NON-INTERVENTIONAL STATISTICAL ANALYSIS PLAN FOR SECONDARY DATA COLLECTION STUDY

VERSION HISTORY

Version	Effective Date	Change Type (New, Revise, Admin)	Summary of Revisions
1.0	22-May-2023	New	-

Non-Interventional Study Protocol
<B9991052>

A Multicenter, Non-Interventional, Retrospective, Observational Study Evaluating Real-World Treatment Outcomes in Japanese Patients with Metastatic Renal Cell Carcinoma (mRCC) Treated using Avelumab plus Axitinib as First-line Therapy: J-DART2

Statistical Analysis Plan
(SAP)

Version: 1.0

Author: PPD

Date: 22-May-2023

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable

2 INTRODUCTION

2.1 STUDY DESIGN

The present study is a multicenter, non-interventional, retrospective, medical chart review of patients with metastatic renal cell carcinoma (mRCC) who received avelumab plus axitinib as first-line therapy in Japan between December 20, 2019, and October 17, 2022.

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

Study population

This retrospective chart review will evaluate patient data derived from the existing medical records of all 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 will range from December 20, 2019, to October 31, 2022. Patients with an index date between December 20, 2019, and October 17, 2022, will be enrolled in this study. To ensure a two-week follow-up period, patients with an index date between December 20, 2019, and October 17, 2022, will be included. The two-week follow-up period is determined based on the dosing interval for avelumab, considering that the time of initiation of avelumab and axitinib may differ.

Index date: The date of the first prescription of avelumab plus axitinib combination therapy.

Observation period: Patients will be followed-up from the index date to October 31, 2022.

※The date of the first prescription of avelumab plus axitinib combination therapy is the administration start date of the drug initiated first.

Data source

Considering the retrospective nature of the study, all data will be collected from patient medical records at the participating study sites.

Treatment/cohort labels

Avelumab plus axitinib combination therapy

2.2 STUDY OBJECTIVES

Primary objective

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

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 progression-free survival (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 applicability of corticosteroids for immune-related adverse events (irAEs) occurring during the course of 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.*

CCI [redacted]

3 HYPOTHESES AND DECISION RULES

3.1 STATISTICAL HYPOTHESES

This study is not intended to test hypotheses.

3.2 STATISTICAL DECISION RULES

A two-sided 95% confidence interval will be calculated for interval estimation. In addition, no multiplicity adjustment will be performed.

4 ANALYSIS SETS/POPULATIONS

4.1 FULL ANALYSIS SET (FAS)

The FAS will comprise patients who meet the inclusion criteria and do not meet the exclusion criteria.

Inclusion criteria

1) Diagnoses of mRCC based on the General Rule for Clinical and Pathological Studies on RCC (Fifth Edition) before the administration of avelumab plus axitinib

as first-line therapy. Patients with mRCC presenting with unresectable disease, either a unresectable locally advanced or metastatic disease.

2) *Age over 18 years at the time of the first administering of avelumab plus axitinib a as first-line therapy for mRCC (baseline).*
3) *Index date from December 20, 2019, to October 17, 2022.*

Exclusion criteria

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

4.2 SAFETY ANALYSIS SET

Not applicable

4.3 OTHER ANALYSIS SET

Efficacy analysis set

The efficacy analysis set is a subset of the FAS comprising patients whose index date is prior to April 30, 2022, to ensure a 6-month follow-up period.

4.4 SUBGROUPS

A subgroup analysis will be considered, including but not limited to the subgroups categorized by IMDC (International Metastatic RCC Database Consortium) risk group, age (≧ 75 years or < 75 years), and the administration of corticosteroid therapy for irAE in the medical record.

5 ENDPOINTS AND COVARIATES

Handling of data on the number of days

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

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

The number of days will be handled as follows:

✓1 week = 7 days

✓1 month = 30.4375 days

✓1 year = 365.25 days

In addition, missing data will be imputed with reference to "6. HANDLING OF MISSING VALUES."

5.1 EFFICACY/EFFECTIVENESS ENDPOINT(S)

＜Derivation of time-to-event variables＞

Item	Derivation method
Real-world progression-free survival (PFS)	Defined as the period from the start date of avelumab plus axitinib combination therapy to

	the date of first disease progression (clinical evaluation based on radiographic, clinical, and pathological examinations, as well as other evaluations by the principal investigator or co-investigator) or death from any cause, whichever occurs earlier. If there is no clinical record of death or disease progression, the following dates will be used for censoring, based on medical records: (1) If first-line therapy is ongoing, the final progression-free confirmation date or the date of the last hospital visit, whichever is earlier, will be used for censoring. (2) If second-line therapy has not been initiated after the end of first-line therapy, the final progression-free confirmation date or the date of the last hospital visit, whichever is earlier, will be used for censoring. (3) If second-line therapy has been initiated, the date of initiating the second-line therapy will be used for censoring. (4) If nephrectomy has been performed, the date of nephrectomy will be used for censoring.
Reasons for real-world PFS events	Reasons for real-world PFS events are defined as follows: "Disease progression after the initiation of avelumab plus axitinib combination therapy" will be selected if there was disease progression after starting avelumab plus axitinib combination therapy. "Death" will be selected if the patient has died.
Reasons for censoring real-world PFS	Reasons for censoring real-world PFS are defined as follows: "No disease progression during or after first-line therapy" will be selected if first-line therapy is ongoing or if second-line therapy has not been initiated after the end of first-line therapy. "Second-line therapy started" will be selected if second-line therapy has been initiated. "Nephrectomy performed" will be selected if nephrectomy has been performed.
Overall survival (OS)	Defined as the period from the initiation of avelumab plus axitinib combination therapy to the date of death from any cause. If there is no

	record of death, the date when the survival of the patient was last confirmed on record (date of last hospital visit) will be used for censoring.
Time to treatment discontinuation (TTD) of avelumab plus axitinib combination therapy as first-line therapy	Defined as the period from the date of initiation of avelumab plus axitinib combination therapy to the date of ending treatment* for any reason (excluding discontinuation due to efficacy). In the case of discontinuation due to efficacy, the date of last administration will be used for censoring. If treatment has not ended, the date of the last hospital visit will be used for censoring. * The end date of treatment is the date of last avelumab administration + 13 days or the date of last axitinib administration, whichever occurs later, or the data-cut date, if performed earlier.
TTD of avelumab as first-line therapy	Defined as the period from the date of initiation of avelumab to the date of ending administration* for any reason (excluding discontinuation due to efficacy). In the case of discontinuation due to efficacy, the date of the last avelumab administration will be used for censoring. If treatment has not ended, the date of the last hospital visit will be used for censoring. * The end date of avelumab therapy is the date of the last avelumab administration + 13 days or the data-cut date, whichever occurs earlier.
TTD of axitinib as first-line therapy	Defined as the period from the date of initiation of axitinib to the date of ending administration* for any reason (excluding discontinuation due to efficacy). In the case of discontinuation due to efficacy, the date of the last axitinib administration will be used for censoring. If treatment has not ended, the date of the last hospital visit will be used for censoring. * The end date of axitinib is the date of the last axitinib administration.
Reasons for the TTD event	Reasons for TTD event are defined as follows: Disease progression/adverse event/other (death)/other (excluding death)
Reasons for censoring TTD	Reasons for censoring TTD are defined as follows: "Treatment ongoing" will be selected if the treatment is ongoing.

	" discontinuation due to efficacy " will be selected in case of discontinuation due to efficacy.

＜Derivation of categorical variables＞

Item	Derivation method
Objective response to avelumab plus axitinib combination therapy	Determination of the best overall response (tumor assessment) is categorized as follow: "Objective response" when "CR" or "PR." "Non-objective response" when "SD," "PD," or "NE".
Objective response of primary lesions	Determination of the best overall response (tumor assessment) is categorized as follow: "Objective response" when "CR" or "PR." "Non-Objective response " when "SD," "PD," or "NE."

CR, complete response; PR, partial response; PD, progressive disease; NE, not evaluable for response; SD, stable disease.

5.2 SAFETY ENDPOINTS

Not applicable

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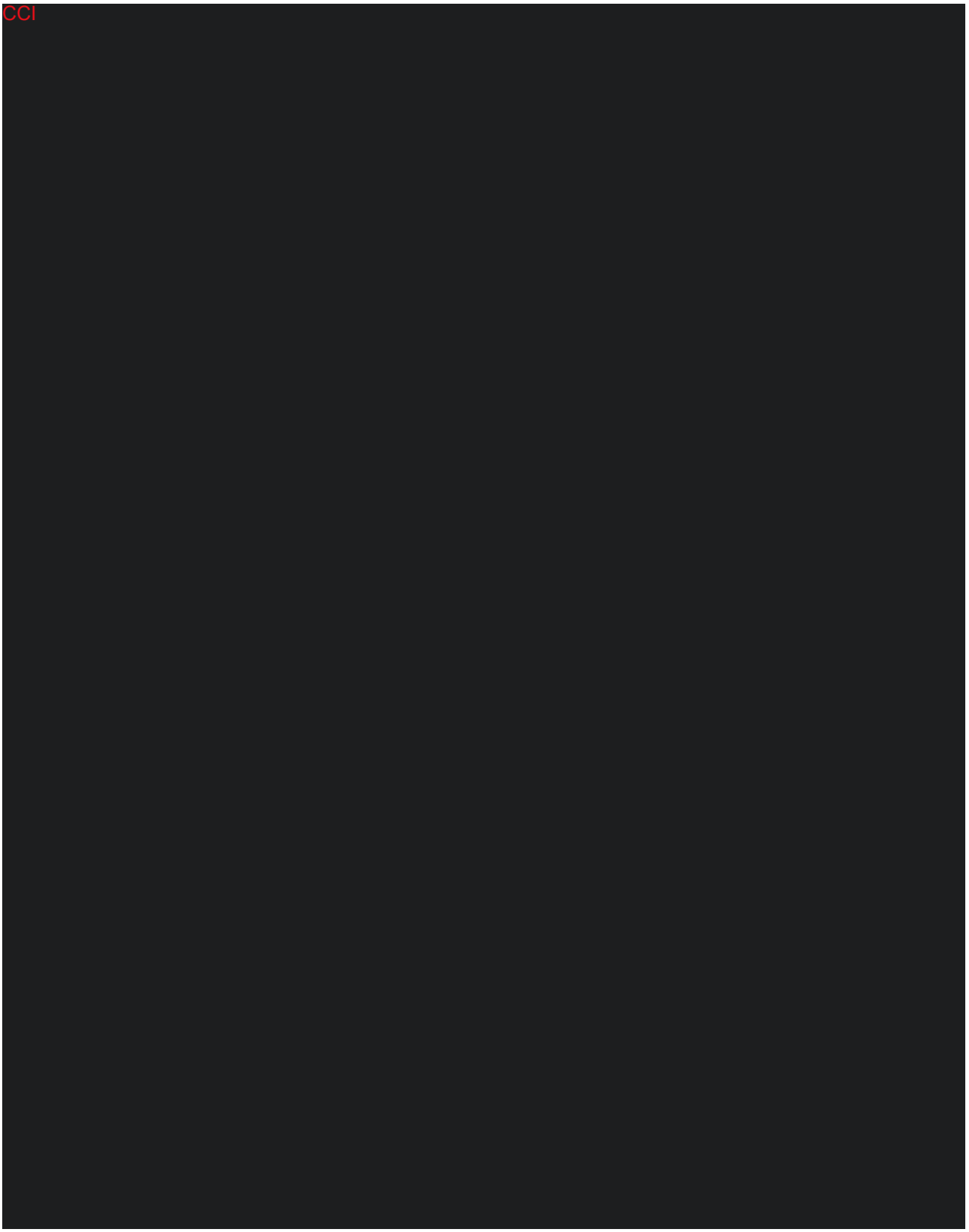
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＜Derivation of categorical variables＞

Item	Derivation method
Age (2 categories)	Age is divided into the following categories: <75 years; ≥75 years
Age (3 categories)	Age is divided into the following categories: <65 years; ≥65 years and <75 years; ≥75 years
Body mass index (BMI) (3 categories)	BMI is divided into the following categories: <25 kg/m^2; ≥25 kg/m^2; Unknown
C-reactive protein (CRP) (3 categories)	CRP is divided into the following categories: <5 mg/L; ≥5 mg/L; Unknown ※Categorized as "Unknown" if CRP is missing (Not measured)
Estimated glomerular filtration rate (eGFR) (3 categories)	eGFR is divided into the following categories: <60; ≥60; Unknown ※Categorized as "Unknown" if eGFR is missing (Not measured)
Fuhrman grade (3 categories)	Fuhrman grade is divided into the following categories: Grade 1 or Grade 2; Grade 3 or Grade 4; Unknown

Metastatic site: Lung	"Yes" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is "Lung." "No" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is not "Lung" or if the presence or absence of metastasis is "No." "Unknown" will be selected if the presence or absence of metastasis is "Unknown."
Metastatic site: Liver	"Yes" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is "Liver." "No" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is not "Liver" or if the presence or absence of metastasis is "No." "Unknown" will be selected if the presence or absence of metastasis is "Unknown."
Metastatic site: Bone	"Yes" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is "Bone." “No” will be selected if the presence or absence of metastasis is “Yes” and the metastatic site is not “Bone” or if the presence or absence of metastasis is “No.” "Unknown" will be selected if the presence or absence of metastasis is "Unknown."
Metastatic site: Brain	"Yes" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is "Brain." "No" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is not "Brain" or if the presence or absence of metastasis is "No." "Unknown" will be selected if the presence or absence of metastasis is "Unknown."
Metastatic site: Regional lymph node	"Yes" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is "Regional lymph node." "No" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is not "Regional lymph node" or if the presence or absence of metastasis is "No."

	"Unknown" will be selected if the presence or absence of metastasis is "Unknown."
Metastatic site: Distant lymph node	"Yes" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is a "Distant lymph node." "No" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is not a "Distant lymph node" or if the presence or absence of metastasis is "No." "Unknown" will be selected if the presence or absence of metastasis is "Unknown."
Metastatic site: Other	"Yes" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is "Other." "No" will be selected if the presence or absence of metastasis is "Yes" and the metastatic site is not "Other" or if the presence or absence of metastasis is "No." "Unknown" will be selected if the presence or absence of metastasis is "Unknown."
ECOG Performance Status ①	ECOG Performance Status is divided into the following categories: 0; 1; ≥2
ECOG Performance Status ②	ECOG Performance Status is divided into the following categories: 0 or 1; ≥2
Number of risk factors (7 categories)	The number of risk factors is divided into the following categories: 0; 1; 2; 3; 4; 5; 6
Initial dose of avelumab [daily dose (mg)]	The initial dose of avelumab is divided into the following categories: <10 mg/kg; 10 mg/kg; >10 mg/kg
Initial dose of axitinib [daily dose (mg)]	The initial dose of axitinib is divided into the following categories: <2 mg; ≥2 mg and <5 mg; ≥5 mg and <10 mg; <10 mg; 10 mg; >10 mg
Presence or absence of changes in the avelumab dose	"Yes" will be selected if the dose of avelumab was changed even once. "No" will be selected if the dose was unchanged.
Presence or absence of changes in the avelumab dose (dose reduction)	"Yes" will be selected if the dose of avelumab was changed (dose reduction) even once. "No" will be selected if the dose was unchanged (dose reduction).

Presence or absence of change in the dose of avelumab (dose increase)	"Yes" will be selected if the dose of avelumab was changed (dose increase) even once. "No" will be selected if the dose was unchanged.
Presence or absence of changes in the axitinib dose	"Yes" will be selected if the dose of axitinib was changed even once. "No" will be selected if the dose was unchanged.
Presence or absence of changes in the axitinib dose (dose reduction)	"Yes" will be selected if the dose of axitinib was changed (dose reduction) even once. "No" will be selected if the dose was unchanged.
Presence or absence of changes in the axitinib dose (dose increase)	"Yes" will be selected if the dose of axitinib was changed (dose increase) even once. "No" will be selected if the dose was unchanged.
Administration of high-dose corticosteroid therapy for iRAE	“Yes” will be selected if the prednisolone-equivalent* daily dose was ≥40 mg. Otherwise, “No” will be selected.

*In addition, the corticosteroid-equivalent dose (prednisolone-equivalent) is calculated as the dose of the drug × prednisolone conversion ratio, according to the table below:

General name	Corresponding dose (mg)	Prednisolone conversion ratio
Cortisone	25	0.2
Hydrocortisone	20	0.25
Prednisolone	5	1
Methylprednisolone	4	1.25
Triamcinolone	4	1.25
Dexamethasone	Approximately 0.75	6.67
Betamethasone	Approximately 0.75	6.67

5.4 COVARIATES

- Age (2 categories)
- Body mass index (BMI) (3 categories)
- C-reactive protein (CRP) (3 categories)
- Estimated glomerular filtration rate (eGFR) (3 categories)
- Smoking history
- ECOG Performance Status
- ECOG Performance Status ①
- ECOG Performance Status ②
- Tumor histological type
- Presence or absence of sarcomatoid component
- Fuhrman grade (3 categories)
- Performance of nephrectomy
- Metastatic site: Lung

- Metastatic site: Liver
- Metastatic site: Bone
- Metastatic site: Brain
- Metastatic site: Regional lymph node
- Metastatic site: Distant lymph node
- Metastatic site: Other
- Number of metastatic organs (5 categories)
- Presence or absence of clinically important comorbidities
- Presence or absence of clinically important concomitant drugs
- Less than 1 year from diagnosis to the initiation of systemic therapy
- Karnofsky Performance Status <80%
- Hemoglobin value below the lower normal limit
- Corrected calcium value above the upper normal limit
- Neutrophil count above the upper normal limit
- Platelet count above the upper normal limit
- IMDC risk group
- Administration of corticosteroid therapy for irAEs

6 HANDLING OF MISSING VALUES

An absence of data for analysis will be treated as missing values, and no special imputation processing will be performed using statistical methods. In addition, the missing data regarding dates will be treated as follows:

✓If "year" is unknown: Missing

✓If "month" is unknown: July

✓If "day" is unknown: day 15

✓If "month" and "day" are unknown: July 1

Other than the above, the imputation of the missing values will not be performed, unless otherwise specified.

If the above imputation measures result in the reversal of dates when calculating the number of days (e.g., the number of days from the initiation to the end of the treatment), it will not be adopted for analysis.

7 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

7.1 STATISTICAL METHODS

Summary statistics

For summary statistics described in this plan, the following values will be calculated, unless otherwise specified:

Number of cases, number of missing cases, mean, standard deviation, minimum, quartiles, and maximum

Number of digits
The percentage (%) of frequency distribution will be rounded to one decimal place, unless otherwise specified, in the individual analysis items. Considering the summary statistics items (number of cases, number of missing cases, mean, standard deviation, minimum, quartiles, and maximum), mean, standard deviation, and quartiles will be rounded such that the decimal places are one digit lower than the original data.

7.2 STATISTICAL ANALYSES

7.2.1 Safety analyses

Not applicable

7.2.2 Analysis of primary, secondary, and CCI

Analysis of primary endpoints

7.2.2.1 Demographic and clinical characteristics of patients

Source population : FAS, Efficacy analysis set

Endpoints :

Continuous variables
Age
Height
Body weight
BMI
CRP
eGFR
Number of metastatic organs
Number of risk factors
Observation duration （months）

Categorical variables
Age (2 categories)
Age (3 categories)
BMI (3 categories)
Gender
CRP (3 categories)
eGFR (3 categories)
Smoking history
ECOG Performance Status
ECOG Performance Status ①
ECOG Performance Status ②
Invasion depth (T factor)
Lymph node metastasis (N factor)
Distant metastasis (M factor)
Tumor histological type
Presence or absence of sarcomatoid component

Fuhrman grade
Fuhrman grade (3 categories)
Proteinuria
Performance of nephrectomy
Presence or absence of metastasis
  Metastatic site
  Metastatic site: Lung
  Metastatic site: Liver
  Metastatic site: Bone
  Metastatic site: Brain
  Metastatic site: Regional lymph node
  Metastatic site: Distant lymph node
  Metastatic site: Other
Number of metastatic organs (5 categories)
Presence or absence of clinically important comorbidities
Presence or absence of clinically important concomitant drugs
Less than 1 year from diagnosis to the initiation of systemic therapy
Karnofsky Performance Status <80%
Hemoglobin value below the lower normal limit
Corrected calcium value above the upper normal limit
Neutrophil count above the upper normal limit
Platelet count above the upper normal limit
IMDC risk group
Number of risk factors (7 categories)
Breakdown of IMDC risk factors by the number of risk factors

Analysis content : The following aggregation will be performed for endpoints:
Summary statistics will be calculated for continuous variables.
A frequency table (number of cases, percentage (%)) will be created for categorical variables.
A frequency table (number of cases, percentage (%)) will also be created for details regarding clinically important comorbidities and concomitant drugs

【Division of categorical variables】

Factor	Category
Age (2 categories)	<75 years; ≥75 years
Age (3 categories)	<65 years; ≥65 years and <75 years; ≥75 years
Gender	Male; Female
Body mass index (3categories)	<25 kg/m^2; ≥25 kg/m^2; Unknown
C-reactive protein (3 categories)	<5 mg/L; ≥5 mg/L; Unknown
Estimated glomerular filtration rate (3 categories)	<60; ≥60; Unknown
Smoking history	No (no past smoking); No (history of past smoking); Yes; Unknown

ECOG Performance Status	0; 1; 2; 3; 4
ECOG Performance Status ①	0; 1; ≥2
ECOG Performance Status ②	0 or 1; ≥2
Invasion depth (T factor)	TX; T0; T1; T1a; T1b; T2; T2a; T2b; T3; T3a; T3b; T3c; T4; Unknown
Lymph node metastasis (N factor)	NX; N0; N1; Unknown
Distant metastasis (M factor)	MX; M0; M1; Unknown
Tumor histological type	Clear cell renal cell carcinoma; Papillary renal cell carcinoma; Chromophobe renal cell carcinoma; Other
Presence or absence of sarcomatoid component	No; Yes
Fuhrman grade	Grade 1; Grade 2; Grade 3; Grade 4; Unknown
Fuhrman grade (3 categories)	Grade 1 or Grade 2; Grade 3 or Grade 4; Unknown
Proteinuria	–; ±; 1+; 2+; 3+; Not measured
Performance of nephrectomy	No; Yes; Unknown
Presence or absence of metastasis	No; Yes; Unknown
Metastatic site	Lung; Liver; Bone; Brain; Regional lymph node; Distant lymph node; Other
Metastatic site: Lung	No; Yes; Unknown
Metastatic site: Liver	No; Yes; Unknown
Metastatic site: Bone	No; Yes; Unknown
Metastatic site: Brain	No; Yes; Unknown
Metastatic site: Regional lymph node	No; Yes; Unknown
Metastatic site: Distant lymph node	No; Yes; Unknown
Metastatic site: Other	No; Yes; Unknown
Number of metastatic organs	0; 1; 2; 3; ≥4
Presence or absence of clinically important comorbidities	No; Yes; Unknown
Presence or absence of clinically important concomitant drugs	No; Yes; Unknown
Less than 1 year from diagnosis to the initiation of systemic therapy	Yes; No
Karnofsky Performance Status <80%	Yes; No
Hemoglobin value below the lower normal limit	Yes; No
Corrected calcium value above the upper normal limit	Yes; No

Neutrophil count above the upper normal limit	Yes; No
Platelet count above the upper normal limit	Yes/; No
IMDC risk group	Low risk; Medium risk; High risk
Number of risk factors (7 categories)	0; 1; 2; 3; 4; 5; 6

Analysis of secondary objectives

7.2.2.2 Real-world progression-free survival

Source population : Efficacy analysis set

Endpoint : Real-world PFS

Analysis content : For the endpoint, the median and its 95% confidence interval will be calculated using the Kaplan–Meier method. In addition, the Kaplan–Meier curve will be plotted, and the PFS rate for every 12 months and its 95% confidence interval will be calculated. Greenwood's formula will be used to calculate the confidence interval for the PFS rate.
In addition, the number of event-onset cases and the number of censored cases will be presented. A frequency table (number of cases, percentage (%)) will be created, considering the reasons for the event and reasons for censoring.
In order to evaluate the observation period, the median observation period and its 95% confidence interval will be calculated by estimating the reverse Kaplan-Meier curve in which censoring patients are regarded as patients with events and patients with events are regarded as censoring patients.

【Division of categorical variables】

Factor	Category
Reasons for the event	Disease progression after the start of avelumab plus axitinib; Death
Reasons for the censoring	No disease progression during or after first-line therapy; second-line therapy started; nephrectomy performed

7.2.2.3 Overall survival (OS)

Source population : Efficacy analysis set

Endpoint : OS

Analysis content : For the endpoint, the median and its 95% confidence interval will be calculated using the Kaplan–Meier method. In addition, the Kaplan–Meier curve will be plotted, and the survival rate for every 12 months

and its 95% confidence interval will be calculated. Greenwood's formula will be used to calculate the confidence interval for the survival rate.
In addition, a frequency table (number of cases, percentage (%)) will be created, considering the event onset, censoring, reasons for the event, and reasons for censoring.
In order to evaluate the observation period, the median observation period and its 95% confidence interval will be calculated by estimating the reverse Kaplan-Meier curve in which censoring patients are regarded as patients with events and patients with events are regarded as censoring patients.

【Division of categorical variables】

Factor	Category
Reasons for the event (cause of death)	Death from primary disease; Death related to avelumab plus axitinib combination therapy; Death not related to avelumab plus axitinib combination therapy
Reasons for censoring	Survival; Untraceable

7.2.2.4 Objective response rate (ORR)

Source population : Efficacy analysis set

Endpoints : ORR
Presence or absence of confirmation of BOR to treatment
Evaluation method
Determination of BOR (tumor assessment)

Analysis content : The number of target cases, number of objective responding cases, and objective response rate and its 95% confidence interval will be calculated to establish the ORR of the endpoint.
In addition, the Clopper–Pearson method will be used to calculate the confidence interval.
In addition, a frequency table (number of cases, percentage (%)) will also be created, considering the achievement of BOR to treatment, evaluation method, and determination of BOR (tumor assessment).

【Division of categorical variables】

Factor	Category
Objective response to avelumab plus axitinib combination therapy	Objective response
Achievement of the best overall response to treatment	No; Yes
Evaluation method	RECIST; Other than RECIST

Determination of best overall response (tumor assessment)	CR; PR; SD; PD; NE

CR, complete response; PR, partial response; PD, progressive disease; NE, not evaluable for response.

7.2.2.5 Best overall response for primary lesions

Source population : Efficacy analysis set

Endpoints : ORR
Presence or absence of confirmation of BOR to treatment
Evaluation method
Determination of BOR (tumor assessment)

Analysis content : The number of target cases, number of objective responding cases, and objective response rate and its 95% confidence interval will be calculated to establish the ORR of the endpoint.
In addition, the Clopper–Pearson method will be used to calculate the confidence interval.
A frequency table (number of cases, percentage (%]) will also be created, considering the achievement of BOR to treatment, evaluation method, and determination of BOR (tumor assessment).

【Division of categorical variables】

Factor	Category
Objective response of primary lesions	Objective response
Achievement of best overall response to treatment	No; Yes
Evaluation method	RECIST; Other than RECIST
Determination of best overall response (tumor assessment)	CR; PR; SD; PD; NE

CR, complete response; PR, partial response; PD, progressive disease; NE, not evaluable for response.

7.2.2.6 Time to treatment discontinuation (TTD) of avelumab plus axitinib combination therapy as first-line therapy

Source population : Efficacy analysis set

Endpoints : TTD of avelumab plus axitinib combination therapy as first-line therapy
TTD of avelumab as first-line therapy
TTD of axitinib as first-line therapy

Analysis content : Considering the endpoints, the median and its 95% confidence interval will be calculated using the Kaplan–Meier method. In addition, the Kaplan–Meier curve will be plotted, and the survival

rate for every 3 months, along with its 95% confidence interval, will be calculated. Greenwood's formula will be used to calculate the confidence interval for the survival rate.
In addition, a frequency table (number of cases, percentage (%)])will be created, considering the event onset, censoring, reasons for the event, and reasons for censoring.

【Division of categorical variables】

Factor	Category
Reasons for the event	Disease progression/adverse event/other (death)/other (excluding death)
Reasons for the censoring	Treatment ongoing; Discontinuation due to efficacy

7.2.2.7 Treatment patterns for avelumab plus axitinib combination therapy as first-line therapy in a real-world setting

Source population : FAS, Efficacy analysis set

Endpoints : Continuous variables
Duration of treatment for avelumab plus axitinib (days)
Duration of treatment for avelumab (days)
Duration of treatment for axitinib (days)
Initial dose of avelumab [daily dose (mg)]
Initial dose of axitinib [daily dose (mg)]
Avelumab dose intensity (DI)
Axitinib DI
Axitinib relative DI (RDI)[1)]

Categorical variables
Initial dose of avelumab [daily dose (mg)]
Initial dose of axitinib [daily dose (mg)]
Presence or absence of changes in the avelumab dose [2)]
Presence or absence of changes in the avelumab dose (dose reduction) [2)]
Reason for changes in the avelumab dose (dose reduction) [2)3)]
Presence or absence of change in the avelumab dose (dose increase) [2)]
Termination of avelumab administration
Reason for termination of avelumab administration
Presence or absence of changes in the axitinib dose [2)]
Presence or absence of changes in the axitinib dose (dose reduction)
Reason for change in the dose of axitinib (dose reduction) [2)3)]
Presence or absence of changes in the axitinib dose (dose increase) [2)]
Termination of axitinib administration

Reason for termination of axitinib administration

Notes:
1) 10 mg/day is set as the criterion.
2) Dose changes will be aggregated based on the input items, considering the administration status in the case report form. The criteria for dose changes will be determined based on the record of the immediately preceding administration for both avelumab and axitinib.
3) Considering the reason for dose reduction, if the same reason is documented in multiple records of the case, each reason will be counted as one case.

Analysis content : The following aggregation will be performed for the endpoints:
Summary statistics will be calculated for continuous variables.
A frequency table (number of cases, percentage (%]) will be created for categorical variables.
In addition, a list presenting the reasons underlying the changes in the avelumab dose (dose increase) and those underlying changes in the axitinib dose (dose increase) will be created.
Furthermore, a swimmer plot with the date of initiation as the avelumab + axitinib administration start date (earlier date if they are different) will be created.

【Division of categorical variables】

Factor	Category
Initial avelumab dose [daily dose (mg)]	<10 mg/kg; 10 mg/kg; >10 mg/kg
Initial axitinib dose [daily dose (mg)]	<2 mg; ≥2 mg and <5 mg; ≥5 mg and <10 mg; <10 mg; 10 mg; >10 mg
Presence or absence of changes in the avelumab dose	No; Yes
Presence or absence of changes in the avelumab dose (dose reduction)	No; Yes
Reason for changes in the avelumab dose (dose reduction)	Disease progression; Adverse event; discontinuation due to efficacy ; Other
Presence or absence of changes in the avelumab dose (dose increase)	No; Yes
Termination of avelumab administration	No; Yes
Reason for termination of avelumab administration	Disease progression; Adverse event; discontinuation due to efficacy ; Other
Presence or absence of changes in the axitinib dose	No; Yes

Presence or absence of changes in the axitinib dose (dose reduction)	No; Yes
Reason for changes in the axitinib dose (dose reduction)	Disease progression; Adverse event; discontinuation due to efficacy ; Other
Presence or absence of changes in the axitinib dose (dose increase)	No; Yes
Termination of axitinib administration	No; Yes
Reason for termination of axitinib administration	Disease progression; Adverse event; discontinuation due to efficacy ; Other

7.2.2.8 Clinical use of corticosteroids for immune-related adverse events (irAEs) occurring during the course of avelumab plus axitinib combination therapy

Source population : FAS, Efficacy analysis set

Endpoints : Continuous variable
Duration of treatment for corticosteroids (days)

Categorical variables
Administration of corticosteroid therapy for irAEs
Administration of high-dose corticosteroid therapy for irAEs (prednisolone-equivalent of ≥40 mg)

Analysis content : The following aggregation will be performed for the endpoints:
Summary statistics will be calculated for continuous variables.
A frequency table (number of cases, percentage (%)) will be created for categorical variables.
In addition, a frequency table (number of cases, percentage (%)) will also be created for the details of other drugs.

【Division of categorical variables】

Factor	Category
Administration of corticosteroid therapy for irAEs	No; Yes; Unknown
Administration of high-dose corticosteroid therapy for irAEs	No; Yes

irAEs, immune-related adverse events

7.2.2.9 Pre-treatment and treatment of infusion-related reactions caused by avelumab

Source population : FAS, Efficacy analysis set

Endpoints : Presence or absence of premedication
Detailed name of the drug
Presence or absence of treatment and coping

Analysis content : A frequency table (number of cases, percentage (%)) will be created for the endpoints.

【Division of categorical variables】

Factor	Category
Presence or absence of premedication	No; Yes; Unknown
Presence or absence of treatment and coping	No; Yes; Unknown

7.2.2.10 Subsequent treatment of avelumab plus axitinib combination therapy

Source population : FAS, Efficacy analysis set

Endpoints : Continuous variables
Second-line therapy period (days)
The period from the end date of first-line therapy to the beginning of second-line therapy (days)

Categorical variables
Performance of nephrectomy after avelumab plus axitinib combination therapy
Presence or absence of second-line therapy
Drug category
Second-line therapy regimen by drug category

Analysis content : The following aggregation will be performed for the endpoints:
Summary statistics will be calculated for continuous variables.
The period from the end date of first-line therapy to the beginning of second-line therapy (days) will also be estimated, considering the reason for termination of administration.
A frequency table (number of cases, percentage (%)) will be created for categorical variables.

【Division of categorical variables】

Factor	Category
Performance of nephrectomy after avelumab plus axitinib combination therapy	No; Yes
Presence or absence of second-line therapy	No; Yes; Unknown
Drug category	TKI; mTOR; IO; Other

mTOR, mammalian target of rapamycin; IO, immunotherapy; TKI, tyrosine kinase inhibitor.

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8 LIST OF TABLES AND TABLE SHELLS

Not applicable

9 REFERENCES

Not applicable

10 APPENDIXES

Not applicable

10.1 APPENDIX 1: DATA DERIVATION DETAILS

Not applicable

A1.1 Definition and use of visit windows in reporting

Not applicable

A1.2 Further definition of endpoints

Not applicable

10.2 APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

Not applicable

A2.1 Further details regarding the statistical methods

Not applicable

10.3 APPENDIX 3: DIAGNOSIS AND PROCEDURE CODES USED IN THE STUDY

Not applicable