NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Retrospective, Multicenter, Observational Study to Evaluate Current Treatment Outcomes in Japanese Patients With Metastatic Renal Cell Carcinoma Treated With Avelumab plus Axitinib as a First-line Therapy
Protocol number	B9991043
Protocol version identifier	Version 2.0
Date	04 Nov 2021
Active substance	Avelumab
Medicinal product	Avelumab (BAVENCIO®)
Research question and objectives	To describe the demographic and baseline characteristics and treatment outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with avelumab plus axitinib as a first-line therapy.
Author	PPD (NI study lead) PPD e-mail address : PPD

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
BMI	body mass index
CI	confidence interval
CR	complete response
CRP	C-reactive protein
CSA	clinical study agreement
DCF	data clarification form
DCT	data collection tool
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
IEC	Independent Ethics Committee
IMDC	International Metastatic RCC Database Consortium
irAE	Immune-related adverse event
IRB	Institutional Review Board
mRCC	metastatic renal cell carcinoma
NIS	non-interventional study
OR	objective response
PD-L1	programmed death ligand 1
PFS	progression-free survival
PD	progressive disease
PR	partial response
RCC	renal cell carcinoma
SAP	Statistical Analysis Plan
SD	stable disease
SD	standard deviation
TKI	tyrosine kinase inhibitor
TNM	tumor-node-metastasis
TTF	time to treatment failure

YRR	your reporting responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

List of Principal Investigators in this study will be prepared as *Annex1*.

4. ABSTRACT

Not applicable

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
2.0	25 Oct 2021	2. LIST OF ABBREVIATIONS, 6. MILESTONES, 9.3. Variables, 10.2.1. For subjects who are alive and still visit the study site, 10.2.2. Subjects who are alive and had been transferred to another medical facility, 10.2.3. Subjects who are deceased, 10.2.4. Handling of study results, etc, 10.2.4.1. Response to important findings and other information concerning the health of subjects, 10.4. Institutional review board (IRB)/Independent ethics committee (IEC), 10.5. Ethical conduct of the study, 10.8. Registration and publication of study, 10.9. Secondary use of specimens and information obtained from subjects, ANNEX 1. LIST OF STAND ALONE DOCUMENTS	2. Deleted the description regarding UMIN-CTR, 6. changed the planned date of milestone, 9.1.2. delete “and/or”, 9.3. added the description that this study will not be collected human genome and gene information, 10.2.1. added "Handling of results and other information obtained from the study", 10.2.2. amended the name of the ethics guidelines, 10.2.3. amended the name of the ethics guidelines, 10.2.4. addded policy for the explanations of study results, etc., 10.2.4.1. added the description regarding response to important findings and other information concerning the health of subjects, 10.4. added the method of review handling, 10.5. amended the name of the ethics guidelines, 10.8. delete the description regarding UMIN-CTR, 10.9. added the details of methods of the handling secondary use, ANNEX 1. added "The responsible parties of the study"	2. to correct typos, 6. to amend the schedule, 9.1.2. to correct typos, 9.3. to clarify that this study will not collect human genome and gene information, 10.2.1. because ethic guidelines has been revised, 10.2.2. because ethic guidelines has been revised, 10.2.3. because ethic guidelines has been revised, 10.2.4. because ethic guidelines has been revised, 10.2.4.1. because ethic guidelines has been revised, 10.4. because ethic guidelines has been revised, 10.5. because ethic guidelines has been revised, 10.8. to correct typos, 10.9. to add the details, ANNEX 1. to correct typos

6. MILESTONES

Milestone	Planned date
Observation period	from index date to 20 Jun 2021
Start of data collection	08 Sep 2021
End of data collection	31 Jan 2022
Analytical dataset lock	31 Jan 2022
Final study report	31 May 2022

7. RATIONALE AND BACKGROUND

Approximately 30,000 patients were diagnosed with renal cancer in Japan in 2017 [1)], and the number of cases has been increasing annually since the 1980s.

Recently, the immunotherapeutic approaches have demonstrated clinical efficacy in several cancer types, and some immune checkpoint inhibitors have been approved for the treatment of renal cell carcinoma (RCC). One of them is avelumab, which is an anti-programmed death ligand 1 (PD-L1) antibody. In December 2019, avelumab plus axitinib combination therapy was approved as a first-line treatment for the unresectable or metastatic renal cell carcinoma (mRCC) in Japan. This is the first-line therapy approved in Japan that combines an immuno-oncology drug with a tyrosine kinase inhibitor (TKI) to treat the patients with RCC.

Several clinical studies have been focused on this therapy for the treatment of RCC, but no real-world data have been collected in Japan. Therefore, the patient's background, treatment status, and outcomes of avelumab plus axitinib combination therapy must be clarified in the real-world clinical settings in Japan.

The Phase 3 JAVELIN Renal 101 trial was conducted to compare avelumab plus axitinib combination therapy with sunitinib monotherapy in previously untreated patients with advanced RCC. The results showed that the progression-free survival (PFS) was significantly longer in patients who were treated with avelumab plus axitinib (median: 13.8 months; 95% confidence interval [CI]: 11.1 to inestimable months) than in those treated with sunitinib (median: 7.2 months; 95% CI: 5.7–9.7 months; hazard ratio for disease progression or death: 0.61; 95% CI, 0.47–0.79; P <0.001) [2)]. Therefore, more than a 1-year of follow-up period is required to assess the real-world effectiveness of this combination therapy, such as PFS. Three studies with long-term follow-up periods were planned. In the present study, B9991043 is to evaluate the current treatment outcomes after a 1-year launch in patients with mRCC treated with avelumab plus axitinib as a first-line therapy. In the future, two other

observational studies will be conducted with follow-up periods of two and five years as per the plan.

8. RESEARCH QUESTION AND OBJECTIVES

To describe the demographic, baseline characteristics and treatment outcomes in patients with mRCC treated with avelumab plus axitinib as a first-line therapy.

8.1. Primary objective

To describe the demographic and baseline characteristics of patients with mRCC treated with avelumab plus axitinib as a first-line therapy in a real-world clinical setting.

8.2. Secondary objectives

1) To evaluate the efficacy of avelumab plus axitinib combination therapy for patients with mRCC treated in Japan.

2) To describe clinical usage of corticosteroid for immune-related adverse events (irAE) during avelumab plus axitinib combination therapy period.

3) To describe pre-treatment and treatment for infusion-related reaction of avelumab.

4) To describe patterns of post progression subsequent treatments.

9. RESEARCH METHODS

9.1. Study design

This study is a multicenter, non-interventional, retrospective, medical chart review of patients with mRCC treated with avelumab plus axitinib as a first-line therapy in Japan between 20 December 2019 and 20 December 2020. All decisions regarding clinical management and treatment of the participating patients were made by the investigator as part of standard care in 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 plus axitinib between 20 December 2019 (launch date) and 20 December 2020
- Observation period: Patients will be followed from index date to 20 June 2021

9.1.1. Primary endpoint

- Patient characteristics at baseline
  - Age
  - Sex
  - Body mass index (BMI)
  - Eastern Cooperative Oncology Group Performance Status (ECOG PS)
  - International Metastatic RCC Database Consortium (IMDC) risk score
  - Pathological diagnosis: Fuhrman grade, histological type, Sarcomatoid compornent
  - Tumor-node-metastasis (TNM) classification,
  - Number of metastatic organs and site of metastases
  - Complications
  - Nephrectomy
  - Renal function: estimated glomerular filtration rate (eGFR), proteinuria
  - C-reactive protein (CRP)
  - Smoking history
  - Concomitant drugs

9.1.2. Secondary endpoints

- Efficacy endpoint
  - Time to treatment failure (TTF) of avelumab plus axitinib as a first-line therapy
  - Real-world PFS
  - Objective response (OR)

- Avelumab-related endpoints
  - TTF
  - Discontinuation and interruption of avelumab
  - Reason for discontinuation and interruption

- Axitinib-related endpoints
  - TTF
  - Dose increase, dose reduction, discontinuation, and interruption of axitinib
  - Reason for dose increase, dose reduction, discontinuation, and interruption

- Corticosteroid-related endpoints
  - Cumulative dose of corticosteroid for irAE during avelumab plus axitinib treatment
  - Duration of corticosteroid treatment for irAE during avelumab plus axitinib treatment
  - Number of corticosteroid administrations for irAE during avelumab plus axitinib treatment

- Infusion-related reaction-related endpoints

- Presence of pre-medication for potential infusion-related reaction of avelumab
- Drugs of pre-medication for infusion-related reaction of avelumab
- Presence of treatment for infusion-related reaction of avelumab

- Subsequent treatment-related endpoints
  - Drugs used after avelumab plus axitinib

9.1.3. Definition of endpoints

9.1.3.1. Time to treatment failure (TTF)

TTF is defined as the following:

- TTF, defined as time from start of avelumab/axitinib treatment to end of treatment for any cause earlier, including death.

9.1.3.2. Real-world PFS

Real-world PFS is defined as the following:

- Real-world PFS, defined as time from start of avelumab/axitinib treatment 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, which ever came first
  If there were no clinical records of death or disease progression, they were censored at the date of initiation of the next line of therapy for the patients undertaking two or more lines of therapy based on the record, or at their last visit date during the study period for the patients undertaking only one line of therapy based on the record.

9.1.3.3. Objective response (OR)

OR is defined as the following:

- Complete or partial response as the best adjudication result (complete response [CR] > partial response [PR] > stable disease [SD] > progressive disease [PD], unknown) in a method complies with RECIST version. 1.1 tumor assessment as closely as possible in clinical practice by investigator’s judgment.

9.2. Setting

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

9.2.1. Inclusion criteria

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

1） Diagnosed with mRCC based on the General Rule for Clinical and Pathological Studies on Renal Cell Carcinoma (4th Edition) before receiving avelumab plus axitinib as a first-line therapy;

2） Over 20 years of age at the time of mRCC diagnosis;

3） Start treatment with avelumab plus axitinib as a first-line therapy for mRCC from 20 December 2019 to 20 December 2020;

4） For patients who are still alive and have routine visits to the study site, evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study. For patients who are still alive and had been transferred to another hospital, evidence that the patient has been informed of all pertinent aspects of the study and oral or written informed consent is obtained.

5） Deceased patients are also included for inclusion criteria 1-3.

9.2.2. Exclusion criteria

There are no exclusion criteria for this study.

9.3. Variables

The following information will be collected in this study. Human genome and gene information will not be collected.

9.3.1. Patient characteristics at baseline

- The following data regarding the patients characteristics will be collected at baseline: age, sex, BMI, ECOG PS, IMDC risk score, pathological diagnosis: Fuhrman grade, histological type, Srcomatoid compornent, Number of metastatic organs and site of metastases, TNM classification,complications, nephrectomy, renal function: eGFR, proteinuria, CRP level, smoking history, and concomitant use of drugs. Patient characteristics to be collected at baseline include the most recent data prior to initial treatment with avelumab plus axitinib.

9.3.2. IMDC risk -related data at baseline

The following IMDC risk-related data will be collected:

1） <1 year from time of diagnosis to systemic therapy;

2） Karnofsky Performance Status <80%;

3） Hemoglobin < lower limit of normal;

4） Corrected calcium > upper limit of normal;

5） Neutrophils > upper limit of normal;

6） Platelets > upper limit of normal.

9.3.3. Clinical outcome (Real-world PFS)

Definitions of Real-world PFS is defined in Section 9.1.3. The following data will be collected to determine the clinical outcomes: date of start of treatment, date of first disease progression or death due to any cause, whichever came first.

9.3.4. Clinical outcome (OR)

Definitions of OR is defined in Section 9.1.3. The following data will be collected to determine the clinical outcomes: tumor assessment (CR, PR, SD, PD, and unknown)

9.3.5. Avelumab treatment (TTF)

Definitions of TTF is defined in Section 9.1.3. The following avelumab treatment data will be collected: date of administration, actual and standard dosage, and reason for discontinuation and interruption.

9.3.6. Axitinib treatment (TTF)

Definitions of TTF is defined in Section 9.1.3. The following axitinib treatment will be collected: date of administration, reason for dose increase, dose reduction, actual and standard dosage, and reason for discontinuation and interruption.

9.3.7. Corticosteroid treatment

The following corticosteroid treatment data for irAE will be collected: date of treatment, drugs of corticosteroid, dose of corticosteroid, cumulative dose of corticosteroid, duration of treatment, and number of administrations during the treatment with avelumab plus axitinib.

9.3.8. Pre-medication and treatment for infusion-related reaction of avelumab

The following pre-medication and treatment data will be collected: Presence of pre-medication, therapeutic drugs for infusion-related reaction of avelumab and presence of treatment for infusion-related reaction of avelumab.

9.3.9. Second-line regimen after avelumab plus axitinib treatment

The following second-line regimen data will be collected: medication after avelumab plus axitinib treatment.

9.4. Data sources

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

9.5. Study size

This study is descriptive study which aims to describe the demographic and baseline characteristics of patients who were treated avelumab plus axitinib in first-line treatment for mRCC, rather than testing any pre-defined hypothesis. Since all the analyses will be descriptive, sample size calculations are not applicable.

The expected number of patients will be approximately 70 patients in total, but the number should be considered flexible.

9.6. 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 anonymized data are included.

When receiving a query from the sponsor 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.

9.6.1. Electronic 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 either a paper form or 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.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, 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 Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

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

9.6.3. Record disposal

Study records must be disposed of appropriately according to each site regulation.

9.7. 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.

9.7.1. Analysis Population

Will be provided in the SAP.

9.7.2. Analysis Methods

Continuous variables will be summarized using descriptive statistics ie, number of non-missing 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.

For the time-to-event endpoints, eg, TTF and Real-world PFS, the Kaplan-Meier estimates (product-limit estimates) will be presented together with a summary of associated statistics including the median Real-world PFS time with 2-sided 95% CIs. In particular, the Real-world PFS rate at several timepoints will be estimated with corresponding 2-sided 95% CIs. These endpoint will also be displayed graphically.

9.7.3. Analysis of Primary Endpoints

See Section 9.1.3. These endpoints will also be displayed graphically if necessary.

9.7.4. Analysis of Secondary Endpoints

Efficacy Endpoints

See Section 9.1.3. These endpoints will also be displayed graphically if necessary.

Other Secondary Endpoints

See Section 9.1.3. These endpoints will also be displayed graphically if necessary.

The SAP must be fixed before data lock. The final analysis will be performed after data lock and may modify the plans outlined in the protocol.

9.8. 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.

9.9. 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.
- High-volume centers 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.

9.10. Other aspects

9.10.1. 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 IRB/ 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 method of the study, to the extent it does not interfere 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 anonymization, when anonymization 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） When the study involves any financial expenditure on or remuneration for the subject, a statement to that effect and details of such;

17） When the study involves any invasiveness, whether compensation will be offered for study-related injury and details of such compensation.

18） 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

19） When the study involves any invasiveness (not including minor invasiveness) and intervention, the fact that the monitor(s), the auditor(s), and IRB or IEC will be granted direct access to the specimens and information acquired from the subjects to the extent necessary, without violating the confidentiality of the subjects.

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 are to be provided to other 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 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 for the patients.

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 for which the data will be used;
2） Item of previously collected data;
3） Person responsible for data management;
4） Organization that will be providing data;
5） How to manage refusal—if the subject refuses participation in the study, their data cannot be used.

10.2.4. Handling of study results, etc.

The principal investigator shall explain the following policy for the explanations of the study results, etc. to patients and obtain their consent.
(Policy for the explanations of study results, etc.)
With regard to the study results, etc., important findings, etc. concerning the health of patients including incidental findings (hereinafter referred to as "important findings, etc. concerning the health of patients"), will not be disclosed to patients individually, except for cases where not disclosing them would result in disadvantages to patients. Instead, the results will be published in the manner described in "10.8 Registration and publication of study".

10.2.4.1. 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 (e.g., 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

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor; the study will follow generally accepted research practices described in the "Ethical Guidelines for Life Science and Medical Research Involving Human Subjects" issued by the Ministry of Health, Labour and Welfare.

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 the study has a retrospective study design.

10.7. Conflicts of interest

This study will be performed with funding from 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, this study and a summary were registered 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 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 (AEs)/ADVERSE REACTIONS

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

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

• All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the CapTool mini® 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

1) National Cancer Center Cancer Information Service. Latest cancer statistics. Available at: https://ganjoho.jp/reg_stat/statistics/stat/summary.html, (reference data 2020-10-01)
2) Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma. N Engl J Med. 2019;380(12):1103-15.

14. LIST OF TABLES

None

15. LIST OF FIGURES

None

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

The responsible parties of the study

ANNEX 2. ADDITIONAL INFORMATION

Not applicable