# 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

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# Statistical Analysis Plan

Version 1.0

| | Affiliation | Name | Title | Signature |
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DOCUMENT HISTORY

| Version | Date of Issue | Summary of Change |
|---|---|---|
| 1.0 | 24 Dec 2021 | Not Applicable |

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# 1 OBJECTIVE OF THIS DOCUMENT

This statistical analysis plan (hereafter referred to as "this document") is prepared for the purpose of describing the detailed statistical analysis in "9.7 Statistical Analysis" of the protocol for the observational study, “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 (J-DART)” (hereafter referred to as "this study"), conducted by Pfizer Japan Inc. (hereafter referred to as "Pfizer"). The results of the analysis described in this document will be presented in the "Sample Statistical Analysis Charts and Figures," which will be prepared separately.

# 2 GLOSSARY AND ABBREVIATIONS

The following are abbreviations and definitions of terms used in this document.

| Abbreviation | Definition |
|---|---|
| CI | Confidence Interval |
| OS | Overall Survival |
| PFS | Progression Free Survival |
| TTF | Time to Treatment Failure |
| ORR | Objective Response Rate |
| CR | Complete Response |
| PR | Partial Response |
| SD | Stable Disease |
| PD | Progressive Disease |
| DI | Dose Intensity |
| Q1 | 1st Quartile |
| Q3 | 3rd Quartile |

# 3 SOFTWARES

The following is a list of software and its versions used in the statistical analysis work of this study.

| Software | Version |
|---|---|
| OS | Windows 10 |
| Statistical analysis | SAS 9.4 |
| Spreadsheet, document creation, slide creation | Microsoft Office 2016 |

# 4 SUMMARY OF STUDY DESIGN

1) Objective

(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.

(2) Secondary objective

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.

2) 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 settings 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

3) Study drug

Avelumab (BAVENCIO®)

4) Inclusion and exclusion criteria

➢ 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.

- Exclusion criteria
  - There are no exclusion criteria for this study.

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.

# 5 ANALYSIS POPULATION

## 5.1 Enrolled patients

All patients enrolled in this study.

## 5.2 Analysis population

Enrolled patients who meet all the inclusion criteria.

# 6 DATA HANDLING

## 6.1 Handling of omitted or missing data

- If date data is missing, it will be handled as follows:
  - If "year" is unknown, it will be treated as missing.
  - If "month" is unknown, July will be used.
  - If "date" is unknown; 15th will be used
  - If "month and date" are unknown, 1st July will be used.
- Except as noted above, missing values will not be supplemented.

- If the above supplementation results in reversal of days in the calculation of the number of days (e.g., the number of days from the start of treatment to the end of treatment), it will not be adopted in the analysis.

## 6.2 Handling of days

- 1 week = 7 days
- 1 month = 30.4375 days
- 1 year = 365.25 days

## 6.3 Derivation variables

1) Survival time analysis

It is defined as follows:

| Endpoint | Start date | End date (event) | End date (censor) |
|---|---|---|---|
| Real-world PFS | Date treatment with avelumab and/or axitinib was initiated (if not on the same day, whichever occurs earlier) | Date of first disease progression (clinical evaluation based on radiological, laboratory, pathological, or other evaluation by the principal investigator) or death from any cause, whichever occurs earlier | Date of last confirmation of progression-free survival or start of subsequent treatment (whichever occurs earlier) |
| TTF of avelumab and axitinib | Date treatment with avelumab and/or axitinib was initiated | Date of completion of treatment with avelumab and/or axitinib | Date of last confirmation of progression-free survival or date of last dose in case of efficacy stopping (whichever date occurs earlier) |
| TTF of avelumab | Date treatment with avelumab was initiated | Date of completion of treatment with avelumab | Date of last confirmation of progression-free survival or date of last dose in case of efficacy stopping (whichever date occurs earlier) |
| TTF of axitinib | Date treatment with axitinib was initiated | Date of completion of treatment with axitinib | Date of last confirmation of progression-free survival or date of last dose in case of efficacy stopping (whichever date occurs earlier) |

2) Objective response rate

ORR is defined as the proportion of patients with a CR or PR as the best overall response in tumor assessment during the observation period, as assessed by an investigator under actual clinical practice, including assessment based on RECIST ver. 1.1.

3) Calculation of duration

| Duration | Definition |
|---|---|
| Duration of avelumab treatment | Date of last dose – date of initial dose + 14 |
| Duration of axitinib treatment | Date of last dose – date of initial dose + 1 |
| Duration of non-administration | Date of end – Date of start + 1 |

4) Corticosteroid equivalent dose (prednisolone equivalent)

This will be calculated as shown in the table below.

| Generic name | Corresponding amount (mg) | Prednisolone conversion ratio |
|---|---|---|
| Cortisone | 25 | 0.2 |
| Hydrocortisone | 20 | 0.25 |
| Prednisolone | 5 | 1 |
| Methylprednisolone | 4 | 1.25 |
| Triamcinolone | 4 | 1.25 |
| Dexamethasone | 0.75 | 6.7 |
| Betamethasone | 0.6 | 8.3 |

5) Date of initial dose

If avelumab and axitinib are administered for different durations, the earlier of the two dates should be used as the date of the initial dose.

6) Date of last confirmation of progression-free survival

If there is no or unknown data of progressive disease (PD) in the [Progressive disease (PD) information] of the CRF, the date of diagnosis shall be the date of confirmation of the last progression-free survival.

# 7 GENERAL INFORMATION ON STATISTICAL ANALYSIS

## 7.1 Multiplicity adjustment

This will not be considered.

## 7.2 Summary statistics

Summary statistics for continuous variables will be calculated for observed and missing values, mean, median, standard deviation, minimum, maximum, first quartile, third quartile, etc. Summary statistics for categorical variables will be calculated for frequency and proportion. Other statistics, if calculated, will be described separately.

## 7.3 Significance level of the test

Unless otherwise specified, the significance level will be set to 5%. When confidence intervals are calculated, they should be two-sided with 95% confidence intervals.

## 7.4 Number of digits

In principle, the number of digits to be displayed shall be as shown below. This indicates the number of digits to be displayed in the output of results of the analysis; moreover, no rounding of values will be performed in the calculation process, unless otherwise specified.

| Items | Number of digits |
|---|---|
| Number of patients, cases | Display as an integer |
| Mean, standard deviation, median, and interquartile range | Round off the last two significant digits of the target data, and display to the last digit. |
| Range | Display as significant digits of the target data. |
| Proportion (%) | Round off the second decimal place, and display to the first decimal place. |

## 7.5 Interim analysis

No statistical interim analysis will be performed.

# 8 ANALYSIS METHODS

## 8.1 Subject disposition

| Analysis set | Enrolled patients |
|---|---|
| Details of analysis | Develop a flow chart of the population to be analyzed (eligible patients) and ineligible patients. For ineligible patients, the number of patients who violated each selection criterion is also calculated. |

## 8.2 Primary endpoint

### 8.2.1 Patient characteristics at baseline

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Aggregate patient characteristics as indicated in the definition. Variables observed in quantitative values are calculated as summary statistics, and qualitative variables are tabulated in terms of the number of patients and proportions of patients relative to overall patients and evaluated patients. |
| Definition | - Age<br>- Sex<br>- Body mass index (BMI)<br>- Eastern Cooperative Oncology Group Performance Status (ECOG PS)<br>- International Metastatic RCC Database Consortium (IMDC) risk score<br>- Pathological diagnosis: Fuhrman grade, histological type, Sarcomatoid component<br>- Tumor-node-metastasis (TNM) classification,<br>- Number of metastatic organs and site of metastases<br>- Complications<br>- Nephrectomy<br>- Renal function: estimated glomerular filtration rate (eGFR), proteinuria<br>- C-reactive protein (CRP)<br>- Smoking history<br>- Concomitant drugs |

### 8.2.2 Details of complications

| Analysis set | Analysis population |
|---|---|

| | |
|---|---|
| Details of analysis | Calculate the number and proportion of patients by SOC and PT for each complication. |

### 8.2.3 Details of concomitant drugs

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Tabulate the frequency of concomitant drug use by drug name. |

## 8.3 Secondary endpoint

### 8.3.1 Efficacy endpoint

#### 8.3.1.1 Time-to-treatment failure (TTF) of avelumab plus axitinib as first-line therapy

| Analysis set | Analysis population |
|---|---|
| Details of analysis | The Kaplan-Meier methods is used to plot the duration of TTF and calculate survival probability (estimate, 95% confidence interval), number of patients at risk, cumulative number of events, and cumulative number of censoring every 3 months.<br>In addition, the median duration of TTF, and incidence of events (/100 person-years) and the 95% confidence interval will be calculated. |
| Supplement | <Calculation method for each 95% confidence interval><br>Survival probability: Pointwise confidence limits<br>Median duration of TTF: Greenwood exponential formula<br>Incidence of events: Mantel-Haenszel method |

#### 8.3.1.2 Real-world PFS

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Perform the same analysis as in 8.3.1.1 for real-world PFS. |

#### 8.3.1.3 Objective Response: OR

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Tabulate the best overall response by presence of confirmed BOR, あ all patients, and evaluation method (RECIST and non-RECIST).<br>In addition, calculate the number and proportion of patients with ORR and its 95% confidence interval. |
| Supplement | <Calculation method for each 95% confidence interval> |

| | |
|---|---|
| | ORR:Clopper-Pearson confidence interval |

#### 8.3.1.4 TTF of avelumab

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Perform the same analysis as in 8.3.1.1 for TTF of avelumab. |

#### 8.3.1.5 TTF of axitinib

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Perform the same analysis as in 8.3.1.1 for TTF of axitinib. |

### 8.3.2 Continuation of first-line treatment

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Tabulate the duration of treatment (months), DI, dosing status, and reason for interruption, dose change, or discontinuation of avelumab and axitinib. |
| Definition | ・ Avelumab<br>DI= (actual dose)/(duration of avelumab treatment [weeks]/2) (mg/kg/2-week cycle)<br>・ Axitinib<br>DI=(actual dose)/(duration of axitinib treatment [weeks]) |

### 8.3.3 Corticosteroid-related endpoints

#### 8.3.3.1 Corticosteroid treatment for irAEs during avelumab plus axitinib treatment

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Tabulate the number of patients treated for irAE with corticosteroids. Presence of high-dose corticosteroids treatment (prednisolone equivalent of 40 mg or more) will also be tabulated. |

#### 8.3.3.2 Cumulative corticosteroids dosages for irAEs during avelumab plus acxitinib treatment or monotherapy

| Analysis set | Analysis population |
|---|---|
| Details of analysis | Calculate summary statistics of corticosteroids dosing information for irAE. The dosages to be tabulated are prednisolone equivalents. |

| | |
|---|---|
| | Presence of high-dose corticosteroids treatment (prednisolone equivalent of 40 mg or more) will also be tabulated. |
| Supplement | If the same patient received multiple doses of corticosteroids, each dose should be tabulated separately (including patients who received multiple doses of the same corticosteroid). |

#### 8.3.3.3 Duration of corticosteroids treatment for irAE during avelumab plus axitinib treatment

| | |
|---|---|
| Analysis set | Analysis population |
| Details of analysis | Perform the same analysis as in 8.3.3.2 for duration of corticosteroid treatment. |
| Supplement | If the patient is on continuous corticosteroid treatment, the period should be up to the cut-off date (20 June, 2021). |

#### 8.3.3.4 Number of corticosteroid administrations for irAEs during avelumab plus axitinib treatment

| | |
|---|---|
| Analysis set | Analysis population |
| Details of analysis | Perform the same analysis as in 8.3.3.2 for the number of corticosteroid administrations. |
| Definition | Number of doses: the number of times treatment has been given, counting "treatment start to treatment end" as one dose. |

### 8.3.4 Endpoints for infusion-related reaction

| | |
|---|---|
| Analysis set | Analysis population |
| Details of analysis | Tabulate presence of avelumab treatment for infusion-related reactions, as well as presence of prior therapies and names of drugs. |

### 8.3.5 Subsequent treatment-related endpoints

| | |
|---|---|
| Analysis set | Analysis population |
| Details of analysis | Calculate summary statistics by drug for duration of subsequent treatment following avelumab plus axitinib treatment. |

### 8.3.6 Outcome information

| | |
|---|---|
| Analysis set | Analysis population |

| | |
|---|---|
| Details of analysis | Tabulate the duration from the date of initial dose to the date of last confirmation of survival (or date of death in the cases of death), with the cause of death and the reason for lost to follow-up.<br>In addition, tabulate the status of the first-line treatment and the reason for its discontinuation if the treatment has been discontinued. |

## 9 CHANGES FROM THE PROTOCOL

Not applicable.

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