## Study information

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| **Title** | 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 number** | B9991048 |
| **Protocol version identifier** | Version 4.1 |
| **Date** | 29 June 2022 |
| **Active substance** | Avelumab |
| **Medicinal product** | Avelumab (BAVENCIO®) |
| **Research question and objectives** | To describe the demographic and baseline disease characteristics and treatment outcomes in patients with locally advanced or metastatic urothelial carcinoma treated with first-line avelumab maintenance. |
| **Main Author** | PPD (non-interventional [NI] study lead)<br>PPD<br>e-mail address : PPD |

# 1. TABLE OF CONTENTS

## 2. LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse Event |
| AEM | Adverse Event Monitoring |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| BSC | Best Supportive Care |
| Carbo | Carboplatin |
| Cht | Chemotherapy |
| CI | Confidence interval |
| Cis | Cisplatin |
| CR | Complete response |
| CRF | Case Report Form |
| CSA | Clinical Study agreement |
| DCF | Data Clarification Form |
| DCT | Data Collection Tool |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | electronic Case Report Form |
| EDC | Electronic Data Capture |
| GC | Gemcitabine and Cisplatin |
| EU | European Union |
| G-Carbo | Gemcitabine Carboplatin |
| Gem | Gemcitabine |
| IEC | Independent Ethics Committee |
| irAE | immune-related Adverse Event |
| IRB | Institutional Review Board |
| LDH | High-density lipoprotein |
| M-CAVI | Methotrexate, Carboplatin and Vinblastine |
| MVAC | Methotrexate, Vinblastine, Adriamycin, and Cisplatin |
| NA | Not Applicable |
| NI | Non-Interventional |
| NIS | Non-Interventional Study |
| ORR | Objective Response Rate |
| OS | Overall Survival |

| Abbreviation | Definition |
|---|---|
| PAS | Post Authorization Study |
| PD | Progressive Disease |
| PD-L1 | Programmed Death Ligand 1 |
| PFS | Progression-Free Survival |
| PR | Partial Response |
| PS | Performance Status |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| SAP | Statistical Analysis Plan |
| SD | Standard Deviation; Stable Disease |
| SOC | Standard of Care |
| TNM | Tumor-Node-Metastasis |
| TTF | Time to Treatment Failure |
| UC | Urothelial Carcinoma |
| YRR | Your Reporting Responsibilities |
| 1L | First-Line |
| 2L | Second-Line |

## 3. RESPONSIBLE PARTIES

### Principal Investigator(s) of the Protocol

PPD

Implementation structure and list of study sites and principal investigators in this study will be prepared as Annex 1.
(This study will be conducted as a company-sponsored clinical study by Pfizer)

## 4. ABSTRACT

Not applicable

## 5. AMENDMENTS AND UPDATES

| Version | Date | Protocol section(s) changed | Summary of amendment(s) | Reason |
|---|---|---|---|---|
| 1.0 | 8 Nov 2021 | New | First edition | new |
| 2.0 | 18 Mar 2022 | | Revision from Advisor's review and Pfizer review as follows<br>9.2. Endpoint 9.2.1. Primary endpoint<br>4) Confirmed date of urothelial carcinoma<br>13) Site of metastasis (Yes [visceral/ non visceral]/ No)<br>14) Recurrence (Yes/No), if yes, recurrence confirmed date<br><br>9.2. Endpoint 9.2.2. Secondary endpoint<br>- rwPFS from chemotherapy (rwPFS-c)<br>- Changes in sum of the longest diameters | Updated description in accordance with the collection items |
| 3.0 | 7 April 2022 | Revise | **9.2. Endpoint 9.2.1Primary Endpoint**<br>6) Tumor-node-metastasis (TNM) classification<br>→<br>6)Tumor-node-metastasis(TNM) classification (the 8th edition of American Joint Committee on Cancer/ Union for | Updated description in accordance with the collection items |

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| | | | International Cancer Control)<br><br>8) Number of Cht cycles received in 1L<br>→<br>8)Start date and end date of administration, Number of Cht cycles received in 1L<br><br>**9.2 Endpoint 9.2.2 Secondary Endpoint**<br><br>□Changes in sum of the longest diameters*<br>The following data will be collected:<br>1) sum of the longest diameters, site (bladder, urethra or upper tract), histology (Urothelial carcinoma/ adenocarcinoma/ squamous cell carcinoma/ small cell carcinoma/ others [details])<br>Data collection scope: At the start of 1L cht/ every 2 cycles from the start of 1L cht/ immediately before the first avelumab administration/ every 12 weeks from the start of avelumab treatment/ at the time of PD judgment<br>→<br>□Changes in sum of the target lesion diameters*<br>The following data will be collected:<br>1) sum of the target lesion diameters, site (bladder / urethra / upper tract / others [details])<br>Data collection points: At the start of 1L cht / immediately before the first avelumab administration/ after the start of avelumab treatment/ at the time of PD judgment<br><br>1)Medication for UC after avelumab maintenance therapy (drug classification, type of treatment, start date of treatment, end date of treatment)<br>→<br>1)Medication for UC after avelumab maintenance therapy (drug name, start date of treatment, end date of treatment)<br><br>2) Data collection points: At the start of 1L | |

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| | | | cht/ immediately before the first avelumab administration/ every 12 weeks from the start of avelumab treatment/ at the time of PD judgment<br>→<br>2) Data collection scope: At the start of 1L cht / immediately before the first avelumab administration/ after the start of avelumab treatment/ at the time of PD judgment<br><br>**ANNEX**<br>CRM Department 2, Clinical Research Promotion Center, EP-CRSU Co., Ltd.<br>→<br>CR Department2, Clinical Research Center, Real World Evidence Business Headquarters, EPS Co., Ltd.<br><br>DS Department 2, Data Solution Center, EP-CRSU Co., Ltd.<br>→<br>CR Data Science Department, Clinical Research Center, Real World Evidence Business Headquarters, EPS Co., Ltd. | |
| 4.0 | 28 April 2022 | Revise | **8.2. Secondary objectives**<br>2) To describe clinical usage of corticosteroid for immune-related adverse events (irAEs) observed during avelumab therapy and within 90 calendar days after the last administration of avelumab therapy.<br>→<br>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.<br><br>**9.2.1. Primary endpoint**<br>12) Treatment of primary lesion (Yes [Surgery/ Radiation therapy /Others]/ No), date of treatment. (Collect treatment data for primary tumor at the most recent after the start of primary anticancer chemotherapy)<br>→<br>12) Treatment of primary lesion (Yes | Updated description in accordance with the collection items |

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| | | | [Surgery/ Radiation therapy /Others]/ No), date of treatment.<br><br>**9.7. Data management**<br>Investigators will fill out electronic case report forms (eCRFs) based on the medical charts by electronic data capture (EDC). After the completion, eCRFs are transferred to a single electronic database. Only the de-identified and anonymized data are included. When receiving a query from the data manager on the completed eCRF (ie, data clarification form [DCF]), investigators will reconfirm the information on source documents, fill out the DCF as required, and submit the DCF.<br>→<br>Investigators will fill out electronic case report forms (eCRFs) based on the medical charts by electronic data capture (EDC). After the completion, eCRFs are transferred to a single electronic database. Only the de-identified and pseudonymized data are included. When receiving a query from the data manager on the completed eCRF (ie, data clarification form [DCF]), investigators will reconfirm the information on source documents, fill out the DCF as required, and submit the DCF.<br><br>**10.2.1. For subjects who are alive and still visit the study site**<br>11) Handling of personal information (including process of anonymization, when anpseudonymization is conducted);<br>11) Handling of personal information (including process of pseudonymization, when anpseudonymization is conducted); | |
| 4.1 | 29 June 2022 | Revise | **Main Author**<br>PPD<br>  <br>  | Updated description in accordance with the collection items |

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|---|---|---|---|---|
| | | | → PPD [redacted] e-mail address : PPD [redacted] | |
| | | | **9.2.1. Primary endpoint**<br>3) Medical history/comorbidity (renal dysfunction/ hepatic dysfunction/interstitial lung disease/autoimmune disease/others) *<br>→<br>3) Medical history/comorbidity (interstitial lung disease/chronic obstructive pulmonary disease/autoimmune disease/cerebrovascular disease/cardiovascular disease/diabetes/others) *<br><br>7) Cht regimens received in 1L (Cisplatin [Cis]/ Gemcitabine [Gem], Carboplatin [Carbo]/Gem, Cis/Carbo/Gem, Methotrexate, Vinblastine, Adriamycin, and Cisplatin [MVAC] regimens, dose dense-MVAC, others)<br>→<br>7) Cht regimens received in 1L (Cisplatin [Cis]/ Gemcitabine [Gem], Carboplatin [Carbo]/Gem, Methotrexate, Vinblastine, Adriamycin, and Cisplatin [MVAC] regimens, dose dense-MVAC, others)<br><br>10) Best response to 1L Cht (complete response [CR], partial response [PR], stable disease [SD], PD)<br>→<br>10) Best overall response to 1L Cht (complete response [CR], partial response [PR], stable disease [SD], PD)<br><br>11) Site (bladder, urethra or upper tract) and histology (Urothelial carcinoma/ adenocarcinoma/ squamous cell carcinoma/ small cell carcinoma/others [details]) of the primary tumor at the time of initial diagnosis. | |

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|---|---|---|---|---|
| | | | →<br>11) Site (bladder, urethra, renal pelvis or ureter) and histology (Urothelial carcinoma/ adenocarcinoma/ squamous cell carcinoma/ small cell carcinoma/others [details]) of the primary tumor at the time of initial diagnosis.<br><br>none<br>→<br>12) Histological atypia<br>13) Histological depth of tumor invasion<br><br>12) Treatment of primary lesion (Yes [Surgery/ Radiation therapy /Others]/ No), date of treatment.<br>→<br>14) Definitive treatment of primary lesion (Yes [Surgery/ Others]/ No), date of treatment.<br><br>13) Site of metastasis (Yes [visceral/ non visceral]/ No)<br>→<br>15) Site of distant metastasis (Yes [visceral/ non visceral]/ No)<br><br>14) Recurrence (Yes/No), if yes, recurrence confirmed date<br>→<br>16) Local recurrence (Yes/No), if yes, recurrence confirmed date<br><br>15) Bajorin risk classification (0/1/2)<br>Risk factor<br>· Karnofsky performance status <80% (>ECOG 2)<br>→<br>17) Bajorin risk classification (0/1/2)<br>Risk factor<br>· Karnofsky performance status <80%<br><br>**9.2.2. Secondary endpoints**<br>Efficacy endpoint<br>· Changes in sum of the target lesion diameters*<br>The following data will be collected: | |

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| | | | 1) sum of the target lesion diameters, site (bladder / urethra / upper tract / others [details])<br>Data collection scope: At the start of 1L cht / immediately before the first avelumab administration/ after the start of avelumab treatment/ at the time of PD judgment<br>* The tumor is evaluated based on medical information.<br>→<br>(deleted)<br><br>Safety endpoints<br>・ Corticosteroid therapy for immune-related adverse events (irAEs)<br>The following data will be collected:<br>3) Dose of corticosteroid<br>→<br>3) Starting dose of corticosteroid<br><br>・ Hematological test (after the start of 1L Cht)<br>1) Red blood cell count/ hemoglobin/ hematocrit/ white blood cell count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)/ platelet count/ C-reactive protein (CRP)/ AST/ ALT/ LDH<br>Data collection scope: At the start of 1L cht / immediately before the first avelumab administration/ after the start of avelumab treatment/ at the time of PD judgment<br>→<br>1) Red blood cell count/ hemoglobin/ hematocrit/ white blood cell count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)/ platelet count/ C-reactive protein (CRP)/ total protein/ albumin/ AST/ ALT/ LDH/ BUN/ creatinine/ Na/ K/ Cl<br>Data collection scope: At the start | |

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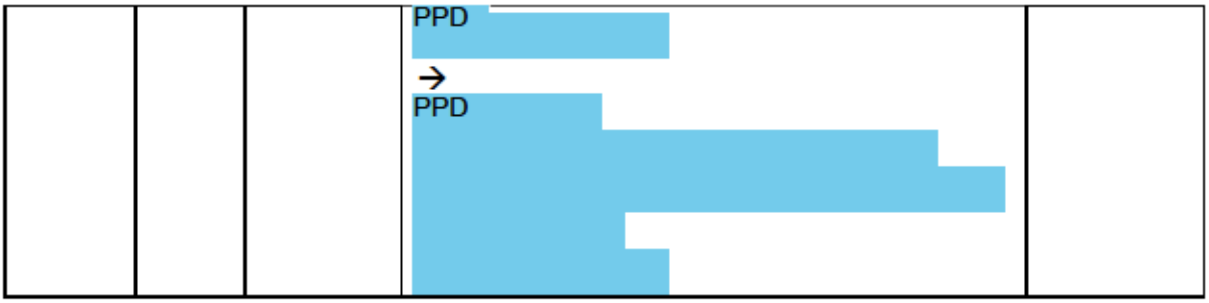
| | | | of 1L cht / immediately before the first avelumab administration/ at the start of fourth cycle of avelumab treatment/ at the time of PD judgment (at the latest test during the observation period for those continuing avelumab treatment without disease progression)<br><br>**9.2.3. Definition of endpoints**<br>**9.2.3.1. Time to treatment failure (TTF)**<br>on the last visit date during the study period.<br>→<br>on the last observation date during the study period.<br><br>**9.2.3.2. rwPFS**<br>or at their last visit date during the study period<br>→<br>or at their last observation date during the study period<br><br>**9.2.3.4. rwPFS-c**<br>or at their last visit date during the study period<br>→<br>or at their last observation date during the study period<br><br>**ANNEX**<br>**Research Sponsor**<br>Responsible Party<br>PPD<br>→<br>PPD<br><br>Medical Writing<br>PPD | |




## 6. MILESTONES

| Milestone | Planned date |
|---|---|
| Patient enrollment period*<br>*Patients who were received avelumab maintenance therapy during the period from 24 February 2021 to 30 November 2021. | From 24 February 2021 to 30 November 2021.<br>24 February 2021 is launch day of avelumab and 30 November 2021 is the date the expected number of patients who were received avelumab maintenance therapy will be approximately CCI patients in total. |
| Observation period | From index date (the date of first prescription for avelumab between 24 February 2021 [launch date] and 30 November 2021) to 30 June 2022.<br>Patients will be followed from index date to 30 June 2022.<br>It is assumed that the period patients who will be followed is at least 7 months (30 November 2021 to 30 June 2022) to evaluate primary endpoint of this study. |
| Study period | From the approval of the Institutional Review Board to 30 April 2023 (final report preparation) |
| Start of data collection | 01 July 2022<br>It is assumed that data collection will start the day after the completion of observation period. |
| End of data collection | 30 November 2022<br>It is assumed that it will take 5 months from start of data collection to end of data collection. |
| Analytical dataset lock | 31 January 2023<br>It is assumed that analytical dataset lock will take 2 months from end of data collection. |
| Final study report | 30 April 2023<br>It is assumed that it will take 3 months from analytical dataset lock to the date for approval of final study report. |

## 7. RATIONALE AND BACKGROUND

Bladder cancer accounts for approximately 90% of Urothelial carcinoma (UC). Approximately 550,000 cases of bladder cancer are newly diagnosed worldwide each year[1]. Each year, 200,000 cases of death are caused by bladder cancer. Bladder cancer incidence and death rates have not changed by 25 annuals[2]. According to the cancer statistical forecast in 2021 conducted by the National Cancer Center Japan, the estimated number of bladder cancers and deaths in 2021 in Japan were 24,300 and 9,700, respectively[3]. Patients with metastatic UC have a dismal prognosis with a 5-year survival rate of only 5%. Platinum-based polychemotherapy regimen is currently the first-line (1L) standard of care (SOC) for patients with advanced/metastatic disease, but despite high initial response rates, durable and complete responses following 1L chemotherapy (Cht) are uncommon, and most patients will ultimately experience disease progression within 9 months after initiation of treatment[4].

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Avelumab (MSB0010718C, BAVENCIO®) is a human immunoglobulin G1 monoclonal antibody directed against the programmed death ligand 1 (PD-L1) . In Japan, Cht is the 1L SOC recommended in guidelines for locally advanced or metastatic UC; CCI

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Avelumab in combination with best supportive care (BSC) as a maintenance treatment had been evaluated versus BSC alone in a Phase 3 randomized trial (JAVELIN Bladder 100) in patients with locally advanced or metastatic UC who had not progressed with 1L platinum-based Cht. The JAVELIN Bladder 100 study has demonstrated a significant 7.1-months improvement in median OS with Avelumab+BSC as 1L maintenance versus BSC alone (median OS, 21.4 months vs 14.3 months), with a 31% reduction of the death risk in the overall population (hazard ratio = 0.69 (95% confidence interval [CI], 0.56, 0.86), p=0.001) [8]. The results of Japanese subgroup analysis in the JAVELIN Bladder 100 were generally consistent with those in the overall population[9]. CCI [redacted]

The present study, B9991048, aims to evaluate the demographic and baseline disease characteristics and current treatment outcomes in patients with locally advanced or metastatic UC treated with avelumab those who had been prescribed Avelumab in a period of 9 months after launch, and had a follow-up duration of 7 months. In CCI [redacted]

# 8. RESEARCH QUESTION AND OBJECTIVES

To describe the demographic and baseline characteristics and treatment outcomes in patients with locally advanced or metastatic UC treated with avelumab as 1L maintenance therapy.

## 8.1. Primary objective

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

## 8.2. 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.

# 9. RESEARCH METHODS

## 9.1. 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

## 9.2. Endpoint

### 9.2.1. Primary endpoint

Patient characteristics at baseline (at the initiation of 1L Cht and the initiation of avelumab maintenance therapy)

The following baseline (at the initiation of 1L Cht and the initiation of avelumab maintenance therapy) patient background will be collected. The latest data before the start of 1L Cht and before the start of avelumab administration will be collected, respectively.

1) Age*
2) Sex*
3) Medical history/comorbidity (interstitial lung disease/chronic obstructive pulmonary disease/autoimmune disease/cerebrovascular disease/cardiovascular disease/diabetes/others) *
   If these diseases are cured by the start of avelumab administration, they are treated as a medical history, and if they continue after avelumab administration, they are treated as comorbidity.
4) Confirmed date of urothelial carcinoma
5) Eastern Cooperative Oncology Group (ECOG)
6) Tumor-node-metastasis (TNM) classification
7) Cht regimens received in 1L (Cisplatin [Cis]/ Gemcitabine [Gem], Carboplatin [Carbo]/Gem, Methotrexate, Vinblastine, Adriamycin, and Cisplatin [MVAC] regimens, dose dense-MVAC, others)
8) Start date and end date of administration, Number of Cht cycles received in 1L
9) Duration between the end date of 1L Cht and the start date of avelumab
10) Best overall response to 1L Cht (complete response [CR], partial response [PR], stable disease [SD], PD)
11) Site (bladder, urethra, renal pelvis or ureter) and histology (Urothelial carcinoma/ adenocarcinoma/ squamous cell carcinoma/ small cell carcinoma/others [details]) of the primary tumor at the time of initial diagnosis.
12) Histological atypia
13) Histological depth of tumor invasion
14) Definitive treatment of primary lesion (Yes [Surgery/ Others]/ No), date of treatment.

15) Site of distant metastasis (Yes [visceral/ non visceral]/ No)
Visceral: Having to do with the viscera, which are the soft internal organs of the body, including the lungs, the heart, and the organs of the digestive, excretory, reproductive, and circulatory systems (Classified as "visceral" if it has visceral metastasis, and classified as "non-visceral" if it has only locally advanced / recurrent lesions and non-visceral lesions without visceral metastasis)
16) Local recurrence (Yes/No), if yes, recurrence confirmed date
17) Bajorin risk classification (0/1/2)
<Bajorin risk classification [10]>

| Risk factor | Classification | |
|---|---|---|
| ・Visceral metastases<br>・Karnofsky performance status <80% | No risk factor | 0 |
| | One risk factor | 1 |
| | Two risk factors | 2 |

18) Concomitant drug

* at the initiation of avelumab maintenance therapy (The latest data before the start of avelumab administration will be collected)

### 9.2.2. Secondary endpoints

Efficacy endpoint

・ Time to treatment failure (TTF) of avelumab
Definition of TTF is provided in 20. The following avelumab treatment data will be collected:
1) Date of start and end of avelumab administration
2) Dosage of avelumab
3) Date of avelumab discontinuation and interruption
4) Reason for avelumab discontinuation and interruption
5) Date of of last survival confirmation

・ Real-world progression-free survival (rwPFS)
Definition of rwPFS is provided in 20. The following data will be collected:
1) Date of start of avelumab treatment (administration)
2) Date of first disease progression or death due to any cause, whichever came first
3) Date of last survival confirmation

・ Objective Response Rate (ORR)
ORR is defined in 21. The following data will be collected:
1) Tumor assessment (CR, PR, SD, PD)

・ rwPFS from chemotherapy (rwPFS-c)
Definition of rwPFS-c is provided in Section 9.2.3.4. The following data will be collected:
1) Date of start of 1L Cht (administration)

2) Date of first disease progression or death due to any cause during avelumab treatment, whichever came first
3) Date of last survival confirmation

Safety endpoints

- Corticosteroid therapy for immune-related adverse events (irAEs)
  The following data will be collected:
  1) Date of treatment
  2) Drug name of corticosteroid
  3) Starting dose of corticosteroid
  4) Duration of corticosteroid treatment
- Premedication for potential infusion-related reaction of avelumab
  The following data will be collected:
  1) Presence of premedication for infusion-related reaction of avelumab
  2) Drug name used for premedication for infusion-related reactions of avelumab
- Treatment for infusion-related reaction of avelumab
  The following data will be collected:
  1) Presence of treatment for infusion-related reaction of avelumab
  2) Drug name used for treatment for infusion-related reaction of avelumab
- Regimen after avelumab maintenance therapy
  The following data will be collected:
  1) Medication for UC after avelumab maintenance therapy (drug name, start date of treatment, end date of treatment)
- Hematological test (after the start of 1L Cht)
  The following data will be collected:
  1) Red blood cell count/ hemoglobin/ hematocrit/ white blood cell count (neutrophils, eosinophils, basophils, monocytes, lymphocytes)/ platelet count/ C-reactive protein (CRP)/ total protein/ albumin/ AST/ ALT/ LDH/ BUN/ creatinine/ Na/ K/ Cl
     Data collection scope: At the start of 1L cht / 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)

### 9.2.3. Definition of endpoints

#### 9.2.3.1. Time to treatment failure (TTF)

TTF is defined as the following:
TTF, defined as the time from start of avelumab maintenance therapy to the date of end of treatment due to any cause including death. If there is no record of the end of treatment, it be discontinued on the last observation date during the study period.

#### 9.2.3.2. rwPFS

rwPFS is defined as the following:
The time from start of avelumab maintenance therapy to date of first disease progression (as

clinically assessed by local investigator based on radiology, laboratory evidence, pathology, or other assessments) or death due to any cause, whichever occurred first. If there were no clinical records of death or disease progression, they will be censored at the date of initiation of the next line of therapy for the patients undertaking 2 or more lines of therapy (subsequent therapy after avelumab maintenance therapy) based on the record, or at their last observation date during the study period for the patients undertaking only 1 line of therapy (only avelumab maintenance therapy) based on the record.

#### 9.2.3.3. Objective response rate (ORR)

OR is defined as the following:
Complete or partial response as the best adjudication result (CR > PR > SD > PD) in a method that complies with Response Evaluation Criteria in Solid Tumors (RECIST) version. 1.1 tumor assessment as closely as possible in clinical practice by investigator's judgment.

#### 9.2.3.4. rwPFS-c

rwPFS-c is defined as the following:
The time from start of 1L Cht to date of first disease progression (as clinically assessed by local investigator based on radiology, laboratory evidence, pathology, or other assessments) or death due to any cause during avelumab treatment, whichever occurred first. If there were no clinical records of death or disease progression, they will be censored at the date of initiation of the next line of therapy for the patients undertaking 2 or more lines of therapy (subsequent therapy after avelumab maintenance therapy) based on the record, or at their last observation date during the study period for the patients undertaking only 1 line of therapy (only avelumab maintenance therapy) based on the record.

## 9.3. Setting

This study is a post-approval, company-sponsored, observational study in Japan.

### 9.3.1. Inclusion criteria

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

1) Diagnosed with locally advanced or metastatic UC before receiving Avelumab 1L maintenance therapy
2) Started 1L maintenance therapy with avelumab for locally advanced or metastatic UC from 24 Feb 2021 (launch date) to 30 Nov 2021
3) Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study
   (1) Written consent is not required for patients who were transferred to a hospital, and registration with verbal consent is acceptable
   (2) Opt-out enrollment is allowed for patients who have already died
4) Deceased patients are also required to meet the inclusion criteria 1)-2)

### 9.3.2. Exclusion criteria

There are no exclusion criteria for this study.

## 9.4. Variables

Collect the information shown in Sections 9.2.1 and 9.2.2 in this study. Human genome and gene information will not be collected.

## 9.5. Data sources

As this is a retrospective study, all data will be collected from medical records at the participating study site in Japan.

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## 9.7. Data management

Investigators will fill out electronic case report forms (eCRFs) based on the medical charts by electronic data capture (EDC). After the completion, eCRFs are transferred to a single electronic database. Only the de-identified and pseudonymized data are included. When receiving a query from the data manager on the completed eCRF (ie, data clarification form [DCF]), investigators will reconfirm the information on source documents, fill out the DCF as required, and submit the DCF.

### 9.7.1. Case report forms (eCRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term CRF should be understood to refer to an electronic data record or both, depending on the data collection method used in this study. An eCRF is required and should be completed for each included patient. The completed original eCRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator shall ensure that the eCRFs are securely stored at the study site in encrypted electronic form and will be password protected to prevent access by unauthorized third parties. The investigator has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the eCRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required.

The eCRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the eCRFs are true. Any corrections to entries made in the eCRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry. The source documents are the hospital or the physician's chart. In these cases,

data collected on the eCRFs must match those charts.

### 9.7.2.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, eg, eCRFs and hospital records), all original signed informed consent documents, copies of all eCRFs, safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to local regulations or as specified in the clinical study agreement (CSA), whichever is longer. The investigator must ensure that the records continue to be stored securely for so long as they are retained.
If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, 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.
Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless the retention period is specified in the contract between each research institution and Pfizer or required by the regulations of the implementing country. Record must be retained for longer than 15 years if required by applicable local regulations.
The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

### 9.7.3.Record disposal
Study records must be disposed of appropriately according to each site regulation.

## 9.8. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment. The SAP must be finalized before data lock. The final analysis will be performed after data lock and may modify the plans outlined in the protocol.

### 9.8.1. Analysis Population

The analysis population is defined in the SAP.

### 9.8.2. Analysis Methods

Continuous variables will be summarized using descriptive statistics ie, number of nonmissing values and number of missing values [ie, n (missing)], mean, median, standard deviation (SD), minimum, maximum and first and third quartile. Qualitative variables will be summarized by frequency counts and percentages. These endpoints will also be displayed graphically, if necessary.

### 9.8.3. Analysis of Primary Endpoints

See 18. These endpoints will be descriptively summarized. These endpoints will also be displayed graphically, if necessary.

### 9.8.4. Analysis of Secondary Endpoints

**Efficacy Endpoints**

See 19. For the time-to-event endpoints, eg, TTF and rwPFS, the Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median time with 2-sided 95% CIs. In particular, the survival rate at several timepoints will be estimated with corresponding 2-sided 95% CIs.

**Other Secondary Endpoints**

See 19. These endpoints will be descriptively summarized. These endpoints will also be displayed graphically, if necessary.

## 9.9. Quality control

The sponsor will train investigators and study site staff with an onsite training visit or web training on the protocol, eCRFs, and any applicable study processes. Any new information relevant to the performance of this study will be forwarded to the investigator and study site staff during the study. Remote data monitoring will be conducted during the life of the study to ensure timely reporting of data, data integrity, and consistency. eCRFs for all included patients will be made available to the remote data monitor for review. The study sites will be queried and managed to request resolution to any issues that may arise during the course of the study.

## 9.10. Limitations of the research methods

- This study is retrospective in nature so only existing data reported in patient records will be available. Variables that are often missing may affect estimation accuracy.
- Center of excellence will be preferentially selected in this study, so site selection and outcome reporting bias may be included. For this reason, the study results may not reflect all Japanese clinical outcomes.
- Evaluation of disease response may differ at each site, and measurement errors may be included in the estimated value.

## 9.11. Other aspects

### 9.11.1. Report to the chief executive of the study site

Each study site's investigator shall report the following to the chief executive of the study site in writing:

1) Measurements to be revised in the protocol;
2) Progression of the study;
3) Termination, discontinuation, and interruption of the study.

# 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 form and will be password protected 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 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

### 10.2.1. For subjects who are alive and still visit the study site

The investigator must ensure that each study subject is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any data is collected. The investigator will retain the original of each subject's signed consent form.
The informed consent form must be in compliance with local regulatory requirements and legal requirements. The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the Institutional Review Board (IRB)/ independent ethics committee (IEC) and Pfizer before use.

Information to be provided to subjects:

1) Title of the study and the fact that approval of the chief executive of the study site has been given concerning its implementation.
2) Names of the study site and the principal investigator [including names of the collaborative study site(s) and principal investigators of such collaborative study site(s), when the study is conducted collaboratively with other study site(s)];
3) Objectives and significance of the study;
4) Method and time period of the study (including purpose of utilization of specimens or information acquired from the subject);

5) Reasons why asked to be enrolled in the study;
6) Burdens to be caused on the subjects and predictable risks and benefits;
7) The fact that subjects may withdraw their consent at any time even after they have given consent with regard to the study being commenced or continued (when it can be difficult to take measures that follow the withdrawal made by the study subject , a statement to that effect and the reason for the difficulty).
8) The fact that the refusal or withdrawal of consent by a study subject with regard to the study is to be commenced or continued does not cause any disadvantage to such subject .
9) Means to make information on the study public;
10) The fact that subjects can request and obtain or read the study protocol and documents concerning the method of the study, to the extent it does not interfere with the protection of personal information, of other subjects, or the originality of the study, as well as the procedure to obtain or read such protocols and documents;
11) Handling of personal information (including process of pseudonymization, when pseudonymization is conducted);
12) Means for storage and disposal of specimens and information;
13) Status of study-related conflicts of interest of the study site, such as study fund resources as well as study-related conflicts of interest of each investigator, such as his/her individual income;
14) Handling of results and other information obtained from the study;
15) Response to consultation made by subjects, and other individuals concerned;
16) With respect to specimens and information acquired from the subject, when any of those may be utilized or provided to other study site(s) for future study that is not identified at the time of obtaining consent from the study subject, a statement to that effect and the contents of utilization assumed at the time of obtaining consent;

### 10.2.2. Subjects who are alive and had been transferred to another medical facility

In accordance with Chapter 4 “Informed Consent” of the “Ethical Guidelines for Life Science and Medical Research Involving Human Subjects”, it is not always necessary to obtain written informed consent when existing information isto be provided to another medical facility, but the individual providing existing information shall obtain oral informed consent. In this study, it is not required to obtain written informed consent from the subjects who had been transferred to another medical facility. In case the subject’s data will be collected from another medical facility for this study, investigator must ask primary doctor who currently cares for the patient at another hospital to obtain oral informed consent for the data collection. In addition, the conduct of this study will be disclosed, and the patients will be guaranteed an opportunity to refuse data collection.

### 10.2.3. Subjects who are deceased

In accordance with Chapter 4 “Informed Consent” of the “Ethical Guidelines for Life Science and Medical Research Involving Human Subjects”, the conduct of this study will be disclosed, and the subjects’ legally acceptable representatives will be guaranteed an opportunity to refuse data collection for the subjects. The following data must be made public:

1）Purpose and method for which the data will be used;

2）Item of information to be used or provided;
3）Name of the person responsible for data management;
4）Range of users;
5）At the request of the subjects' legally acceptable representatives, the use of information that identifies the research subject or the provision to other research institutes will be suspended. And how to accept the request of the research subject's agent

### 10.2.4. Response to important findings and other information concerning the health of subjects

With regard to the explanation of important findings and other information on the health of subjects obtained throughout this study, the principal investigator shall confirm at the time of obtaining consent whether disclosure is required in advance. If disclosure is required, an explanation shall be provided. In doing so, the following items shall be considered:

1) Whether the results are sufficiently accurate and reliable as information to assess the health, etc., of subjects;
2) Whether the results are important facts for the health, etc., of subjects;
3) Whether the explanation of the results may significantly impede the proper conduct of the study.

If the subject does not wish to receive an explanation of the results obtained from this study, his or her wishes will be respected. However, even if the subject does not wish to receive an explanation of the results obtained from the study, and if it is known that the results will have a serious impact on the life of the subject, blood relatives, etc., and if there is an effective way to deal with the situation, the principal investigator shall seek opinions from the IRB/IEC regarding whether to give an explanation, and the details and method of the explanation after considering the following:

1) Effect on the lives of study subjects and their blood relatives, etc.;
2) The availability of effective treatment and the health of study subjects;
3) The possibility that blood relatives may be affected by the same disease;
4) Description of the explanation of the results of the study at the time of informed consent

Based on the opinions of the IRB or IEC, the principal investigator shall provide sufficient explanation to the subject, etc., and confirm the intention of the subject; if the subject still does not wish to receive the explanation, no explanation shall be provided.
If the subject does not give consent, the principal investigator will not, in principle, explain the results obtained from the study pertaining to the subject to anyone other than the subject. However, if a legally acceptable representative, blood relative, etc., of the subject wishes to receive an explanation of the results obtained from the study, etc., the principal investigator shall provide such explanation as necessary, after obtaining the opinions of the IRB/IEC as to whether such explanation is permissible, based on the reason for the request and the necessity of the explanation.

## 10.3. Patient withdrawal

### 10.3.1. Subjects who are alive and still visit the study site, or subjects who are alive and had been transferred to another medical facility

During the course of this study, the subject can withdraw his/her consent at any time. In any circumstance, every effort should be made to document patient outcomes, if possible. If the patient withdraws from the study and 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 withdrawal of consent.

### 10.3.2. Subjects who are deceased

When the subjects' legally acceptable representatives refuse to participate in the study during the study period, all of their data must be excluded from the analysis dataset. If the results of this study are disclosed on paper or conference at the time of refusal, the subject's data cannot be excluded.

## 10.4. Institutional Review Board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. The IRB/IEC to which the review is requested shall be selected in accordance with the policy established by each medical institution, and the details of the review requesters shall be described in Annex 1. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer. Pfizer Inc. and the principal investigator will respond appropriately to the information on the status of the review.

## 10.5. Ethical conduct of the study

To ensure legal, regulatory and scientific purposes, values and rigor, This study will be conducted in accordance with the Helsinki Declaration of 1964 and later versions and "Ethical Guidelines for Life Science and Medical Research Involving Human Subjects" issued by the Ministry of Education, Culture, Sports, Science and Technology, the Ministry of Health, Labour and Welfare and the Ministry of Economy, Trade and Industry in Japan.

## 10.6. Predictable risks and benefits

### 10.6.1. Risk

The subjects' data will be collected retrospectively in this study, so there is no added risk to any individual subject.

### 10.6.2. Benefits

For individual subjects, there is no particular benefit because this study isa retrospective study design.

## 10.7. Conflicts of interest

This study will be sponsored by Pfizer Inc. The investigators will review any conflicts of interests that may affect the planning of this study or the interpretation of results by the IRB/IEC or the Conflicts of Interest Committee, according to the regulations of the study site. When the results of the study are published, accurate information will be disclosed by self-reporting in compliance with the guidelines of the academic society or journal used for

publishing the results of the study.

### 10.8. Registration and publication of study

Prior to implementation of this study, summary of this study will beregistered in the public database of ClinicalTrials.gov. Registered content will be properly updated without delay.

### 10.9. Secondary use of specimens and information obtained from subjects

The data obtained from this study may be used in other studies with different purposes, such as another study linked to this study or an integrated analysis (meta-analysis, etc.) with other research data. Such use will only be possible if another protocol is developed and approved by the IRB/IEC, and in such a case, information on the newly specified purpose of use, etc., shall be notified or disclosed to the subjects and the opportunity for refusal from the subjects, etc., shall be guaranteed, in principle, regarding the implementation of another study. In addition, the provision of information collected in this study from organizations or individuals to outside of the responsible parties of this study shall be limited to cases in which Pfizer Inc. agrees. The ownership of rights, etc., arising from secondary use or provision to external parties shall be determined through consultation with Pfizer Inc. and the parties to which secondary use or provision is made.
Furthermore, the possibility of future secondary use or external provision of the collected information will be explained to the subjects at the time of their participation in this study, and their informed consent will be obtained.

### 10.10. Responding to consultations from subjects and other related parties

The principal investigator will set up a helpline for handling consultations about this study from subjects and other related parties. Information about each site helpline is included in the informed consent form and document related to opt-out.

# 11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans (Magnetic resonance imaging, computed tomography, positron emission tomography, etc.), 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) to Pfizer. 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. Pfizer will contact the manufacturer, Merck BioPharma, Inc. under the Safety Data Exchange Agreement if it obtains an AE that indicates a clear causal relationship with avelumab. 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 EDC (cubeCDMS®) 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 the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least one patient identifier (eg, gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement “A 35-year-old female...” or “An elderly male...” Other identifiers will have been removed. Additionally, the onset/start dates and stop dates for “Illness”, “Study Drug”, and “Drug Name” may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY ) format.

All research staff members must complete the following Pfizer training requirements:

“Your Reporting Responsibilities (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

The results of this study are not part of any regulatory submission. The results of this study will be submitted for abstracts and publications. The final output will be filed in Pfizer's Global Document Management System upon final study completion.

In the event of any prohibition or restriction imposed (eg, 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.

## 13. REFERENCES

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## 14. LIST OF TABLES

None

## 15. LIST OF FIGURES

None

## ANNEX 1. IMPLEMENTATION STRUCTURE AND LIST OF STUDY SITES AND PRINCIPAL INVESTIGATORS OF THE STUDY

There are no plans to revise the protocol at this time, but when the protocol is to be revised in the future, these changes will be added to the protocol. Until then, please keep this document together with the protocol and treat it as part of the protocol. If necessary, please submit this document to the IRB/IEC.

## ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

None

## ANNEX 3. ADDITIONAL INFORMATION

Not applicable