PASS INFORMATION

Title	Non-interventional post-marketing safety study (PMSS) to collect information on hepatic function disorders among Japanese patients with radically unresectable or metastatic renal cell carcinoma treated with pembrolizumab in combination with axitinib.
Protocol Version identifier	3475-A97/000
Date of last version of protocol	23-MAR-2020
EU PAS Register No:	Study has not yet been registered.
Active substance	L01XC18, monoclonal antibody, pembrolizumab L01XE17, Protein-kinase inhibitors, axitinib
Medicinal product(s):	Keytruda®, pembrolizumab Inlyta®, axitinib
Product reference:	EU marketing authorisation number: EU/1/15/1024/001 EU/1/15/1024/002
Procedure number:	EMA procedure number: EMEA/H/C/003820/II/0069
Marketing authorisation holder(s) (MAH)	MSD K.K.
Joint PASS	No
Research question and objectives	The specific aim of this research study is to collect information on hepatic disorders, including clinical events and/or laboratory elevations with or without hepatic dysfunction among Japanese patients with radically unresectable or metastatic renal cell carcinoma who receive treatment with pembrolizumab in combination with axitinib and to describe treatment and resolution of these adverse events in real-world clinical practice.
Country(-ies) of study	Japan

Author	PPD Drug Safety Operations PPD Drug Safety Operations MSD K.K. 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo, Japan
Merck Final Repository (RCAM) Date	23-MAR-2020
Date of Health Authority Approval of Protocol	The drug-use results survey (DURS) protocol will be reviewed and approved by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) prior to study enrollment.

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CTCAE-JCOG	Common Terminology Criteria for Adverse Events – Japanese Clinical Oncology Group
DURS	Drug-Use Results Survey
EDC	Electronic Data Capture
EMA	European Medicines Agency
GGT	Gamma Glutamyltransferase
GPSP	Good Post-market Study Practice
HCP	Healthcare Practitioner
HR	Hazard Ratio
IDF	Iyakuhinmei Data File
IMDC	International Metastatic RCC Database Consortium
IRB/ERC	Institutional Review Board/ Ethics Review Committee
JPSUR	Japan Periodic Safety Update Report
KN	Keynote
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
MSD	Merck Sharp & Dohme
MSD	Merck Sharp & Dohme
ORR	Objective Response Rate
PASS	Post-authorization safety study
PMDA	Pharmaceutical and Medical Devices Agency
PMS	Post-marketing surveillance
PMSS	Postmarketing safety study
PQC	Product Quality Complaint
PSUR	Periodic Safety Update Report
RCC	Renal Cell Carcinoma
SAP	Statistical Analysis Plan
SDV	Source Data Verification

1 RESPONSIBLE PARTIES

Contact details for the responsible parties at Merck Sharp & Dohme (MSD) KK and designees (such as contract research organization [CRO]) are available upon request.

2 ABSTRACT

Title	Non-interventional post-marketing safety study (PMSS) to collect information on hepatic function disorders among Japanese patients with radically unresectable or metastatic renal cell carcinoma treated with pembrolizumab in combination with axitinib.
Protocol Number / Version	3475-A97/000
Date	23-MAR-2020
Author	PPD Drug Safety Operations PPD Drug Safety Operations Merck Sharp and Dohme (MSD) KK 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo, Japan
Rationale & Background	In KEYNOTE-426 (KN426), a Phase III randomized, open-label study, treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate, than treatment with sunitinib, among previously untreated advanced renal cell carcinoma (RCC) patients. The observed safety profiles of pembrolizumab plus axitinib and of sunitinib were as expected on the basis of the known profiles of these three drugs, although the incidence of grade 3 or 4 elevations in liver enzyme levels in the pembrolizumab plus axitinib group was higher than expected given the known safety profiles of each drug when used as monotherapy.

	As part of the risk management plan (RMP), the Japanese health authority (Pharmaceutical and Medical Devices Agency [PMDA]) is requesting a drug-use results survey (DURS) to collect information on hepatic function disorders in patients with radically unresectable or metastatic renal cell carcinoma treated with pembrolizumab in combination with axitinib, and to describe treatment and resolution of these adverse events. The DURS is a regulated post-marketing surveillance system unique to Japan to collect information on treatment outcomes in routine clinical practice.
Research Question(s) & Objective(s)	The specific aim of this research study is to collect information on hepatic disorders, including clinical events and/or laboratory elevations with or without hepatic dysfunction among Japanese patients with radically unresectable or metastatic renal cell carcinoma who receive treatment with pembrolizumab in combination with axitinib and to describe treatment and resolution of these adverse events in real-world clinical practice.
Study Design	Prospective, open-label, multicentre, observational, Phase 4 study, conducted in Japan.
Population	Patients with radically unresectable or metastatic renal cell carcinoma treated who receive treatment with pembrolizumab in combination with axitinib
Variables	The primary exposure variables include variables related to administration of pembrolizumab and axitinib including date of administration, dose, discontinuation and interruption of treatment. The primary outcome variables include hepatic disorders including adverse events based on clinical events and/or laboratory elevations. Additional covariate data (e.g., baseline demographic and medical history and concomitant therapies) will also be collected.
Data Sources	Healthcare practitioners will be surveyed for information related to treatment with pembrolizumab in combination with axitinib as used in routine clinical practice.

Study Size	Data on approximately 150 patients will be collected, as agreed with the Japanese health authority during review of the pembrolizumab RCC marketing application. There is no formal hypothesis testing or power calculation.
Data Analysis	Descriptive statistics will be reported, including measures of central tendency (mean, median) and dispersion (standard deviation, range) for continuous variables and frequency and percentages for categorical variables. Comparison of characteristics in subgroups will be performed using Chi-square test, or Fisher's exact test for categorical/binary variables, and Student's t-test for continuous data. Other test statistics may be used, as relevant, depending on data distributions and normality assumptions.
Milestones	
Start of data collection:	1Q 2020
End of data collection:	1Q 2022
Interim report(s) of study results:	Not required.
Study progress report(s):	Progress of the survey and adverse drug reactions will be created according to JPSUR submission schedule regulated in Japan.
Final report of study results:	1Q 2023

3 AMENDMENTS AND UPDATES

None.

4 MILESTONES

Milestone	**Planned Date**
Start of data collection	1Q 2020
End of data collection	1Q 2022
Study progress reports	Progress of the survey and adverse drug reactions will be created according to JPSUR submission schedule regulated in Japan
Registration in the EU PAS register	Study will be registered within 35 days of PMDA approval of the protocol.
Final report of study results	1Q 2023

5 RATIONALE AND BACKGROUND

KEYNOTE-426 (KN426) is a Phase III randomized, open-label study to evaluate the efficacy and safety of pembrolizumab in combination with axitinib versus sunitinib monotherapy as a first-line treatment for locally advanced or metastatic renal cell carcinoma (RCC). [Rini, B. I., et al 2019] In the open-label, Phase 3 trial, 861 chemotherapy-naïve patients with previously untreated advanced clear-cell renal-cell carcinoma were randomized in a 1:1 fashion to receive pembrolizumab (200 mg) intravenously once every 3 weeks plus axitinib (5 mg) orally twice daily (432 patients) or sunitinib (50 mg) orally once daily for the first 4 weeks of each 6-week cycle (429 patients). The study was a multinational study with 24%, 24%, and 52% of patients randomized in North America, Western Europe and Rest of World, respectively. The study included a total of 94 Japanese patients.

After a median follow-up of 12.8 months, the estimated percentage of patients who were alive at 12 months was 89.9% in the pembrolizumab plus axitinib group and 78.3% in the sunitinib group (hazard ratio [HR] for death, 0.53; 95% confidence interval [CI], 0.38 to 0.74; P<0.0001). Among patients with previously untreated advanced RCC, treatment with pembrolizumab plus axitinib resulted in significantly longer overall survival and progression-free survival, as well as a higher objective response rate (ORR), than treatment with sunitinib. Median progression-free survival was 15.1 months in the pembrolizumab plus axitinib group and 11.0 months in the sunitinib group (HR for disease progression or death, 0.69; 95% CI, 0.56 to 0.84; P<0.001). The ORR was 59.3% (95% CI, 54.5 to 63.9) in the pembrolizumab plus axitinib group and 35.7% (95% CI, 31.1 to 40.4) in the sunitinib group (P<0.001). The benefit of pembrolizumab plus axitinib was observed across the International Metastatic RCC Database Consortium (IMDC) risk groups (i.e., favorable, intermediate, and poor risk) and regardless of programmed death ligand 1 expression.

Grade 3 or higher adverse events (AEs) of any cause occurred in 75.8% of patients in the pembrolizumab plus axitinib group and in 70.6% in the sunitinib group. The observed safety profiles of pembrolizumab plus axitinib and of sunitinib were as expected on the basis of the known profiles of these three drugs, although higher than expected given the known safety profile of each drug when used as monotherapy. Approximately 20% (91/429) of patients treated with pembrolizumab plus axitinib experienced grade 3 or 4 hepatic AEs. In KN426, the majority (79.2%, 168/212 patients) of hepatic events (including grade 3 or 4 events) occurred within 6 months of treatment, and majority (68.6%, 24/35 patients) of serious hepatic adverse events resolved within 3 months of occurrence. Within a 9-month period, the majority of hepatic events were observed and resolved during that timeframe. There were no deaths related to hepatic adverse events in the pembrolizumab plus axitinib group.

The use of pembrolizumab in combination with axitinib has been approved in the US, EU and other countries around the world for 1L treatment of RCC, with a recent approval in December 2019 in Japan by the Pharmaceuticals and Medical Devices Agency (PMDA). As condition of approval, the PMDA is requesting a drug-use results survey (DURS), or more specifically a specific use results survey, to collect information on hepatic disorders in Japanese patients who receive the product in real-world clinical practice. The DURS is a regulated post-marketing surveillance system unique to Japan to collect information on treatment outcomes

in routine clinical practice. This study is not required by the European Medicine's Agency (EMA) but, given the objective to quantify and characterize a specific identified risk as a condition of approval, the MAH considers this a voluntary post-authorization safety study (PASS).

It is important to recognize that different regions and countries have specific requirements and guidance for post-marketing commitment and may name them differently (e.g. post-market surveillance [PMS] studies in Japan and PASS in Europe. [Haque, A., et al 2017] While the overall intent of these studies may be similar, the approach to study design and execution can vary considerably, as a result of different governing regulatory frameworks. In Europe, the development of PASS protocols are guided by the EMA's Guideline on Good Pharmacovigilance Practices, Module VIII; post-market studies. In Japan, however, PMS studies must be conducted in accordance with ministerial ordinance Good Post-market Study Practice (GPSP), which generally allows for five potential designs: 1) general drug-use results survey of all AEs or specific AEs (such as hepatotoxicity), 2) special survey for specific population (such as children), 3) drug use results comparative survey, 4) post-marketing database survey, and 5) post-marketing clinical trials. The GPSP also does not recognize the need to collect data on a comparator drug and does not allow for source data verification (SDV) at participating clinical sites. These and other limitations of Good Pharmacoepidemiology Practice (GPP) does not allow for an unbiased assessment of treatment causality.

Although sufficient rigor will be applied to design and execution of the study described herein, the results of this exploratory analysis should be cautiously interpreted given the noted limitations imposed by the governing local regulatory framework within which this study is to be conducted.

6 RESEACH QUESTION AND OBJECTIVES

The study is exploratory and descriptive in nature. The specific aim of this research study is to collect information on hepatic disorders including clinical events and/or laboratory elevations with or without hepatic dysfunction among Japanese patients with radically unresectable or metastatic renal cell carcinoma who receive treatment with pembrolizumab in combination with axitinib, and to describe treatment and resolution of these adverse events in real-world clinical practice. There is no formal hypothesis testing. These research aims will be addressed with the following specific study objectives.

6.1 Primary Objectives

Among Japanese patients with radically unresectable or metastatic RCC who receive treatment with pembrolizumab in combination with axitinib, to describe the proportion of patients with hepatic disorders, including clinical events and/or laboratory elevations with or without hepatic dysfunction.

6.2 Secondary Objectives

Among the overall population:

1. To describe the demographic and baseline medical history;

2. To describe baseline medication use;

3. To describe the proportion of patients who discontinue one or both drugs due to hepatotoxicity (overall, serious and grade 3 or higher), including clinical events and/or laboratory elevations, and time to discontinuation;

4. To describe the proportion of patients with one or both drugs interrupted due to hepatotoxicity (overall, serious and grade 3 or higher), including clinical events and/or laboratory elevations, time to interruption, and time to resumption of the index drug (s);

5. To describe the proportion of patients with a dose reduction for one or both drugs due to hepatotoxicity (overall, serious and grade 3 or higher), including clinical events and/or laboratory elevations, and time to dose reduction;

Among patients with hepatic disorders (overall, serious and grade 3 or higher), including clinical events and/or laboratory elevations:

6. To describe the demographic and baseline medical history;

7. To describe baseline and concomitant medication use;

8. To describe the proportion of patients with hepatic AEs that resolve;

9. To describe the proportion of patients using systemic corticoid steroids and other treatments;

10. To describe the time from initiation of pembrolizumab in combination with axitinib to onset of hepatic AEs;

11. To summarize the type of hepatic disorders.

Subgroup analyses will be conducted for drug-related adverse events, based on investigator assessed causality.

7 RESEARCH METHODS

7.1 Study Design

The study design is a non-interventional cohort study of Japanese patients with radically unresectable or metastatic RCC treated with pembrolizumab in combination with axitinib. There will be no systematic sampling of patients at each site, and patients approached regarding the study will be at the investigator's discretion. Patients participating in the study will be

treated according to normal clinical practice and no intervention will be assigned in accordance with the study protocol. In all cases, the decision to treat the patients with pembrolizumab in combination with axitinib will be made by the patient's healthcare practitioner (HCP) prior to the decision to enroll the patient into the study. Given the observational nature of the study, all safety assessments will be performed according to standard clinical practice of each clinical site, and are not mandated by the study design nor protocol.

The index date will be the date of the first prescription or dispensing record for the index drugs including pembrolizumab plus axitinib (Figure 1, below) As a general rule, patients should be registered within 14 days from the starting date of index drug administration (index date, day 0). Healthcare practitioners will be surveyed to collect information on the risk of hepatic events and treatment of those events occurring within 9-months of treatment. Follow-up will continue until the end of the observation period or early termination due to withdrawal of consent, loss to follow-up, death.

The study design includes a 9-month period of observation given that hepatic dysfunction disorders in KN-426 plateaued after approximately 6-months of therapy, and a majority of patients with serious liver-related adverse events recovered within 3-months of follow-up:

- In KN426, the incidence rate of hepatic dysfunction was 111 (25.9%) patients within 3 months, 57 (13.3%) patients within 3-6 months, 21 (5.5%) patients within 6-9 months, 15 (4.5%) patients within 9-12 months, and 8 (3.1%) patients after 12 months. 79.2% (168/212) of the patients had hepatic AEs which occurred within 6 months and the incidence did not tend to increase thereafter.

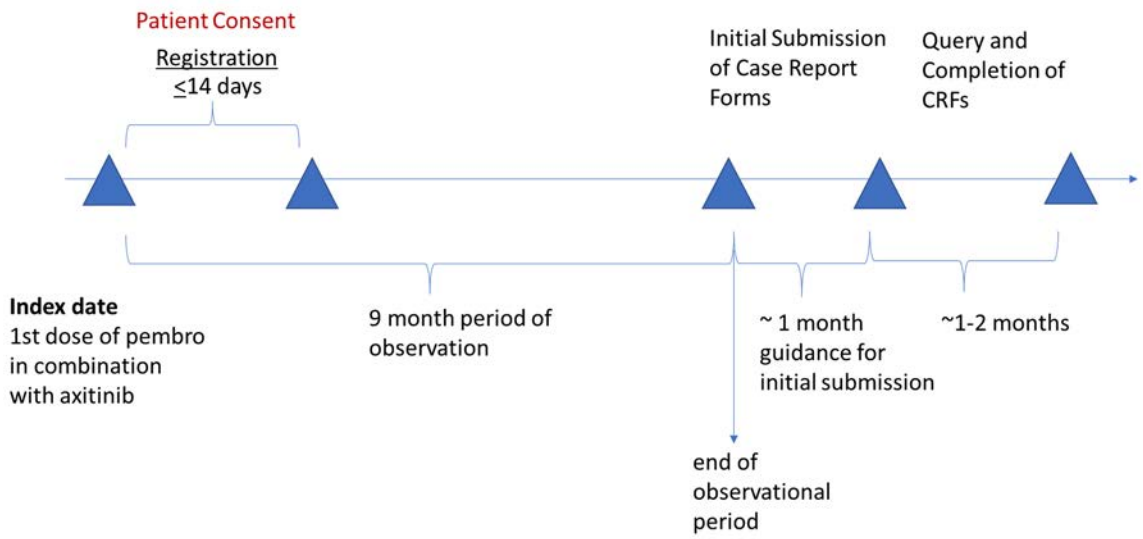
- For Grade 3 or higher hepatic AEs, there were 60 patients (14.0%) patients within 3 months, 20 patients (4.7%) within 3-6 months, 7 patients (1.8%) within 6-9 months, 2 patients (0.6%) within 9-12 months, and 2 patients (0.8%) after 12 months. 87.9% (80 of 91) had hepatic Grade 3 or higher hepatic AEs which occurred within 6 months and the incidence did not tend to increase thereafter.

- In addition, 68.6% (24 of 35) of patients with serious liver-related adverse events recovered within 3 months.

- The resolution of liver-related adverse events could be ascertained by observing the patients for 3 months after onset.

Based on the above, considering the 6 months before onset and the 3 months before resolution, the observation period for this study was set at 9 months. Based on the incidence of hepatic AEs, we anticipate collecting information on approximately 30 patients with Grade 3 or higher events in this survey (see Section 7.5). The Japanese regulatory authority agreed that a 9-month period of observation would be sufficient.

Figure 1 Study Diagram



7.2 Setting

This study will include the collection of data from multiple institutions in urology, medical oncology, etc. Plans are for patient recruitment to begin in 1Q2020, and continue for approximately 1 year, and data collection will be completed in 1Q2022.

7.2.1 Study Population and Eligibility Criteria

Japanese patients with radically unresectable or metastatic RCC treated with pembrolizumab in combination with axitinib will be eligible for study participation. Given the rare nature of RCC in pediatric patients, it is expected that most study participants will be adult patients. There are no exclusion criteria for this study.

The study will enroll approximately 200 patients with evidence of at least one dose of pembrolizumab plus axitinib at baseline, assuming that approximately 25% of patients will be excluded from the analysis population given missing or incomplete data on safety outcomes. The goal is to analyze data on approximately 150 advanced RCC patients treated with pembrolizumab plus axitinib.

7.2.2 Patient Withdrawal

Patients have the right to withdraw from the study at any time, without prejudice to their medical care, and without giving a reason. Any withdrawal must be fully documented in the case report form (CRF) and source documents. Discontinuation from the study for any other reasons (e.g., death) must be documented in the CRF.

7.3 Variables

7.3.1 Exposure

The study is non-interventional and there is no assignment of drug. Patients receiving pembrolizumab in combination with axitinib as part of their routinely administered healthcare and consent to study participation will be followed. The study does not include collection of data on any comparator drug or drug combination. Information on pembrolizumab and axitinib exposure (e.g. date of first dose, dose, date of dose interruption/change, discontinuation and reason for discontinuation) will be collected via survey from HCPs. The Iyakuhinmei Data File (IDF) coding system, which is used in Japan when reporting medication safety data to PMDA, will be used.

It is anticipated that the treating physicians will treat patients in accordance with the local health authority approved product information as well as local treatment guidelines. In accordance with the approved Japanese product circular, the recommended dose of pembrolizumab for adults is 200 mg administered as an intravenous infusion over 30 minutes every 3 weeks. As such, although it is not dictated per protocol, it is anticipated that patients will have clinic visits with their HCP approximately every 3 weeks.

It is assumed that HCPs will complete the survey/electronic CRFs at the end of the observational study period (9 months) with data transcribed from the patient's medical records; although, there will be no source data validation of exposure data for this study. When hepatic AEs occur, investigators will be instructed to report the minimal information required for AE reporting via the EDC system per the AE reporting guidelines outlined in Section 9 of this protocol.

7.3.2 Outcomes

Health outcomes of interest include hepatic adverse clinical events and other abnormal changes in laboratory values related to liver dysfunction, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), GGT (gamma glutamyltransferase), total bilirubin, ALP (alkaline phosphatase). Hepatic adverse events will be coded using the Japanese version of the Medical Dictionary for Regulatory Activities (MedDRA). Data captured will include the absence or presence of the event, grade based on CTCAE v5.0-JCOG (common terminology criteria for adverse events v5.0-Japanese Clinical Oncology Group), the date of the outcome, interruption date or discontinuation date of pembrolizumab and/or axitinib, treatment for the AE (e.g. corticosteroids, other therapies), whether there is improvement after discontinuation or interruption of therapy (dechallenge), information related to rechallenge (when conducted by the investigator), laboratory values related to the AEs, and causal relationship of pembrolizumab and/or axitinib as assessed by the local HCP. If there are multiple hepatic adverse events, each should be reported separately.

It is assumed that HCPs will complete the survey/electronic CRFs at the end of the observational study period (9 months) with data transcribed from the patient's medical records; although, there will be no SDV of outcomes data for this study.

7.3.3 Covariates

The HCPs will be asked to record this information in the electronic CRFs. As for exposure and outcomes, there will be no SDV using medical records of any of the following covariate data.

Baseline demographic and clinical characteristics (prior to the index date)

- patient identification number †,
- gender,
- birth date (or age at the start of treatment),
- inpatient/outpatient category,
- reason for use of the index drug,
- pregnancy status (female only),
- height, weight,
- presence or absence of allergy history and content,
- presence or absence of smoking history and content,
- drinking habits, amount of drinking per day,
- presence or absence of medical history and details,
- presence or absence of viral hepatitis,
- presence or absence of history of drug-induced liver dysfunction (including immunotherapy-induced liver dysfunction)
- prior history of RCC (date of diagnosis, onset information, IMDC risk, type of disease, stage of disease, and metastasis) and RCC treatment (e.g. surgical treatment, radiotherapy, chemotherapy, immunotherapy)
- Karnofsky performance status
- presence or absence of complications and details,
- Child-Pugh classification

†: A unique number or symbol by which the physician can identify the case

Concomitant therapy (post-index date)

- name of concomitant therapy[surgical procedure, radiation therapy, concomitant drugs (only for patients with reported hepatic AEs)],
- duration or date of treatment,
- total dose of radiation (for radiation therapy)

7.4 Data Sources

Study-specific CRFs will be completed by HCPs and submitted using an electronic data capture (EDC) system. It is assumed that patient data will be sourced from the patient's medical records, but there will not be independent source data verification of the data submitted by each site.

In the registration form/CRF, the site will enter a unique number (patient identifier), which only the treating investigator and/or authorized personnel will be able to use to identify the patient. Common to all CRFs for the patient will be a case registration number, which will be used by the MAH to manage the cases.

The MAH will be the controller of data collected from the clinical sites. The MAH, as data controller, will take appropriate steps to ensure that personal data are protected. Data management and handling procedures will be developed for the study, and will mainly cover EDC system construction and organization for survey implementation, registration/CRF related activities (e.g. procedures of system linkage with other systems, ID issuance of the EDC system, workflow after registration and receiving CRF, query creation, etc.).

EDC data will be collected and stored until re-examination results are provided from the local regulatory authority, MHLW (Ministry of Health, Labour and Welfare), and there is reconfirmation of the clinical usefulness of the study drugs. There will be restricted access to the EDC data, and only study personnel with assigned user IDs will be able to access the system.

7.4.1 Study Procedures

Patients will be observed from initiation of pembrolizumab plus axitinib until the end of observation due to withdrawal of consent, loss to follow-up, death, or until end of the study period. The study period is intended to extend for up to 9 months after initiation of therapy. Visits will not occur according to a set schedule, and will be driven by clinical management of patients at each site. However, it is expected that site visits will occur approximately every 3 weeks, based on the dosing recommendations for pembrolizumab in the product label.

After the decision by HCP to treat the patients with pembrolizumab in combination with axitinib, patients recruited for the study will consent to study participation, in accordance with local ethics committee requirements. As a general rule, patients should be registered within 14 days from the starting day of the index drugs. Sites will complete and submit a patient

registration CRF using an electronic data capture (EDC) system, and the CRF will include some baseline information include patient identifier number, gender, year and month of birth or age at the start of treatment, treatment at an inpatient or outpatient facility, starting date of drug administration, and reason for drug use (see Table 1, below). The additional CRFs will be collected and submitted at the end of the 9-month observational period for each patient. Site guidance will be to complete and submit the CRFs within 1 month after the 9-month period of observation, and it is anticipated that an additional 1-2 months will be needed for MAH to query and correct/update entries, as needed (see Figure 1). Training on the EDC data capture system will be performed by the MAH designee (CRO).

After the 9-month period of observation, the CRO will send an email request to the HCP asking him or her to submit the complete CRFs via the EDC system. An email reminder is sent to the site at least once a month until the CRFs are completed and submitted using the EDC system.

Table 1 Schedule for Completion/Submission of Case Report Forms

	Completion and Submission of Registration Forms (guidance is to register patients within 14 days of index date[1])	Completion and Submission of Additional Case Report Forms (guidance is to complete/submit within one month after the 9-month period of observation)
Name of facility	√	
Name of department	√	
Date of form completion	√	
Patient Identification Number	√	
Gender	√	
Year or Month of Birth, or Age at Start of Treatment	√	
Inpatient/Outpatient Category	√	
Starting Date of Drug Administration	√	
Reasons for Drug Use	√	
History of Hypersensitivity to Drug Administration	√	
Additional Exposure Data (see Section 7.3.1, above)		√
Outcomes Data (see Section 7.3.2, above)		√
Additional Covariate Data (see Section 7.3.3, above)		√
Outcomes Data (see Section 7.3.2, above)		√

[1] index date is date of pembrolizumab plus axitinib
[2] When hepatic AEs occur, investigators will be instructed to report them via EDC per the AE reporting timelines outlined in Section 9 of this protocol.

7.5 Study Size

Statistical analyses will be of an explorative and descriptive nature. The study is not aimed to confirm or reject pre-defined hypotheses, and no formal power calculation has been performed.

The goal is to collect complete data on approximately 150 patients, as discussed with the PMDA. With data on 150 patients, some information on treatment patterns, interruption, treatment, and re-administration may be available from this study given what was observed in KN-426 as subsequently noted.

- In KN426, the incidence of patients with hepatic function disorder (adverse events) was 49.4% (212 of 429 patients), of whom the incidence of Grade 3 or higher was 21.2% (91 of 429 patients). If the true incidence rate in this population is the same, a sample size of 150 patients would be sufficient to observe approximately 30 patients with Grade 3 or higher events.

- In KN426, 14.9% (64 of 429), 20.3% (87 of 429), and 11.4% (49 of 429) of patients, respectively, experienced hepatic adverse events leading to treatment interruption with drug, axitinib, or both. Therefore, approximately 22 patients, 30 patients, and 17 patients, respectively, would be anticipated to be observed.

- In KN426, 10.0% (43 of 429), 6.8% (29 of 429), and 3.0% (13 of 429), respectively, of patients discontinued drug, axitinib, or both due to hepatic adverse events. Therefore, approximately 15 patients, 10 patients, and 5 patients, respectively, would be anticipated to be observed .

- In KN426, 15.9% (68 of 429) of the patients whose ALT increased to 3 times the upper limit of normal were treated with systemic corticosteroids. Therefore, approximately 24 patients treated with corticosteroids for liver-related adverse events would be anticipated to be observed.

- In addition, 21.4% (92 of 429) of the patients in KN426 who experienced an increase in ALT 3 times the upper limit of normal who were re-administered any investigational drug after recovery. Therefore, re-administration information on approximately 32 patients would be anticipated to be observed.

A sample size of 150 patients would also provide reasonable statistical precision around the estimated risk of grade 3 and 4 AEs in KN426 (see Table 2, below)

Table 2 Half width of 95% CI estimates for AE assumptions and proposed sample size for study

N	AE Incidence Rate (%)	95% Confidence Interval (%)	
		Lower bound	Upper bound
100	10	4.9%	17.6%
100	20	12.7%	29.2%
100	30	21.2%	40.0%
150	10	5.7%	16.0%
150	20	13.9%	27.3%
150	30	22.8%	38.0%
180	10	6.0%	15.3%
180	20	14.4%	26.6%
180	30	23.4%	37.3%
200	10	6.2%	15.0%
200	20	14.7%	26.2%
200	30	23.7%	36.9%

AE= adverse event; CI= confidence interval; CI based on Binomial (Clopper-Pearson) 'exact' method based on the beta distribution

7.6 Data Management

All data will be collected, processed, and stored centrally via an electronic data capture (EDC) system PPD The EDC system is a secure web application for building and managing online databases. It provides secure access for sites, with an audit trail to track the history of data entry and revisions. The database for the study will be developed with built into logic and consistency checks, intended to minimize data errors at the point of entry. As received, the MAH designee will review the CRF entries and, as needed, the clinical site may be asked by the designee to add, correct, or confirm conflicting or unclear entries through the EDC system.

7.7 Data Analysis

Statistical analyses will be of an explorative and descriptive nature. Descriptive statistics will be reported including measures of central tendency and dispersion (mean, median, standard deviation, range) for continuous variables and frequency and percentages for categorical scale variables. Comparison of characteristics in subgroups will be performed using Chi-square test, or Fisher's exact test for categorical/binary variables, and Student's t-test for continuous data. Other test statistics may be used, as relevant, depending on the data distributions and normality assumptions.

Statistical analyses will be performed using SAS software (version 9.3 or higher) or other validated statistical software as required. Subgroup analyses stratified by prognostic /

predictive factors may be explored. Details of the statistical analyses including handling of missing data, and sensitivity analyses, will be included in a separate Statistical Analysis Plan (SAP), and mock data tables, that will be finalized prior to database lock. A final report will be generated for this study.

7.8 Quality Control

Participating medical institutions sign contracts stating that the HCPs will conduct the survey based on the protocol and physicians guide, and in compliance with governing laws and regulations including the GPSP. The site contract stipulates that quality control procedures will be followed for the conduct of the study.

All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

7.9 Limitations of the Research Methods

Given its observational nature, the study is prone to potential forms of bias including, for example selection bias, surveillance bias and information bias. Also, the results may not be generalizable to patients treated within other countries and healthcare systems.

A potential form of bias for this study is selection bias, which occurs when patients in the study differ systematically from the population of interest (patients with radically unresectable or metastatic RCC), limiting the generalizability of results to the broader patient population. For this study, there will likely be some degree of selection bias given the index drugs are commercially available and patient consent to study participation will be necessary. The descriptive baseline demographic and medical history for patients included in this study can be qualitatively compared with other trial and realworld evidence studies of patients with advanced RCC to help put these results into context.

With the introduction of new drugs for a given indication, there is also the potential for another form of selection or allocation bias due to the channeling of newly marketed drugs to more severe cases. This may result in channeling bias with a higher risk of adverse events being reported than would be expected for the general population of patients receiving drug. Comparison of baseline characteristics with other general RCC study populations may also help in identifying the potential degree of channeling bias.

The study may also suffer from bias due to increased surveillance, screening or testing of the outcome or associated symptoms given the noted primary objective of the study. One way to help with interpretation of results in this instance would be to include a comparator drug to allow for the assessment of relative risk. However, inclusion of a comparator group is not possible in this study given the DURS design and limitations imposed by governing ordinances (GPSP) for these surveillance studies. It is also likely that the outcomes reported for the study

are generally more severe in nature, than otherwise would be observed and potentially attributable to treatment. This bias is hard to address given the observational study design, and is a notable limitation of this study.

The study also is prone to information bias due to missing data, misclassification errors, or transcription errors. For this study, quality control and data handling procedures will be implemented to help mitigate this potential form of bias. Given the inability to perform source data verification, this bias is also another notable limitation of this study.

Given the potential forms of bias noted for this study, the results should be very cautiously interpreted and cannot, given the current design possible with the governing Japan ministerial ordinance (GPSP), serve as the basis for assessing causality of reported hepatic disorders.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent

The physician in charge shall explain the purpose of the survey, the information collected through the survey and the method for using the survey results (e.g., presentation at scientific meetings, manuscript publication). Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the information consent form, signed and dated, will be given to the patient or legally acceptable representative prior to participation in the study.

Informed consent requirements will adhere to IRB/ERC requirements, applicable laws and regulations.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol, and there are no procedures required as part of this protocol.

9.1 Adverse Event Reporting

The following guidelines for adverse event (AE) apply to the reporting of hepatic events, as described in this protocol. The reporting for product quality complaints and non-hepatic adverse events will follow local reporting guidelines.

9.1.1 INVESTIGATOR RESPOSIBILITY

If hepatic adverse events (AEs) are identified following use of pembrolizumab, then the AE* must be reported according to Table 3.

*For the purposes of this protocol, the term "AE" collectively refers to the following reportable events (refer to section 9.2 for definitions):

- Serious adverse events (SAEs), including death due to any cause
- Non-serious adverse reactions (NSARs)
- Study-specific Health Outcomes of Interest (HOIs) that meet criteria for SAE/NSAR or special situation

Hepatic AEs will be captured using the eDC for each patient and reported according to Table 3.

The investigator must evaluate each SAE for causality and record causality on the CRF for each SAE and NSAR reported.

Table 3 AE Reporting Timeframes and Process for Investigators and Supplier

AEs	**INVESTIGATOR TIMEFRAMES**	**SUPPLIER TIMEFRAMES**
	Investigator to Supplier [1], [2]	**Supplier to MSD KK [3]**
Hepatic SAE regardless of causality (including study-specific HOIs that meet criteria for SAE)	24 hours from receipt	1 BD/3 CD from time of receipt from investigator
Hepatic NSAR (including study-specific HOIs that meet criteria for NSAR)	10 CD from receipt	1 BD/3 CD from time of receipt from investigator
Follow-up to any AE-submit using above timeframes		
BD-Business Day; CD-Calendar Day		
[1] Investigator to Supplier: Hepatic AEs for Merck study product are submitted to Supplier via eDC **[2]** Investigator enters hepatic AEs for Merck study product into study database for tabulation in study report **[3] Supplier to MSD KK:** Supplier submits hepatic AEs for Merck study product to MSD KK using EngageZone for reporting to worldwide regulatory agencies as appropriate		
Submitting Hepatic AEs to Local PV Submitting Hepatic AEs to Local PV Japan: All hepatic AEs must be submitted to Local PV using EngageZone as described in the data management procedure for Supplier.		

9.1.2 STUDY REPORT

The final DURS study report will include aggregate listings of hepatic AEs collected for pembrolizumab and will be provided to Japanese regulatory agencies by the sponsor as required. The final PASS study report will include aggregate listings of all hepatic and non-hepatic AEs collected for study drug under this protocol. The Risk Management Subteam (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report. The safety and conclusion sections of the final study report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

9.1.3 PERIODIC SAFETY UPDATE REPORTS

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

9.2 DEFINITIONS

9.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

9.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

9.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment

in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

9.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 7.2.3.

9.2.5 Health Outcome of Interest (HOI)

Health Outcomes of Interest (HOIs) are clinical events or outcomes that are collected according to the protocol. HOIs may be represented as diagnoses, treatment or procedures. Examples of HOIs include syncope, disease progression, or hypoglycaemia collected as study endpoints. HOIs may meet the criteria of an SAE/SAR, NSAR or special situation, and if so, must be collected as such, in addition to being collected as an HOI. Specifically, collected HOI data must be assessed for the criteria described herein and reported accordingly.

9.2.6 Sponsor's product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

9.2.7 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

9.3 AE Reconciliation

Reconciliation will be performed between the safety database and study data to ensure all reportable AEs were reported and received. Starting from when the first patient is enrolled through the end of data collection, all AEs will be reconciled on a periodic basis.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The Risk Management Subteam (RMST) Lead /Clinical Safety Risk Manager (CSRM) Physician will be notified if any safety data are generated in the final study report or any . The safety and conclusion sections of the final study report must be reviewed by the RMST Lead/CSRM Physician prior to finalization of the report. The review by the CSRM Physician must occur prior to any release of results to the public domain in the form of abstracts, posters, presentations or manuscripts.

The main results are foreseen to be published in one manuscript, and at least one scientific conference. Manuscript authors will be defined based on guidelines established by the International Committee of Medical Journal Editors (http://www.icmje.org/).

As captured in the consent document, all patient-level data will be anonymized and shared in aggregate through external publication of the data and during review with external collaborators.

11 REFERENCES

[Haque, A., et al 2017]	Haque A, Daniel S, Maxwell T, Boerstoel M. Postmarketing surveillance studies-an industry perspective on changing global requirements and implications. Clin Ther. 2017 Apr;39(4):675-85.	05DQYW
[Rini, B. I., et al 2019]	Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med. 2019 Mar 21;380(12):1116-27.	05706K

12 ATTACHMENTS

12.1 Annex 1 List of stand-alone documents

No.	Date
1. Informed Consent Document	TBD
2. Case Report Forms	TBD
3. Statistical Analysis Plan	TBD

TBD= documents that are not available at the time of protocol creation but will be finalized at a later date.

12.2 Annex 2 ENCePP Checklist for Study Protocols (Revision 4)

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Non-interventional post-marketing safety study (PMSS) to collect information on hepatic function disorders among adult Japanese patients with radically unresectable or metastatic renal cell carcinoma treated with pembrolizumab in combination with axitinib.

EU PAS Register® number: Study has not yet been registered
Study reference number (if applicable):

Section 1: Milestones	Yes	No	N/A	Section Number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	2,4, 7.2
1.1.2 End of data collection[2]	☒	☐	☐	2,4, 7.2
1.1.3 Progress report(s)	☐	☐	☒	N/A
1.1.4 Interim report(s)	☐	☐	☒	N/A

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Pr Proprietary

Section 1: Milestones	Yes	No	N/A	Section Number
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4, 7.7, 9.12, 10

Comments:

Section 2: Research question	Yes	No	N/A	Section Number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	6
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	N/A
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	N/A

Comments:

The study is exploratory and descriptive in nature. There is no formal hypothesis testing.

Section 3: Study design	Yes	No	N/A	Section Number
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	N/A
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9

Comments:

No comparator is included in the study. As such, the protocol does not specify measures of association.

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.1 Is the source population described?	☒	☐	☐	7.1

Section 4: Source and study populations	Yes	No	N/A	Section Number
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	7.2
4.2.2 Age and sex	☒	☐	☐	7.2
4.2.3 Country of origin	☒	☐	☐	7.2.1
4.2.4 Disease/indication	☒	☐	☐	7.2.1
4.2.5 Duration of follow-up	☒	☐	☐	7.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Section Number
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	7.3.1, 7.9
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	7.3.1

Comments:

Exposure is defined by initial dose and discontinuation of therapy and not based on biological MOA. Duration of observation is based on time window for events seen in clinical trial and expectations of PMDA.

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	7.9

Section 6: Outcome definition and measurement	Yes	No	N/A	Section Number
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

No HTA assessments applicable.

Section 7: Bias	Yes	No	N/A	Section Number
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.9

Comments:

Section 8: Effect measure modification	Yes	No	N/A	Section Number
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

There is no measure of association nor comparative safety analyses

Section 9: Data sources	Yes	No	N/A	Section Number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.3.1
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.3.1
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3.3

Section 9: Data sources	Yes	No	N/A	Section Number
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	7.3.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.3.2
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

No linked databases are used. Data collection is via prospective HCP survey

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.5
10.3 Are descriptive analyses included?	☒	☐	☐	7.7
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	7.7

Comments:

No measures of association and no plans to control for confounding of effect.

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7.4
11.2 Are methods of quality assurance described?	☒	☐	☐	7.6
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	7.9

Section 12: Limitations	Yes	No	N/A	Section Number
12.1.2 Information bias?	☒	☐	☐	7.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	7.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☐	☒	

Comments:

There are no formal feasibility assessments. Sites will be selected based on prior experiences working with the sites and involvement in prior drug use results surveys.

Section 13: Ethical/data protection issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	7.4.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	7.3.3, 7.6

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☐	☐	☒	

Comments:

This is the original version of the protocol

Section 15: Plans for communication of study results	Yes	No	N/A	Section Number
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	9.1.3
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

Name of the main author of the protocol: PPD MSD KK

Date: 19 December 2019

Signature: PPD

12.3 Annex 3 Administrative and Regulatory Details

The following terms and conditions are covered under the site contract with each participating institution. The contract stipulates that investigational sites shall comply with local laws and regulations for conduct of this study, including the Ministerial Ordinance on Standards for Implementation of Post-Marketing Surveillance and Studies on Drugs (GPSP), the Act on Securing Quality, Efficacy and Safety of Drugs, the Enforcement Ordinance, the Enforcement Regulations, etc.

Confidentiality:

Confidentiality of Data

Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

Confidentiality of Subject Records

The investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

Confidentiality of Investigator Information

The investigator's name and business contact information may be included when sharing the results with Merck & Co., Inc, Kenilworth, NJ., U.S.A and its affiliated companies and when reporting the results and certain serious adverse events to regulatory agencies or to other investigators.

Administrative:

Compliance with Financial Disclosure Requirements

Financial disclosure requirements are outlined in the Japanese regulatory guidelines for this study.

Compliance with Law, Audit and Debarment

The investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice and all applicable federal, state and local laws, rules and regulations relating to the conduct of the study.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with applicable federal, state and local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Compliance with Study Registration and Results Posting Requirements

A redacted version of the protocol will be posted in ENCePP.

12.4 Annex 4 Qualified Person for PharmacoVigilance (QPPV)

PPD

European Union Qualified Person for Risk Management and Pharmacovigilance
Office of the European Union Qualified Person for Pharmacovigilance (EU QPPV)
Merck Sharp & Dohme (Europe), Inc.
Siège d'exploitation : 5, Clos du Lynx 1200 Bruxelles
Exploitatiezetel : Lynx Binnenhof, 5 1200 Brussel
PPD

Emergency/Out of Hours: GSM number above or via +44 (0)1992 467272

Dear Sir/Madam

Re: EU QPPV Signature Page for PASS

INN: Pembrolizumab
Product: MK-3475
Protocol No.: 3475-A97-000
Epidemiology No.: EP05026.076
Protocol Date: 19-March-2020
MAH: MSD K.K.

In line with the Guideline on Good PharmacoVigilance Practice (GVP), Module VIII – Post-Authorisation Safety Studies (PASS) and according to MSD internal SOPs, this study has been reviewed and approved by the European Qualified Person for Pharmacovigilance.

Yours faithfully

PPD

PPD

EU Qualified Person for Pharmacovigilance