NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	A Multicenter, NI, Retrospective, Observational Study Evaluating Real-World Treatment Outcomes in Japanese Patients with Metastatic Renal Cell Carcinoma (mRCC) Treated with Avelumab plus Axitinib as First-line Therapy: J-DART2
Protocol number	B9991052
Protocol version identifier	Version 1.2
Date	31 October 2022
Active substance	Avelumab
Medicinal product	Avelumab (BAVENCIO®)
Research question and objectives	To describe the demographic and clinical characteristics and treatment outcomes of Japanese patients with mRCC who were treated with avelumab plus axitinib as first-line therapy in a real-world setting.
Author	PPD

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	adverse event monitoring
BOR	best overall response
CI	confidence interval
CR	complete response
CRFs	Case report forms
CSA	clinical study agreement
CRP	C-reactive protein
DCF	data clarification form
DCTs	Data collection tools
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
ECOG	Eastern Cooperative Oncology Group
EDC	electronic data capture
FAS	Full analysis set
HR	hazard ratio
IMDC	International Metastatic RCC Database Consortium
IEC	independent ethics committee
irAE	immune-related adverse event
IRB	Institutional Review Board
JUA	Japanese Urological Association
mRCC	metastatic renal cell carcinoma

NIS	non-interventional study
NE	not Evaluable
NI	non-interventional
OS	Overall survival
ORR	objective response rate
PR	partial response
PD	progressive disease
PD-L1	anti-programmed death ligand 1
PFS	progression-free survival
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SD	stable disease
TNM	tumor-node-metastasis
TKI	tyrosine kinase inhibitor
TTD	time to treatment discontinuation
YRR	your reporting responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

The implementation structure of this study will be prepared in Annex 1.

4. ABSTRACT

Not applicable

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
1.1	14 Oct 2022	6. MILESTONES 9.8. Quality control 10.2.4. Disclosing study findings to patients ANNEX 1. LIST OF STAND ALONE DOCUMENTS	6. added anticipated study start date 9.8. added data monitoring procedure 10.2.4. addded plans to communicate study results to participants ANNEX 1. changed the name of the site	6. to clarify study period 9.8. to clarify data monitoring procedure 10.2.4.to clarify how to deal with study results including incidental or secondary findings ANNEX 1. to correct typos
1.2	31 Oct 2022	9.8. Quality control	9.8. added the affiliation of the data manager	9.8. to clarify who is in charge of data monitoring

6. MILESTONES

Milestone	Planned date
Study start date	Date of approval at each site
Start of data collection	15 December 2022
End of data collection	30 April 2023
Final study report	30 November 2023

7. RATIONALE AND BACKGROUND

In Japan, nearly 30,000 patients were diagnosed with renal cancer in 2018, and the number of patients has increased annually since the 1980s [1)]. The 5-year relative survival rate for renal/urinary tract cancer (excluding bladder cancer) was 68.6% between 2009 and 2011. In 2020, Nine Thousand Seven Hundred Twelve deaths occurred, with a mortality rate of 7.6 per 100,000 persons. Although the incidence of renal cell carcinoma (RCC) in Japan is lower than that in other modernized countries, it continues to increase [1,2)].

Recently, the immunotherapeutic approaches have demonstrated clinical efficacy in several types of cancer, and certain immune checkpoint inhibitors have been approved for the treatment of RCC. [3-7)] One of these immune checkpoint inhibitors is avelumab, an anti-programmed death ligand 1 (PD-L1) antibody. In December 2019, avelumab plus axitinib combination therapy was approved in Japan as the first-line treatment for unresectable or mRCC. [4)] This is the first therapy approved in Japan that has combined an immuno-oncology drug with a tyrosine kinase inhibitor (TKI) in order to treat patients with mRCC. The recent Japanese Urological Association (JUA) guidelines for renal cancer recommended the combination of avelumab and axitinib as first-line therapy for RCC [Grade B]. [8)]

The Phase 3 JAVELIN Renal 101 trial compared the combination of avelumab plus axitinib with sunitinib monotherapy in previously untreated patients with advanced RCC. [4)] The results showed a statistically significantly longer median progression-free survival (PFS) in those treated with the combination therapy (13.8 months; 95% confidence interval [CI]: 11.1–inestimable) as compared with sunitinib (7.2 months; 95% CI: 5.7–9.7) as well as a hazard ratio (HR) of 0.61 for disease progression or death (95% CI: 0.47–0.79; P <0.001). These findings were sustained even after a minimum follow-up of 13 months (HR: 0.62; 95% CI: 0.49–0.78; one-sided P <0.0001), [9)] and similar results were obtained in subgroup analyses within each age category (<65 years, 65-74 years, ≥75 years), including the population aged 75 years and over. [10)]

Although several clinical trials have focused on avelumab plus axitinib regimens in the treatment of mRCC, there is limited evidence in real-world settings in Japan. Moreover, because more than 1-year follow-up period is required to assess the real-world effectiveness of this combination therapy, such as in regard to PFS, we planned a series of 3 studies with different long-term follow-up periods. As the first of these studies, J-DART1-B9991043, was conducted to evaluate the treatment outcomes over the course of 1-year in Japanese patients with mRCC who were treated with avelumab plus axitinib as first-line therapy in a real-world clinical setting (NCT05012865). This second study, J-DART2-B9991052, is being conducted in order to describe the demographic and characteristics of the patients as well as the treatment outcomes over the course of more than 2-years of follow-up in Japanese

patients with mRCC who were treated with avelumab plus axitinib as first-line therapy in a real-world clinical setting.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Primary objective

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

8.2. Secondary objectives

- To evaluate the treatment outcomes of avelumab plus axitinib as first-line therapy for patients with mRCC in a real-world setting, as determined by the following endpoints:
  - Real-world PFS.
  - Overall survival (OS) .
  - Objective response rate (ORR).
  - Best overall response (BOR) for primary lesions.
  - Time to treatment discontinuation (TTD) of avelumab plus axitinib as first-line therapy.
- To describe the treatment patterns for avelumab plus axitinib as first-line therapy in a real-world setting.
- To describe the clinical use of corticosteroids for immune-related adverse events (irAEs) occurring during the course of administering avelumab plus axitinib combination therapy.
- To describe the pre-treatment and treatment of infusion-related reactions caused by avelumab.
- To describe the subsequent treatment of avelumab plus axitinib combination therapy.

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9. RESEARCH METHODS

9.1. Study design

This study is a multicenter, NI, retrospective, medical chart review of patients with mRCC who were treated with avelumab plus axitinib as first-line therapy in Japan between 20 December 2019 and 17 October 2022.

The source population comprises patients who initiated avelumab plus axitinib as first-line therapy between 20 December 2019 and 17 October 2022.

9.2. Setting

This retrospective chart review will evaluate patient data derived from patient's existing medical records from the enrolled patients. All decisions regarding the clinical management and treatment of the patients are made by the investigator as part of standard care in a real-world setting and are not contingent upon the patient's participation in the study. Data will be collected at each study site (if available).

The study period is from 20 December 2019 to 31 October 2022. Patients with index date between 20 December 2019 and 17 October 2022 will be enrolled in this study. To ensure a 2 weeks follow up period, patients with an index date between 20 December 2019 and 17 October 2022 will be included in this study. The period of 2 weeks is determined based on the dosing interval for avelumab, in consideration of the fact that the start times of administration for avelumab and axitinib may differ.

- Index date: The date of first prescription of avelumab plus axitinib combination therapy.
- Observation period: Patients will be followed from the index date to 31 October 2022.

9.2.1. Inclusion criteria

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

1） Diagnoses of mRCC based on the General Rule for Clinical and Pathological Studies on RCC (Fifth Edition) before receiving avelumab plus axitinib as first-line therapy. Patients with mRCC who have unresectable disease, either unresectable locally advanced or metastatic disease.
2） Age over 18 years at the time of the first administration of avelumab plus axitinib as first-line therapy for mRCC (baseline).
3） Index date from 20 December 2019 to 17 October 2022.

9.2.2. Exclusion criteria

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

1） Patients participating in a prospective interventional clinical trial assessing an investigational product during the observation period.
2） Patients (or a patient's legally representative) refusing to provide patient data during the consent process.

9.3. Variables

Only data available from the treating physician's routine clinical assessments as per local standard of care will be collected. Variables and data sources are described in Table 1. Detailed definitions will be included in the Statistical Analysis Plan (SAP).

Table 1. Variables in this study

Variable	Role	Data source(s)	Operational definition
Patient characteristics	Baseline characteristics, sub-group idntifiers	Patient medical records	Patient characteristics at baseline, including the most recent data prior to initial treatment with avelumab plus axitinib: age, sex, height, weight, body mass index, smoking history, comorbidities, concomitant use of drugs, Eastern Cooperative Oncology Group (ECOG) performance status, pathological diagnosis (Fuhrman grade, TNM classification, histological type sarcomatoid compornent) , the number of metastatic organs and the site of metastasis, the presence or absence of

			nephrectomy, laboratory data (C-reactive protein (CRP), estimated glomerular filtration rate (eGFR), proteinuria) , and International Metastatic RCC Database Consortium (IMDC) risk score - <1 year from time of diagnosis to systemic therapy - Karnofsky Performance Status <80% - Hemoglobin < lower limit of normal - Corrected calcium > upper limit of normal - Neutrophils > upper limit of normal - Platelets > upper limit of normal)
Avelumab plus axitinib treatment patterns	Exposure, outcome, sub-group idntifier	Patient medical records	Start and end date of avelumab plus axitinib as first-line therapy.
Management of AE	Exposure, outcome, sub-group idntifier	Patient medical records	Corticosteroid treatment for irAEs occurring during treatment with avelumab plus axitinib (drug, dose), the presence or absence of pre-medication and treatment for infusion-related reactions.
Subsequent treatment patterns	Exposure, outcome, sub-group idntifier	Patient medical records	Subsequent treatment (drug name and duration of use for second-line therapy).
Clinical outcomes	Outcome	Patient medical records	BOR, assessment of disease progression, real-world PFS, OS, ORR, TTD. For the patients not nephrectomized at baseline: BOR for the primary lesion, the date of nephrectomy after administration of avelumab plus axitinib.

9.3.1. Definition of clinical outcome measures

Real-world progression-free survival (PFS)

Real-world PFS is defined as the time from the start of treatment with avelumab plus axitinib to the date of first disease progression (as clinically assessed by a local investigator based on a radiology assessment, laboratory evidence, pathological data, and/or other assessments) or death due to any cause, which ever came first. If there are no clinical records of death or disease progression, patients will be censored at the date of initiation of the next line of therapy for those undertaking 2 or more lines of therapy based on the details in their medical records or at their last visit date during the study period for those undergoing only first line of therapy. However, if the nephrectomy is performed earlier than the above date, the data is to be treated as censored at the date of nephrectomy.

9.3.1.1. Overall Survival (OS)

OS is defined as the time from the start of treatment with avelumab plus axitinib to the date of death due to any cause. If there are no clinical records of death, the date when the patient was last documented to be alive will be confirmed based on medical records. The data will be censored at the date of last contact.

9.3.1.2. Objective response rate (ORR)

The ORR is defined as the proportion of patients with a documented BOR (complete response (CR) or partial response (PR)) by the invesetigator during treatment with avelumab plus axitinib as first-line therapy. The BOR is defined as the best tumor response recorded during the observation period. The definitions of tumor responses are as follows:
Complete or PR as the best adjudication result (CR > PR > stable disease [SD] > progressive disease [PD], not Evaluable[NE]) complies with the RECIST tumor assessment guidelines as closely as possible in clinical practice.

9.3.1.3. Time to treatment discontinuation (TTD)

TTD is defined as the time from the start of treatment with avelumab plus axitinib to the end of treatment due to any cause except the effectiveness of the treatment.

9.4. Data sources

As this is a retrospective study, all data are to be collected from the patient medical records at the participating study sites.

9.5. Study size

This descriptive study aims to describe the demographic and baseline characteristics for patients treated with avelumab plus axitinib as first-line therapy for mRCC, rather than testing any predefined hypothesis. Since all analyses are descriptive, sample size calculations are not applicable.

The expected number of patients is approximately 150 patients in total. However, this number should be considered flexible.

9.6. Data management

Investigators will complete electronic case report forms (eCRFs) based on medical charts reviews using electronic data capture (EDC). After completion, the eCRFs are transferred to a single electronic database. Only the de-identified and anonymized data will be included in this database.

When receiving a query from the sponsor regarding the completed eCRF (ie, a data clarification form [DCF]), investigators will reconfirm the information in the source documents, fill out the DCF as required, and submit the DCF.

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

As used in this protocol, the term CRF should be understood to refer an electronic data record in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs 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 CRFs 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 CRFs 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 CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs 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 CRFs 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, CRFs and hospital records), all original signed informed consent/assent documents, copies of all CRFs, 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 study site and Pfizer have expressly agreed to a different period of retention via a separate written agreemen or as 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. Data analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a 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 fixed prior to data lock. The analysis is to be performed after the data lock.

9.7.1. Analysis Population

Full analysis set (FAS): The FAS will consist of patients who meet the inclusion criteria and do not meet the exclusion criteria.

Efficacy analysis set: The efficacy analysis set is a subset of the FAS that includes patients whose index date is prior to 30 April 2022 to ensure a 6-months follow-up period.

Subgroups: A subgroup analysis will be considered, including but not limited to subgroups categorized by IMDC risk group, age (≥ 75 years or < 75 years), and the presence or absence of corticosteroid administrations for irAE in the medical record.

9.7.2. Analysis Methods

Continuous variables will be summarized using descriptive statistics (ie, the number of non-missing and missing values [ie, n (missing)], the mean, median, standard deviation [SD], minimum and maximum, and the first and third quartiles).

Qualitative variables will be summarized using frequency count and percentages.

For the time-to-event endpoints (for eg, OS, TTD and real-world PFS), Kaplan-Meier estimates will be presented together with a summary of the associated statistics including the median time with 2-sided 95% CIs. In particular, the survival rate at several time points will be estimated along with the corresponding 2-sided 95% CIs. These endpoints will be displayed graphically.

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9.8. Quality control

The sponsor will train the investigators and study site staff in regard to the protocol, eCRFs, and any applicable study processes via an on-site training visit or web training. Any new information relevant to the performance of this study will be forwarded to the investigators and the study site staff during the course of the study. Remote data monitoring will be conducted during the study period to ensure the timely reporting of data, data integrity, and consistency. The eCRFs for all included patients will be made available to the remote data monitor for review. The study sites may be queried and should be capable of resolving any issues that may arise during the course of the study. On-site monitoring visits have not been planned for this study. The data manager from the contract research organization commissioned by the sponsor prepares and submits the data monitoring report to the sponsor before the database is locked. The data monitoring report includes the number of cases, the completion of eCRF, queries, and the possible issue or protocol deviation.

9.9. Limitations of the research methods

- This study is retrospective in nature. Therefore, only existing data reported in patient records is available for the present research. Missing data may affect the estimation accuracy.
- High-volume centers were preferentially selected for this study, potentially leading to site selection and outcome reporting biases. Therefore, the study results may not accurately reflect clinical outcomes for all Japanese centers.
- The evaluation of disease response may differ at each site, and measurement errors may be included in the estimated values.

9.10. Other aspects

9.10.1. Reporting to the chief executive of the study site

Each investigator will report the following information to the chief executive at the study site:

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 CSA and applicable privacy laws.

10.2. Patient consent

The investigator must obtain informed consent from the patients regarding the use of their medical records for this study as well as data provision to a third party prior to collecting the data for this study.

The informed consent form must comply with local regulatory 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 independent ethics committee (IEC) and by Pfizer.

10.2.1. For patients who are alive and continue to visit the study site

The investigator must obtain written informed consent from each patient before data collection. After obtaining written informed consent, the investigators must retain the original signed consent form for each patient. When obtaining the oral informed consent in consideration of the patient's condition or situation, the investigator will document the method and content of the explanation as well as the details of the obtained consent.

10.2.2. Patients who are alive and were transferred to another medical facility

Investigators must obtain oral informed consent for data collection from each patient who was transferred to another hospital before data collection. When obtaining oral informed consent, the investigator will document the method and content of the explanation as well as the details of the obtained consent.

When it is difficult to obtain oral informed consent for the following reasons, consent will not be required based on the Act on the Protection of Personal Information Article 27 (1) - (iii) and the Frequently Asked Questions related to the article:

- The study site does not obtain valid patient contact information.
- When considering the time available and research costs incurred in obtaining oral informed consent at the study site, it is concluded that obtaining oral informed consent at the study site could significantly impact the conduct of the study.

Even in these cases, the study information must be disclosed, and the patients' legally acceptable representatives will be guaranteed an opportunity to refuse to provide patient data to the sponsor.

10.2.3. Patients who are deceased

In accordance with Chapter 4 ("Informed Consent") of the "Ethical Guidelines for Life Science and Medical Research Involving Human Subjects," the study information needs to be disclosed, and the patients' legally acceptable representatives will be guaranteed an opportunity to refuse providing the patient's data to the sponsor.

10.2.4. Disclosing study findings to patients

Human genome and gene information will not be collected in this study. It is highly improbable that study results include incidental findings or secondary findings, and the disclosure of the study results to patient individually is not planned for this reason. The study results will be published in the manner described in "10.8 Registration and publication of study".

10.3. Patient withdrawal

10.3.1. Patients who are alive and continue to visit the study site, or were transferred to another medical facility

During the course of this study, the patient can withdraw consent at any time. In any circumstance, every effort should be made to document patient outcomes, whenever possible. If the patient disagrees, the patient's data will be removed from the study database. However, if published already, in such as within a congress presentation or in peer-reviewed manuscripts, the patient's data will not be removed.

10.3.2. Patients who are deceased

When patients' legally acceptable representatives refuse study participation on behalf of the deseased patient during the study period, all data must be removed from the dataset. If the results of this study had disclosed via publication or at a conference at the time of refusal, the patient's data cannot be removed.

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. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

In addition, based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects issued by the Ministry of Education, Culture, Sports, Science and Technology, the Minister of Health, Labour and Welfare, and Welfare and the Ministry of Economy, Trade and Industry, a multicenter study should be reviewed by the central IEC together. However, it is not prohibited for a review to be conducted by the individual IEC at each site.

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 and follow generally accepted research practices described in the "Ethical Guidelines for Life Science and Medical Research Involving Human Subjects" .

10.6. Predictable risks and benefits

This study is a retrospective chart review study. Therefore, participation in this study does not pose specific risks or benefits to individual patients.

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 through 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 through self-report, 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

Before implementation, this study will be registered at the ClinicalTrials.gov. The registered content will be properly updated without delay.

10.9. Secondary use of information obtained from subjects

The data obtained from this study may be used within other studies for different purposes, such as within another study linked to this study or an integrated analysis (meta-analysis) using other research data. Such use will only be possible if another protocol is developed and approved by the IRB/IEC. In such a case, information on the newly specified purpose of use, among other considers, 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 to organizations or individuals outside of the parties responsible for this study shall be limited to cases in which Pfizer Inc. agrees. The ownership of rights, arising from secondary use or provision to external parties shall be determined through consultation with Pfizer Inc. and the parties to which the secondary use or provision of study data is made.

Furthermore, the possibility of future secondary use or external provision of the collected information will be explained to the participants at the time of their enrollment in this study, and informed consent will be obtained.

10.10. Responding to consultations from patients and other related parties

The investigator will set up a helpline for consultations with the patients and other related parties in regard to this study. Information about each site's helpline will be included in the informed consent form and in documents related to opt-outs.

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, 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 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 exposure during pregnancy in studies of pregnant women, data on the exposure to avelumab during pregnancy, are not reportable unless associated with serious or non-serious AEs.

- 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.*”

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 YRR 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 to conferences and/or peer-reviewed journals. 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

15. LIST OF FIGURES

None.

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

”Implementation Structure in This Study” will be prepared independently.

Number	Document reference number	Date	Title
1	ANNEX 1	14 Oct 2022	Implementation structure of this study

ANNEX 2. ADDITIONAL INFORMATION

Not applicable