.1.4 Analysis of continuous longitudinal data

Changes from baseline at specified follow-up assessment time points will be analyzed using a mixed model for repeated measures (MMRM) under the MAR framework. Analyses will include the fixed, categorical visit (including baseline). An unstructured (co)variance structure will be used to model the within-participant errors. If this analysis fails to converge, the following structures will be tested: a heterogeneous Toeplitz covariance structure followed by the heterogeneous first-order autoregressive covariance structure will be considered. The covariance structure converging to the best fit, as determined by Akaike's information criterion, will be used as the primary analysis. The Kenward-Roger approximation will be used to estimate de-nominator degrees of freedom. Mean changes from baseline will be assessed using appropriate contrasts of least-squares means. Two-sided 95% confidence intervals will be provided.

8.2 STATISTICAL ANALYSES

All analyses will be at least provided overall and by histological status (UC with variant; UC without variant). For some effectiveness endpoints, additional subgroup analyses will be specified hereafter.

8.2.1 Primary criterion analyses

The primary criterion is the Overall Survival, evaluated in the FAS.
This criterion will be analyzed using the Kaplan-Meier method and survival curves will be presented. The starting date to be used is the date of first intake of study treatment.

The censoring and event date options to be considered for the OS analysis are defined as follows:

Table 1: Event Date and Outcome for Overall Survival

Scenario	Date of Event/Censoring	Outcome
Death during study	Date of death	Event
Death after treatment discontinuation	Date of death	Event
Alive	Date of last contact	Censored
Lost to follow-up	Date of last contact	Censored

OS will also be described by subgroup (See section 5.3 for subgroup definition).

8.2.2 Secondary criteria analyses

8.2.2.1 Overall survival 2

For OS since chemotherapy initiation, endpoint will be analyzed using survival analysis method, using the same censorship as for primary criterion (Table 1), in the FAS. The starting date to be used is the date of first intake of chemotherapy as reported in the medical history. To avoid any immortal time bias between first intake of chemotherapy and the start of study treatment (avelumab), a modified Kaplan-Meier estimator will be provided using right censoring and left truncation, stabilising the estimates when small samples (n< 5) are present (Lai and Ying method – See section 8.1.3).

8.2.2.2 Progression free survival (PFS)

The PFS will be analyzed using survival analysis method, in the FAS, using the following table for censorship, and date of first study treatment intake as starting date.

Table 2: Event Date and Outcome for PFS

Scenario	Date of Event/Censoring	Outcome
Progression recorded before discontinuation of treatment	Progression date	Event
Death (without any previous recorded progression of treatment)	Death Date	Event
Final discontinuation of treatment during the study before any progression or death	Treatment Discontinuation Date	Censored
Lost to follow-up or early study discontinuation without progression or death	Last News Date	Censored

PFS will also be described by subgroup (See section 5.3 for subgroup definition).

8.2.2.3 Progression Free Survival (PFS) 2

For PFS 2, endpoint will be analyzed using a survival analysis, in the FAS, using the following table for censorship, and date of first study treatment intake as starting date. For this analysis, only participants who initiated a 2nd line post-avelumab systemic treatment will be considered. Local treatments as radiotherapy are not considered as second line post-avelumab.

Table 3: Event Date and Outcome for PFS

Scenario	Date of Event/Censoring	Outcome
Progression recorded during 2nd line of post-avelumab treatment	Progression date	Event
Death (without any previous recorded progression of treatment) during 2nd line of post-avelumab treatment	Death Date	Event
Final discontinuation of 2nd line of post-avelumab treatment during the study before any progression or death	Treatment Discontinuation Date	Censored
Lost to follow-up or early study discontinuation without progression, death or 2nd line of post-avelumab treatment discontinuation	Last News Date	Censored

8.2.2.4 Objective response rate (ORR)

ORR will be described overall and by subgroup defined in section 5.3.
Participants who do not have a post-baseline radiographic tumor assessment due to early progression, who receive anti-tumor therapies other than the study treatments prior to reaching a CR or PR, or who die, progress, or drop out for any reason prior to reaching a CR or PR will be counted as non-responders in the assessment of OR. Each participant will have an objective response status (0: no OR; 1: OR). OR rate (ORR) is the proportion of participants with OR in the FAS.
ORR will be calculated along with the 2-sided 95% CI using the Clopper-Pearson method (exact CI for a binomial proportion as computed by default by the FREQ procedure using the EXACT option).
ORR will also be described by subgroup (See section 5.3 for subgroup definition).

8.2.2.5 Duration of response (DOR)

For DOR, endpoint will be analyzed using a survival analysis, in the FAS, using the following table for censorship, and date of first response (Complete Response or Partial Response) as starting date.

Table 4: Event Date and Outcome for DORs

Scenario	Date of Event/Censoring	Outcome
Tumor assessment with a reported progressive disease, after response was observed.	Progression Date	Event
Death (whatever the cause) without treatment discontinuation	Death Date	Event
No reported progressive disease during the study nor death.	Last News Date	Censored
Lost to follow-up or early study discontinuation without stopping treatment	Last News Date	Censored
Treatment discontinuation	Discontinuation Date	Censored

DOR will also be described by subgroup (See section 5.3 for subgroup definition).

8.2.2.6 Duration of treatment (DOT)

DOT will be analyzed using a survival analysis, in the FAS, using the following table for censorship, and date of first study treatment intake as starting date.

Table 5: Event Date and Outcome for DOTs

Scenario	Date of Event/Censoring	Outcome
Permanent Treatment discontinuation	Discontinuation Date	Event
Death (whatever the cause)	Death Date	Event
No permanent discontinuation reported at the end of the study	Last News Date	Censored
Lost to follow-up or early permanent study discontinuation without stopping treatment	Last News Date	Censored

DOT will also be described by subgroup (See section 5.3 for subgroup definition).

8.2.2.7 Patterns of progression under avelumab

Progression under avelumab will be described:

- Progression of known lesions, target, or non-target (Yes/No)
  - If 'No', description of the site for the new lesions.

8.2.2.8 OS of subsequent treatment

For OS of subsequent treatment, endpoint will be analyzed thanks to survival analysis method, using the same censorship as for primary criterion (Table 1). The analysis will be

made in the FAS for participants receiving at least one dose of subsequent treatment. The starting date to be used is the date of first intake of subsequent treatment.
The subsequent treatment is defined as the line of treatment following the maintenance with avelumab.

8.2.2.9 PFS of subsequent treatment

For PFS of subsequent treatment, endpoint will be analyzed using survival analysis method, in the FAS for participants receiving at least one dose of subsequent treatment, using the following table for censorship, and date of first intake of subsequent treatment starting date.

Table 6: Event Date and Outcome for PFSs

Scenario	Date of Event/Censoring	Outcome
Progression recorded before discontinuation of subsequent treatment (and after initiation)	Progression date	Event
Death (without any previous recorded progression of disease)	Death Date	Event
Final discontinuation of subsequent treatment during the study before any progression or death	Treatment Discontinuation Date	Censored
Lost to follow-up or early study discontinuation without progression or death	Last News Date	Censored

8.2.2.10 ORR of subsequent treatment

ORR will be described and analyzed according to the specifications mentioned in section 8.2.2.4.

8.2.2.11 DOT of subsequent treatment

For DOT, endpoint will be analyzed using survival analysis, in the FAS, using the following table for censorship, and date of first intake of subsequent treatment starting date.

Table 7: Event Date and Outcome for DOTs

Scenario	Date of Event/Censoring	Outcome
Treatment discontinuation	Discontinuation Date	Event
Death (whatever the cause)	Death Date	Event
No discontinuation reported at the end of the study	Last News Date	Censored

Lost to follow-up or early study discontinuation without stopping treatment	Last News Date	Censored

8.2.2.12 FBlSI-18 score

Scores will be described at the following timepoint:

- Avelumab initiation (baseline)
- After initiation if the participant is still treated with avelumab:
    - 6 weeks,
    - 3 months,
    - Every three months for up to 2 years,
    - Tumor progression if so,
- Avelumab discontinuation (whatever the reason is).

The FBlSI-18 score will be analyzed using a MMRM based on the windowing defined in section 11.1.1.

8.2.2.13 EQ-5D-5L score

EQ-5D-5L score will be described at the same timepoints as FBlSI-18 score and will be analyzed using a MMRM. based on the windowing defined in section 11.1.1.

8.2.2.14 EQ VAS

EQ VAS will be described at the same timepoints as FBlSI-18 score and will be analyzed using a MMRM based on the windowing defined in section 11.1.1

8.2.2.15 Premedication

For this endpoint, descriptive statistics for the number of participants pre-medicated with acetaminophen and/or antihistamine will be presented at each injection/cycle. Furthermore, the participant's global number of cycles with pre-medication will also be presented (with one global value per participant), with absolute value and relative value (number of cycles with pre-medication / number of cycles received by the participant * 100).

8.2.3 Safety analyses

Safety analyses will be performed on the safety analysis set (SAF), by histology group (Pure adenocarcinoma / Pure urothelial carcinoma / Urothelial carcinoma with variant / Other / Missing) and overall. Additional summary of adverse events by type of subsequent treatment (ADC / Chemotherapy / Immunotherapy / Targeted therapy / Other) will be made.

Analyses of use of avelumab

Patterns of use of avelumab, such as treatment duration and exposure, temporary and final discontinuation, prescribed doses, reasons for changes will be described.

Treatments prescribed in combination with tofacitinib (pre-specified categories) and after possible treatment discontinuation will also be described.

Adverse events

A summary table of adverse events will be provided including:

- Number of participants with at least one AE,
- Number of participants with at least one Treatment-Emergent AE (TEAE),
- Number of participants with at least one serious AE
- Number of participants with at least one non-serious AE
- Number of participants with at least one AE leading to interruption or discontinuation,
- Number of participants with at least one AE leading to death.

An overall summary table of AE information, classified by SOC and PT, will be presented to summarize the frequencies and percentages of participants experiencing one or more of the following:

- AEs,
- TEAEs,
- Serious AEs,
- Non-serious AEs,
- Non-serious AEs in ≥ 10% of subjects,
- AEs leading to interruption or discontinuation,
- Related AEs leading to death.

If a participant has more than one occurrence of the same PT, the participant will be counted only once within that preferred term in the summary tables.
AE tables will be sorted by descending frequency of SOC and then within each SOC by descending frequency of PT.

The summary tables and descriptions by SOC and PT will be performed for all collected AEs and then for AEs which are collected prospectively or are retrospective and related to avelumab.

The duration of these adverse events will be described in a summary table and a listing.

8.2.4 Further descriptive analyses

In addition to the analyses above-mentioned, the following descriptive analyses will be conducted to describe inclusions and follow-up visits:

- Number of participants included,
- Number of participants excluded from the analyses and reason for exclusion,
- Deviation to protocol,
- Flow chart of participants' inclusions
- Number of participants with progression/dead/alive at time of analysis.
- Number of participants 'Lost to Follow-up'
- Number of participants withdrawn from the study.

Early treatment discontinuation before progression together with reason for discontinuation will be described.

Finally, demography and baseline characteristics will be described in the Full Analysis Set and in the Safety Analysis Set, by histology group (Pure adenocarcinoma / Pure urothelial carcinoma / Urothelial carcinoma with variant / Other / Missing) and overall. Additional demography will be provided by patient's progression status (see section 5.3) and by type of subsequent treatment (ADC versus other, see section 5.3).

8.2.5 Summary of analyses

Outcome	Analysis Set	Supports Protocol Objective Number	Subgroups	Statistical Method	Covariates/ Strata	Missing Data
OS	FAS	1	NA	Kaplan-Meier	NA	Excluded
OS	FAS	1	See section 5.3	Kaplan-Meier	NA	Excluded
OS 2	FAS	2	NA	Kaplan-Meier	NA	Excluded
PFS	FAS	2	NA	Kaplan-Meier	NA	Excluded
PFS 2	FAS	2	NA	Kaplan-Meier	NA	Excluded
ORR	FAS	2	NA	Descriptive statistics	NA	Excluded
DOR	FAS	2	NA	Kaplan-Meier	NA	Excluded
DOT	FAS	2	NA	Kaplan-Meier	NA	Excluded
Progression description	FAS	2	NA	Descriptive statistics	NA	Excluded
OS subsequent	FAS	2	NA	Kaplan-Meier	NA	Excluded
PFS subsequent	FAS	2	NA	Kaplan-Meier	NA	Excluded
ORR subsequent	FAS	2	NA	Descriptive statistics	NA	Excluded
DOT subsequent	FAS	2	NA	Kaplan-Meier	NA	Excluded
FBISI-18 score	FAS	2	NA	Descriptive statistics + MMRM	NA	Excluded
EQ-5D-5L score	FAS	2	NA	Descriptive statistics + MMRM	NA	Excluded
EQ-VAS score	FAS	2	NA	Descriptive statistics + MMRM	NA	Excluded
Premedication	FAS	2	NA	Descriptive statistics	NA	Excluded
Safety analyses	SAF	2	Histological group Subsequent treatment category	Descriptive statistics	NA	Excluded
Baseline characteristics	FAS & SAF	2	Progression status Subsequent treatment category	Descriptive statistics	NA	Excluded

9 LIST OF TABLES AND TABLE SHELLS

Please refer to the Excel file CT24-WI-GL14-RF04 2.0 Non-Interventional Study List of Tables 01-Jul-2019.xlsx

10 REFERENCES

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11 APPENDICES

11.1 APPENDIX 1: DATA DERIVATION DETAILS

11.1.1 Definition and use of visit windows in reporting

Data will be summarized in tables by visit (timepoint) when applicable. The following visit label and visit windows will be applied for all PRO endpoints:

Visit Label	Target Day	Visit Window
Baseline	1	Day 1 or before
Week 6	42	Day 2 to Day 66
Month 3	91	Day 67 to Day 137
Month 6	183	Day 138 to Day 228
Month 9	274	Day 229 to Day 320
Month 12	365	Day 321 to Day 410
Month 15	456	Day 411 to Day 501
Month 18	548	Day 502 to Day 593
Month 21	639	Day 594 to Day 684
Month 24	730	Day 685 to Day 775

In case of multiple observations falling within a given window, the observations selected for analysis will be identified as follows:

1. The observation closest to the target day will be used.
2. If the observations are at equal distance from the target day in absolute value, the one with a correct nominal visit label will be used.

3. If neither (1) nor (2) can be used to identify the observation windowing, then the latest observation within the analysis window will be used.

11.1.2 Imputation of missing/partially missing dates

Missing data will not be imputed unless otherwise specified.

Age: The day is not recorded in the eCRF and will be defaulted to the 1st day of the month specified in the eCRF. If the month field is missing, impute missing day and month as July 1st. If the year field is missing, age will be set as missing.

For safety analyses, incomplete date of last dose of study drug and incomplete start date of a new antitumor treatment for urothelial carcinoma that are missing the day of the month, the 15th of the month will be used to impute the missing data. When imputing partial last dose dates, the last assessment date and death date will be taken into consideration. This imputation rule will be used to determine the treatment-emergent period.

Adverse Events and Concomitant Medications:
The imputation rule for the safety analyses will be used to address the issues with partial dates. The imputed dates will be used to determine the treatment-emergent period. For adverse events with a partial date, available date parts (year, month, and day) of the partial date will be compared with the corresponding date components of the start date and end date of the treatment-emergent period to determine if the event is treatment emergent. When in doubt, the adverse event will be considered treatment emergent by default. The following rules will be applied to impute partial dates for adverse events:

If start date of an adverse event is partially missing, impute as follows:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date
- If both month and day are missing and year ≠ year of treatment start date, then set to January 01
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date
- If day is missing and month and year ≠ month and year of treatment start date, then set to first of the month
- If start date is completely missing, set to treatment start date as long as adverse event end date is not before treatment start date

If end date of an adverse event is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

- If end date is completely missing, do not impute

When the start date or end date of a medication is partially missing, the date will be imputed to determine whether the medication is prior or concomitant (or both). The following rules will be applied to impute partial dates for medications:

If start date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to January 01
- If only day is missing, then set to the first of the month

If end date of a medication is partially missing, impute as follows:

- If both month and day are missing, then set to December 31
- If only day is missing, then set to last day of the month

If start date or end date of a medication is completely missing, do not impute.

Diagnosis of urothelial carcinoma

If the diagnosis date of urothelial carcinoma is partially missing, the following rules will be applied to impute partial dates:

- If both month and day are missing and year = year of treatment start date, then set to treatment start date.
- If both month and day are missing and year ≠ year of treatment start date, then set to December 31.
- If day is missing and month and year = month and year of treatment start date, then set to treatment start date.
- If day is missing and month and year ≠ month and year of treatment start date, then set to the last day of the month.