Retrospective, Multicenter, Observational Study to Evaluate Current Treatment patterns and Outcomes in Japanese Patients with Locally Advanced or Metastatic Urothelial Carcinoma Treated with First-line Avelumab Maintenance

Principal Investigator

PPD

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Statistical Analysis Plan (SAP)

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Research Sponsor Medical Affairs, Oncology, Pfizer Japan Inc.	Approval date :
Chief statistical analyst CR Data Science Department, Clinical Research Center, Real World Evidence Business Headquarters, EPS Co., Ltd.	Approval date :

Table of Contents

1 PURPOSE

The purpose of this statistical analysis plan is to define the details of statistical methods for the statistical analysis activities related to "Retrospective, Multicenter, Observational Study to Evaluate Current Treatment patterns and Outcomes in Japanese Patients with Locally Advanced or Metastatic Urothelial Carcinoma Treated with First-line Avelumab Maintenance - (Protocol No.: B9991048)" (hereinafter referred to as "Study").

2 Analysis Environment

2.1 Statistical analysis, tabulation software

The software and version expected to be used are shown below. The software and version eventually used should be clearly stated in the analysis results.

Items	Software and Version
OS	Microsoft Windows 10
Statistical analysis software	SAS Ver. 9.4
Tabulation software	Microsoft Excel 365

3 Overview of Study Design

3.1 Primary objectives

To describe the demographic and baseline disease characteristics of patients with locally advanced or metastatic UC treated with avelumab as 1L maintenance therapy in a real-world clinical setting.

3.2 Secondary objectives

1) To evaluate the effectiveness of 1L avelumab maintenance therapy for patients with locally advanced or metastatic UC treated in Japan.
2) To describe clinical usage of corticosteroid for immune-related adverse events (irAEs) observed during avelumab therapy and after the last administration of avelumab therapy.
3) To describe premedication and treatment for infusion-related reaction of avelumab.
4) To describe the patterns of subsequent UC therapy.

3.3 Study design

This study is a multicenter, non-interventional, retrospective, medical chart review of

locally advanced or metastatic UC patients who were prescribed avelumab as 1L maintenance therapy between 24 February 2021 and 30 November 2021 in Japan. All decisions regarding clinical management and treatment of the participating patients were made by the investigator as part of standard care in a real-world clinical setting and were not contingent upon the patient's participation in the study. Data will be collected if available per study site.

- Index date: The date of first prescription for avelumab between 24 February 2021 (launch date of avelumab) and 30 November 2021
- Observation period: Patients will be followed from index date to 30 Jun 2022

4 Endpoints

4.1 Primary endpoint

・Patient characteristics at baseline (at the initiation of first line chemotherapy and the initiation of avelumab maintenance therapy)

4.2 Secondary endpoints

Efficacy endpoints

・Time to treatment failure (TTF) of avelumab
・Real-world progression-free survival (rwPFS)
・Objective Response Rate (ORR)
・Real-world progression-free survival from chemotherapy (rwPFS-c)

Safety endpoints

・Corticosteroid therapy for immune-related adverse events (irAEs)
・Premedication for potential infusion-related reaction of avelumab
・Treatment for infusion-related reaction of avelumab
・Regimen after avelumab maintenance therapy
・Hematological test (At the start of first-line chemotherapy/ immediately before the first

avelumab administration/ at the start of fourth cycle of avelumab treatment/ at the time of PD judgment (at the latest test during the observation period for those continuing avelumab treatment without disease progression)

5 Handling of study population and data

5.1 Analysis set/populations

Among patients who were enrolled in the study and received maintenance avelumab treatment between 24 February 2021 and 30 November 2021, patients meeting all the inclusion criteria will be analyzed.

5.2 Handling of missing values

An absence of data for analysis will be treated as missing values, and no special imputation processing will be performed using statistical methods.

However, if there are specifications for handling of missing values in subsequent each specification, they are followed.

5.3 Handling of data on the number of days

The number of days from the start date to the target date will be calculated as follows:

・The target date is earlier than the start date = Target date － Start date

・The target date is on or after the start date = Target date － Start date + 1

If the data for "year" and "month" among the date data are missing, no calculation will be performed.

If the data on "day" of the date is missing, data will be substituted by 1.

The number of days in one month is converted to 30.

5.4 Steroid equivalent dose (prednisolone-equivalent dose)

The corticosteroid-equivalent dose (prednisolone-equivalent) is calculated as the dose of the starting drug × prednisolone conversion ratio, according to the table below.

General name	Corresponding dose (mg)	Prednisolone conversion ratio
Cortisone	25	0.2
Hydrocortisone	20	0.25
Prednisolone	5	1
Methylprednisolone	4	1.25
Triamcinolone	4	1.25

Dexamethasone	Approximately 0.75	6.67
Betamethasone	Approximately 0.75	6.67

5.5 Derived variable

The items and definitions of variables whose derivation is necessary at the time of statistical analysis are shown below.

Continuous variable

Item	Derivation method
Treatment-free interval: Time from the end date of first-line chemotherapy to the start date of avelumab administration (days)	Start date of initial administration with avelumab – end date of first-line chemotherapy administration + 1
Duration of treatment of first-line chemotherapy (days)	End date of first-line chemotherapy administration – start date of first-line chemotherapy administration + 1
Duration of treatment (irAE treatment) of corticosteroid (days)	End date of corticosteroid administration – start date of corticosteroid administration + 1
Time to treatment failure of avelumab (TTF)	Defined as the period from the date of start of avelumab to the date of end of treatment* for any reasons including death. If there is no record of end of treatment, patients will be censored at the date of last observation during the study period. *The following sensitivity analysis will also be performed. Considering its clinical meaning, "interruption due to being well-controlled" does not correspond to "treatment failure"; it should be treated as an event on the day when the death or discontinuation was observed prior to the last observation date. If no death or discontinuation occurred before the date of the last observation, data will be censored at the date of the last observation.
Real-world progression-free survival (rwPFS)	Defined as the period from the start date of avelumab maintenance therapy to the date of first

	disease progression (clinical evaluation based on imaging examinations, laboratory tests, and pathological tests, as well as other evaluations by the investigators of each institution) or death from any cause, whichever occurs earlier. If there is no record of death or disease progression, patients on second or later lines (following avelumab maintenance therapy) will be censored at the start of the second-line treatment, and patients on only avelumab maintenance therapy will censored at the date of the last visit during the study, based on the medical record.
Real-world progression-free survival from chemotherapy (rwPFS-c)	Defined as the period from the start date of first-line chemotherapy to the date of first disease progression (clinical evaluation based on imaging examinations, laboratory tests, and pathological test, as well as other evaluations by the investigators of each institution) or death from any cause, whichever occurs earlier. If there is no record of death or disease progression, patients on second or later lines (following avelumab maintenance therapy) will be censored at the start of the second-line treatment, and patients on only avelumab maintenance therapy will censored at the date of the last visit during the study, based on the medical record.
Starting dose of corticosteroid (Steroid equivalent dose)	Calculate according to "5.4 Steroid equivalent dose (prednisolone-equivalent dose."
Duration of treatment of corticosteroid (days)	Last administration date – date of first administration of the first steroid drug + 1
Duration of treatment of avelumab maintenance (days)	Last administration date – date of first administration + 1.
Duration of treatment of each regimen (days)	Last administration date – date of first administration + 1.

Categorical variable

Item	Derivation method
Age (2 divisions)	Age is divided into the following categories: <65 years/65 years or older
Site of primary tumor (2 divisions)	The primary site is divided into the following categories: "upper urinary tract" for renal pelvis or ureter "lower urinary tract" for bladder and urethra
Tumor histological type (2)	The histological types are divided into the following categories. "Urothelial carcinoma" for urothelial carcinoma "Non-urothelial carcinoma" for adenocarcinoma, squamous cell carcinoma, small cell carcinoma, or others
Presence or absence of visceral metastasis	"Presence" will be selected if the metastatic site is "lung," "liver," "adrenal gland," "pancreas," "kidney," "spleen," or "other" which is regarded as visceral metastasis. If the metastatic site is not regarded as visceral metastasis, "absence" will be selected.
Presence or absence of non-visceral metastasis	" Presence" will be selected if the metastatic site is "bone," "distant lymph nodes," or "other" which is regarded as non-visceral metastasis. If the metastatic site is not regarded as non-visceral metastasis, "absence" will be selected.
ECOG Performance Status at start of first-line chemotherapy (1) *For at the start of avelumab administration, " at the start of first-line chemotherapy administration" should be read as "at the start of avelumab administration."	ECOG Performance Status at start of first-line chemotherapy is categorized as follows. 0/1 or higher
Performance Status at start of first-line chemotherapy (2) *For at the start of avelumab	ECOG Performance Status at start of first-line chemotherapy is categorized as follows. 0/1/2 or higher

<table>
<tr><td>administration, " at the start of first-line chemotherapy administration" should be read as "at the start of avelumab administration."</td><td></td></tr>
<tr><td>Number of cycles in first-line chemotherapy (3 divisions)</td><td>Number of cycles in first-line chemotherapy is divided into the following categories.
3 or less/4 to 6/7 or more</td></tr>
<tr><td>Karnofsky performance status (2 divisions)</td><td>Karnofsky performance status is divided into the following categories.
<80%/>=80%</td></tr>
<tr><td>Bajorin risk classification</td><td>Bajorin risk classification is categorized as follows based on the number of risk factors.
<Risk factors>
・Visceral metastasis is "present"
・Karnofsky performance status is "<80%"
If there is no risk factor, "0 (no risk factor)".
If there is one risk factor, "1 (single risk factor)".
If there are two risk factors, "2 (two risk factors)".</td></tr>
<tr><td>Clinical stage classification: Bladder</td><td>Clinical stage is categorized using primary tumor (T factor), reginal lymph nodes (N factor), distant metastasis (M factor) as follows.
<table>
<tr><th>Primary tumor (T factor)</th><th>Reginal lymph nodes (N factor)</th><th>Distant metastasis (M factor)</th><th>Clinical stage</th></tr>
<tr><td>Ta</td><td>N0</td><td>M0</td><td>0a</td></tr>
<tr><td>Tis</td><td>N0</td><td>M0</td><td>0is</td></tr>
<tr><td>T1</td><td>N0</td><td>M0</td><td>I</td></tr>
<tr><td>T2a, T2b</td><td>N0</td><td>M0</td><td>II</td></tr>
<tr><td>T3a, T3b, T4a</td><td>N0</td><td>M0</td><td>IIIA</td></tr>
<tr><td>T1, T2a, T2b, T3a, T3b, T4a</td><td>N1</td><td>M0</td><td>IIIA</td></tr>
<tr><td>T1, T2a, T2b, T3a, T3b, T4a</td><td>N2、N3</td><td>M0</td><td>IIIB</td></tr>
<tr><td>T4b</td><td>Any N</td><td>M0</td><td>IVA</td></tr>
<tr><td>Any T</td><td>Any N</td><td>M1a</td><td>IVA</td></tr>
<tr><td>Any T</td><td>Any N</td><td>M1b</td><td>IVB</td></tr>
</table></td></tr>
<tr><td>Clinical stage classification:</td><td>Clinical stage is categorized using primary tumor (T</td></tr>
</table>

<table>
<tr><td>Urethra</td><td>factor), reginal lymph nodes (N factor), distant metastasis (M factor) as follows.
<table>
<tr><th>Primary tumor (T factor)</th><th>Reginal lymph nodes (N factor)</th><th>Distant metastasis (M factor)</th><th>Clinical stage</th></tr>
<tr><td>Ta</td><td>N0</td><td>M0</td><td>0a</td></tr>
<tr><td>Tis</td><td>N0</td><td>M0</td><td>0is</td></tr>
<tr><td>T1</td><td>N0</td><td>M0</td><td>I</td></tr>
<tr><td>T2</td><td>N1</td><td>M0</td><td>II</td></tr>
<tr><td>T1, T2</td><td>N1</td><td>M0</td><td>III</td></tr>
<tr><td>T3</td><td>N0, N1</td><td>M0</td><td>III</td></tr>
<tr><td>T4</td><td>N0, N1</td><td>M0</td><td>IV</td></tr>
<tr><td>Any T</td><td>N2</td><td>M0</td><td>IV</td></tr>
<tr><td>Any T</td><td>Any N</td><td>M1</td><td>IV</td></tr>
</table></td></tr>
<tr><td>Clinical stage classification:
Renal pelvis, Ureter</td><td>Clinical stage is categorized using primary tumor (T factor), reginal lymph nodes (N factor), distant metastasis (M factor) as follows.
<table>
<tr><th>Primary tumor (T factor)</th><th>Reginal lymph nodes (N factor)</th><th>Distant metastasis (M factor)</th><th>Clinical stage</th></tr>
<tr><td>Ta</td><td>N0</td><td>M0</td><td>0a</td></tr>
<tr><td>Tis</td><td>N0</td><td>M0</td><td>0is</td></tr>
<tr><td>T1</td><td>N0</td><td>M0</td><td>I</td></tr>
<tr><td>T2</td><td>N0</td><td>M0</td><td>II</td></tr>
<tr><td>T3</td><td>N0</td><td>M0</td><td>III</td></tr>
<tr><td>T4</td><td>N0</td><td>M0</td><td>IV</td></tr>
<tr><td>Any T</td><td>N1、N2</td><td>M0</td><td>IV</td></tr>
<tr><td>Any T</td><td>Any N</td><td>M1</td><td>IV</td></tr>
</table></td></tr>
<tr><td>Treatment-free interval: Time from the end date of first-line chemotherapy to the start date of avelumab administration (3 divisions)</td><td>Time from the end date of first-line chemotherapy to the start date of avelumab administration is divided into the following categories.
<4 weeks/4 to 10 weeks/>10 weeks</td></tr>
<tr><td>Response (avelumab maintenance)</td><td>Determination of the best overall response to avelumab maintenance is categorized as following:
"Objective response" when "CR" or "PR."
"Non-objective response" when "SD" of "PD"</td></tr>
<tr><td>Response (first-line chemotherapy)</td><td>Determination of the best overall response to first-line chemotherapy is categorized as following:</td></tr>
</table>

	"Objective response" when "CR" or "PR." "Non-objective response" when "SD" of "PD"
Best overall response to first-line chemotherapy (2)	Determination of the best overall response to first-line chemotherapy is categorized as following: CR＋PR/SD
Presence or absence of prednisolone	"Presence" will be selected when "prednisolone" is selected for the corticosteroid administration drug name, and "absence" will be selected when "No" is selected for the drug name.
Presence or absence of methylprednisolone	"Presence" will be selected when "methylprednisolone" is selected for the corticosteroid administration drug name, and "absence" will be selected when "No" is selected for the drug name.
Presence or absence of betamethasone	"Presence" will be selected when "betamethasone" is selected for the corticosteroid administration drug name, and "absence" will be selected when "No" is selected for the drug name.
Presence or absence of dexamethasone	"Presence" will be selected when "dexamethasone" is selected for the corticosteroid administration drug name, and "absence" will be selected when "No" is selected for the drug name.
Presence or absence of hydrocortisone	"Presence" will be selected when "hydrocortisone" is selected for the corticosteroid administration drug name, and "absence" will be selected when "No" is selected for the drug name.
Presence or absence of others	"Presence" will be selected when "other" is selected for the corticosteroid administration drug name, and "absence" will be selected when "No" is selected for the drug name.
Presence or absence of treatment with non-high-dose corticosteroid	"Absence" will be selected if the prednisolone-equivalent starting dose is 40 mg or higher. "Presence" will be selected if it is less than 40 mg.
Presence or absence of treatment with high-dose corticosteroid	"Absence" will be selected if the prednisolone-equivalent starting dose is less than 40 mg. "Presence" will be selected if it is 40 mg or higher.

Presence or absence of steroid pulse therapy	"Absence" will be selected if the prednisolone-equivalent starting dose is less than 625 mg. "Presence" will be selected if it is 625 mg or higher.
NLR	Neutrophil count (/μL)/lymphocyte count (/μL)
Hematological test (Red blood cell count, hemoglobin, hematocrit, white blood cell count, neutrophil count, eosinophil, basophil, monocyte, lymphocyte, platelet count, CRP, total protein, albumin, AST, ALT, LDH, BUN, creatinine, Na, K, Cl, NLR (2 divisions)	Hematological test (Red blood cell count, hemoglobin, hematocrit, white blood cell count, neutrophil count, eosinophil, basophil, monocyte, lymphocyte count, platelet count, CRP, total protein, albumin, AST, ALT, LDH, BUN, creatinine, Na, K, Cl, NLR) is categorized as following: < median/≥ median
Hemoglobin (g/dL) (2)	Hemoglobin is divided into the following categories: <10 g/dL/>=10 g/dL
White blood cell count (2)	White blood cell count is divided into the following categories: <8000/μL/>=8000/μL
NLR (2)	NLR is divided into the following categories: <3/>=3
NLR (3)	NLR at the start of the first-line chemotherapy and at the start of first cycle of avelumab is divided into the following categories, regarding NLR at the start of first cycle of avelumab as a starting point. "Low→Low" when changed from NLR <3 (Low) to NLR <3 (Low), "Low→High" when changed from NLR <3 (Low) to NLR ≥3 (High), "High→Low" when changed from NLR ≥3 (High) to NLR <3 (Low), "High→High" when changed from NLR ≥3 (High) to NLR ≥3 (High)

5.6 Variable conversion

No variable conversion is performed.

6 Statistical processing

6.1 Confidence interval/significance level

The significance level of hypothesis testing will be two-sided 5%. A two-sided 95% confidence interval will be calculated if interval estimation is performed.

6.2 Multiple comparisons/multiplicity

Multiplicity will not be adjusted.

6.3 Details of statistical analysis

6.3.1 Summary statistics

If summary statistics is described in this plan, the following values will be calculated unless otherwise specified.

Number of subjects, number of subjects with missing, mean, standard deviation, minimum value, quartile point (25% point, 50% point [median], 75% point), maximum value

6.3.2 Number of digits

Percentages will be rounded to 1 decimal place for the fraction distribution, unless the details of the individual items are specified. Among the summary statistics (number of subjects, mean standard deviation, minimum value, quartiles (25% point, 50% point [median], 75% point), and maximum value), the mean, standard deviation, and quartiles (25% point, 50% point [median], 75% point) are rounded up to where a decimal place is one digit below the original data.

7 Analysis of primary endpoints

7.1 Patient characteristics at baseline (at the start of the first-line chemotherapy and at the start of the avelumab administration)

Target population : Analysis set

Endpoints : 1) Primary lesion at initial diagnosis

Categorical Variable

Site of the primary tumor

Histology of primary lesion[1)]

Presence or absence of variant histology

Subtype

Histologic dysplasia

Two-step grade

Three-step grade

Histological depth

Presence/absence of definitive treatment of primary lesion

Treatment

Surgery

2) At the start of the first-line chemotherapy

Continuous variable

Number of cycles of first-line chemotherapy

Number of cycles at the evaluation of best overall response to first-line chemotherapies

Treatment-free interval: Time from the end of first-line chemotherapy to the start date of avelumab administration (days)

Duration of first-line chemotherapy (days)

Categorical Variable

ECOG Performance Status

Karnofsky performance status (%)

Karnofsky performance status (2 divisions)

Bajorin risk classification

Staging (TNM classification)

Primary tumor (T factor)

Metastases to regional lymph nodes (N factor)

Distant metastasis (M factor)

Clinical Stage

Bladder

Urethra

Renal pelvis and ureter

Presence/absence of distant metastasis

distant metastasis site
Presence or absence of visceral metastasis
Presence or absence of non-visceral metastasis
Number of metastatic organs
Number of metastases in one organ
Number of distant metastases
Presence/absence of local recurrence
Regimen for first-line chemotherapy
Best overall response to first-line chemotherapies

3) At the start of avelumab administration

Continuous variable

Age

Categorical Variable

Gender
ECOG Performance Status
Karnofsky performance status (%)
Karnofsky performance status (2 divisions)
Bajorin risk classification
Staging (TNM classification)
Primary tumor (T factor)
Metastases to regional lymph nodes (N factor)
Distant metastasis (M factor)
Clinical Stage
Bladder
Urethra
Renal pelvis and ureter
Presence/absence of distant metastasis
Site of distant metastasis
Presence or absence of visceral metastasis
Presence or absence of non-visceral metastasis
Presence or absence of past medical history[2)]
Details of past medical history
Details of past medical history of auto-immune disease
Details of other medical history

Presence or absence of complication[2)]

Details of Complication

Details of complication of auto-immune disease

Details of other complications

Presence/absence of concomitant medication with steroid or immunosuppressant

Details of concomitant drugs using steroids and immunosuppressants

1) If multiple selections are made, the following will be used to determine the tissue type:

Small cell carcinoma > Urothelial carcinoma > It is determined by the order of predominant histological type in terms of quantity.

i. If there is any "small cell carcinoma," "small cell carcinoma" is adopted. (If both small cell carcinoma and urothelial carcinoma are selected, small cell carcinoma is adopted.)

ii. If there is no "small cell carcinoma," and "urothelial carcinoma" exists, "urothelial carcinoma" is adopted.

iii. If neither "small cell carcinoma" nor "urothelial carcinoma" exists, the tissue type listed in the EDC comment section as the predominant tissue type in terms of quantity is adopted.

2) If disease is cured by the start of avelumab administration, it is regarded as past medical history. If it is continued after the administration of avelumab, it is regarded as complication.

Statistical analysis : The following tabulation will be performed for end points.
Summary statistics will be calculated for continuous variables.
A frequency table (number of subjects, proportion (%)) will be prepared for categorical variables.
A frequency table (number of subjects and proportion (%)) will be prepared also for the details of past medical history of auto-immune disease, other past medical history, complication of auto-immune disease, other complication, and concomitant medications of steroids and immunosuppressants.

【Division of categorical variables】

Factor	Division

Site of the primary tumor	bladder/urethra/renal pelvis/ureter
Histology of primary lesion	Urothelial carcinoma/adenocarcinoma/squamous cell carcinoma/small cell carcinoma/other
Presence or absence of variant histology	presence/absence/unknown
Subtype	nested, including large nested/microcystic/micropapillary/lymphoepithelioma-like/plasmacytoid/signet ring cell/diffuse/sarcomatoid/giant cell/poorly differentiated/lipid-rich/clear cell/other
Histologic dysplasia	two step grades (low grade, high grade)/three step grades (G1, G2, G3)/unknown
Histologic dysplasia: two-step grade	low grade/high grade
Histologic dysplasia: three-step grade	G1/G2/G3
Histological depth	Bladder: pTX/pT0/pTa/pTis/pT1/pT2a/pT2b/pT3a/pT3bpT4a/pT4b Urethra: pTX/pT0/pTa/pTis/pT1/pT2/pT3/pT4 Renal pelvis: pTX/pT0/pTa/pTis/pT1/pT2/pT3/pT4 Ureter: pTX/pT0/pTa/pTis/pT1/pT2/pT3/pT4
Presence/absence of definitive treatment of primary lesion	absence/presence/unknown
Treatment	surgery/others
Surgery	Data will be aggregated based on the combination of the data obtained.
Gender	male/female
ECOG Performance Status	0/1/2/3/4
Karnofsky performance status (%)	100/90/80/70/60/50/40/30/20/10/0
Karnofsky performance status (2 divisions)	<80%/>=80%
Bajorin risk classification	0 (no risk factor)/1 (single risk factor)/2 (two risk factors)
Staging (TNM classification): Primary tumor (T factor)	Bladder: T0/Ta/Tis/T1/T2a/T2b/T3a/T3b/T4a/T4b/unknow

	n/other Urethra: T0/Ta/Tis/T1/T2/T3/T4/ unknown/other Renal pelvis: T0/Ta/Tis/T1/T2/T3/T4/ unknown/other Ureter: T0/Ta/Tis/T1/T2/T3/T4/unknown/other
Staging (TNM classification): Metastases to regional lymph nodes (N factor)	Bladder: N0/N1/N2/N3/unknown Urethra: N0/N1/N2/unknown Renal pelvis: N0/N1/N2/unknown Ureter: N0/N1/N2/unknown
Staging (TNM classification): Distant metastasis (M factor)	Bladder: M0/M1a/M1b/unknown/other Urethra: M0/M1/unknown/other Renal pelvis: M0/M1/unknown/other Ureter: M0/M1/unknown/other
Clinical Stage: Bladder	0a/0is/I/II/IIIA/IIIB/IVA/IVB
Clinical Stage: Urethra	0a/0is/I/II/III/IV
Clinical Stage: Renal pelvis	0a/0is/I/II/III/IV
Clinical Stage: Ureter	0a/0is/I/II/III/IV
Presence/absence of distant metastasis	presence/absence/unknown
Site of distant metastasis	lung/liver/adrenal/pancreas/kidney/spleen/bone/ distant lymph nodes/other
Presence or absence of visceral metastasis	presence/absence
Presence or absence of non-visceral metastasis	presence/absence
Number of metastatic organs	Single organ metastasis/multiple organ metastasis
Number of metastases in one organ	single/multiple
Number of distant metastases	single ("single organ metastasis" and "single")/multiple ("multiple organ metastasis" + "single organ metastasis" and "multiple")
Presence/absence of local recurrence	presence/absence/unknown
Presence or absence of past medical history	presence/absence/unknown
Details of past medical history	interstitial lung disease/chronic obstructive pulmonary disease (COPD)/auto-immune

	disease/cerebrovascular disorder/cardiovascular disorder/diabetes mellitus/other
Presence or absence of complication	presence/absence/unknown
Details of Complication	interstitial lung disease/chronic obstructive pulmonary disease (COPD)/auto-immune disease/cerebrovascular disorder/cardiovascular disorder/diabetes mellitus/other
Presence/absence of concomitant medication with steroid or immunosuppressant	presence/absence/unknown
Regimen for first-line chemotherapy	gemcitabine + cisplatin/gemcitabine + carboplatin/MVAC/dose dense-MVAC/other
Best overall response to first-line chemotherapies	CR/PR/SD/PD

8 Statistical Analysis of Secondary endpoints

8.1 Efficacy endpoints

8.1.1 Time to treatment failure (TTF) of avelumab

Target population : Analysis set

Endpoint : Time to treatment failure (TTF) of avelumab

Statistical analysis : For the endpoint, the median and its 95% confidence interval will be calculated using the Kaplan–Meier method. In addition, the Kaplan–Meier curve will be plotted, and the TTF rate for every 2 months and its 95% confidence interval will be calculated. Greenwood's formula will be used to calculate the confidence interval for the TTF rate.
In order to evaluate the overall observation period of the study, the median observation period will be calculated by estimating the reverse KM curve in which censoring patients are regarded as patients with events and patients with events are regarded as censoring patients.
In addition, as a sensitivity analysis, " interruption due to being well-controlled" will be treated as an event based on the day when death or discontinuation was observed before the date of the last

observation, and if no death or discontinuation or death occurred before the date of the last observation, data will be censored at the date of the last observation.

8.1.2 Real-world progression-free survival (rwPFS)

Target population	:	Analysis set
Endpoint	:	**Real-world progression-free survival (rwPFS)**
Statistical analysis	:	For the endpoint, the median and its 95% confidence interval will be calculated using the Kaplan–Meier method. In addition, the Kaplan–Meier curve will be plotted, and the rwPFS rate for every 2 months and its 95% confidence interval will be calculated. Greenwood's formula will be used to calculate the confidence interval for the rwPFS rate. In order to evaluate the overall observation period of the study, the median observation period will be calculated by estimating the reverse KM curve in which censoring patients are regarded as patients with events and patients with events are regarded as censoring patients.

8.1.3 Objective Response Rate (ORR)

Target population	:	Analysis set
Endpoint	:	**Objective Response Rate (ORR)**
Statistical analysis	:	For the end point in the avelumab maintenance and first-line chemotherapy, the number of patients included, the number of responders, and the response rate will be calculated along with its 95% confidence interval. In addition, summary statistics will be calculated for the number of cycles at the time of determination of best overall response. The denominator for each proportion (%) will be the analysis set, and patients with missing value for the end point will be excluded from the denominator. Clopper-Pearson method will be used to calculate the confidence

interval.

【Division of categorical variables】

Factor	区分
Response	Objective response/ Non-objective response

8.1.4 Real-world progression-free survival from chemotherapy (rwPFS-c)

Target population : Analysis set

Endpoint : Real-world progression-free survival from chemotherapy (rwPFS-c)

Statistical analysis : For the endpoint, the median and its 95% confidence interval will be calculated using the Kaplan–Meier method. In addition, the Kaplan–Meier curve will be plotted, and the rwPFS-c rate for every 2 months and its 95% confidence interval will be calculated. Greenwood's formula will be used to calculate the confidence interval for the rwPFS-c rate.
In order to evaluate the overall observation period of the study, the median observation period will be calculated by estimating the reverse KM curve in which censoring patients are regarded as patients with events and patients with events are regarded as censoring patients.

8.2 Safety endpoints

8.2.1 Corticosteroid therapy for immune-related adverse events (irAEs)

Target population : Analysis set

Endpoint : <u>Continuous variable</u>
Corticosteroid starting dose[1)] (prednisolone equivalent)
Duration of treatment with corticosteroid (days)

<u>Categorical variable</u>
Presence/absence of corticosteroid administration to irAE
Presence or absence of prednisolone
Presence or absence of methylprednisolone

Presence or absence of betamethasone
Presence or absence of dexamethasone
Presence or absence of hydrocortisone
Presence or absence of others
Details of other drugs

Presence or absence of treatment with non-high-dose corticosteroid (prednisolone-equivalent starting dose is less than 40)
Presence or absence of treatment with high-dose corticosteroid (prednisolone-equivalent starting dose is 40 mg or higher)
Presence or absence of steroid pulse therapy (prednisolone-equivalent starting dose is 625 mg or higher)

1) As the Instruction on the EDC and the EDC operation manual describes the instruction to "enter starting dose (dose change after the start of tapering is unnecessary)", it is likely that only the starting dose is collected. However, if there is any entry of dose change (dose increase) according to the instruction, the dose should be used to determine the starting dose of corticosteroid (the maximum value of the starting dose of each case (including administration change) is used as the starting dose of corticosteroid. When administrations of multiple drugs overlap with the duration of administration, the total dose is considered to be the value of the starting dose.

Statistical analysis : The following aggregation will be performed for endpoints:
Summary statistics will be calculated for continuous variables.
A frequency table (number of cases, proportion [%]) will be created for categorical variables.
A frequency table (number of cases, proportion (%)) will also be created for details regarding other drugs.

【Category Variable Classification】

Factor	Division
Presence/absence of corticosteroid administration to irAE	Absence/Presence/Unknown/Missing
Presence or absence of prednisolone	Absence/Presence
Presence or absence of methylprednisolone	Absence/Presence

Presence or absence of betamethasone	Absence/Presence
Presence or absence of dexamethasone	Absence/Presence
Presence or absence of hydrocortisone	Absence/Presence
Presence or absence of others	Absence/Presence
Presence or absence of treatment with non-high-dose corticosteroid	Presence
Presence or absence of treatment with high-dose corticosteroid	Presence
Presence or absence of steroid pulse therapy	Presence

8.2.2 Premedication for potential infusion-related reaction of avelumab

Target population : Analysis set

Endpoint : Premedication for potential infusion-related reaction of avelumab
Detailed name of the drug
Detailed name of the other drug

Statistical analysis : A frequency table (number of cases, proportion (%)) will be created for the endpoints.

【Division of categorical variables】

Factor	Division
Presence or absence of premedication for potential infusion-related reaction of avelumab	Absence/Presence/Unknown
Detailed name of the drug	Acetaminophen/diphenhydramine hydrochloride/chlorpheniramine maleate/Other

8.2.3 Treatment for infusion-related reaction of avelumab

Target population : Analysis set

n

Endpoint : Treatment for infusion-related reaction of avelumab
Detailed name of the drug

Statistical analysis : A frequency table (number of cases, proportion (%)) will be created for the endpoints.

【Division of categorical variables】

Factor	Division
Presence or absence of treatment for infusion-related reaction of avelumab	Absence/Presence/Unknown

8.2.4 Regimen after avelumab maintenance therapy

Target population : Analysis set

Endpoint : Continuous variable
Duration of Treatment after avelumab maintenance therapy (Days)

Categorical variable
Presence/absence of UC treatment after avelumab maintenance therapy
Regimen after avelumab maintenance therapy

Statistical analysis : The following aggregation will be performed for the end point.
For continuous variables, summary statistics will be calculated for each treatment. A frequency table (number of subjects, proportion (%)) will be created for the presence or absence of UC treatment after avelumab maintenance therapy.
A frequency table (number and proportion (%)) will be created for the second-line, third-line and subsequent treatment regimens for the second-line and subsequent treatment after avelumab maintenance therapy.

In addition, a listing of patients will be prepared.

【Division of categorical variables】

Factor	Division
Presence or absence of treatment after avelumab maintenance therapy	Absence/Presence/Unknown/Missing

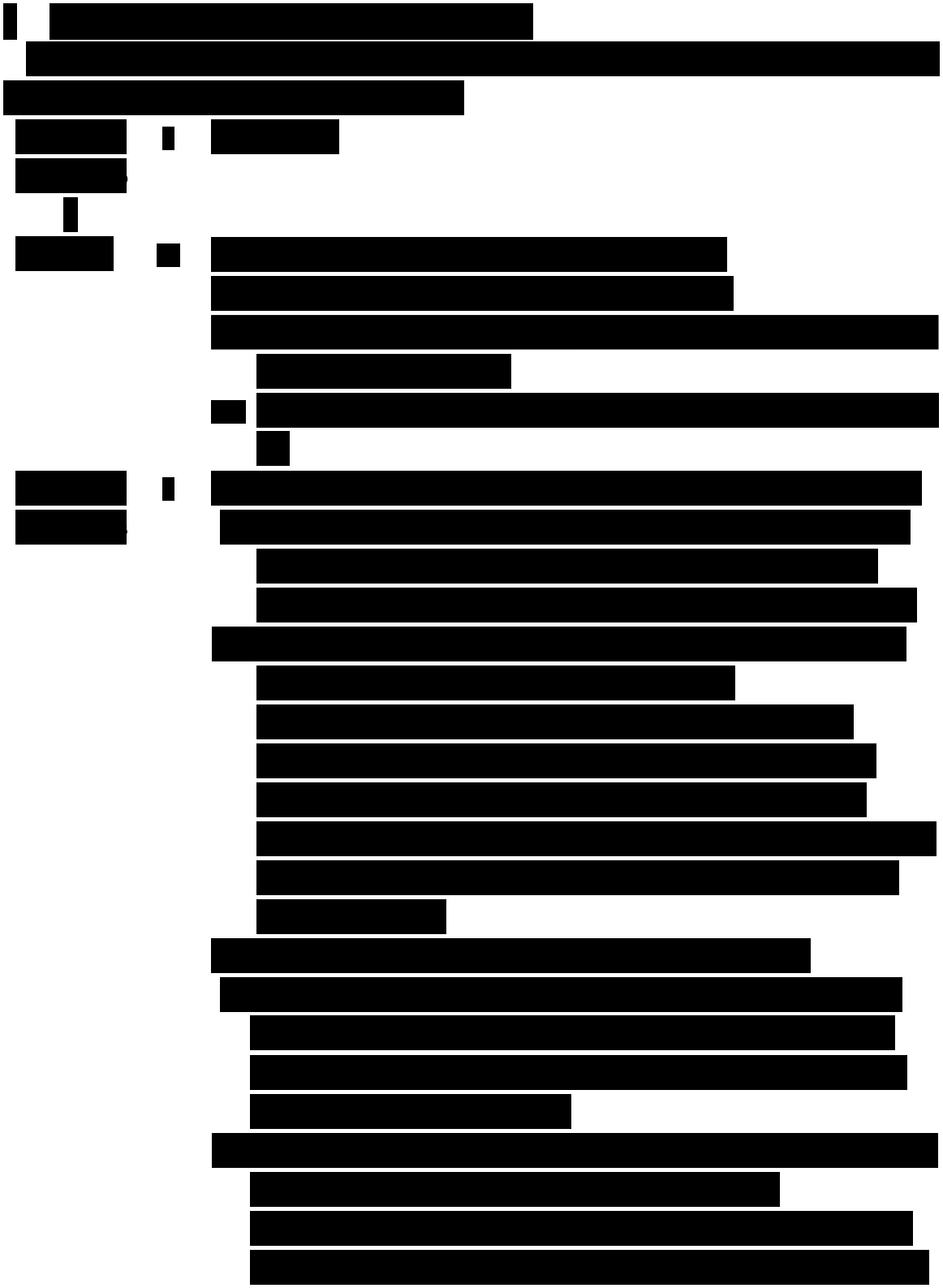
8.2.5 Hematological test (from the start of the first anticancer chemotherapy)

Target population : Analysis set

Endpoint : red blood cell count (×10^4/μL)
hemoglobin (g/dL)
hematocrit (%)
white blood cell count (/μL)
neutrophil count (/μL)
eosinophil (%)
basophil (%)
monocyte (%)
lymphocyte count (/μL)
platelet count (×10^4/μL)
CRP (mg/dL)
total protein (g/dL)
albumin (g/dL)
AST (IU/L)
ALT (IU/L)
LDH (U/L)
BUN (mg/dL)
creatinine (mg/dL)
Na (mEq/L)
K (mEq/L)
Cl (mEq/L)
NLR

Statistical analysis : Summary statistics of end points will be calculated by each timing of evaluation (At the start of first line chemotherapy/ immediately before the first avelumab administration/ at the start of fourth cycle of avelumab treatment/ at the time of PD judgment (at the latest test during the observation period for those continuing avelumab

treatment without disease progression).



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12 Revision record

Version	Date of creation	Reason for revision
Version 1.0	2 November 2022 EPSCo., Ltd. Hanae Uemura	New document
Version 1.1	21 December 2022 EPSCo., Ltd. Hanae Uemura	Correction of typographical errors Addition of determination rules for tumor histological type Addition of the starting dose of corticosteroid

End of document