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
Version identifier of the final study report	1.0
Date of previous version of the final study report, if applicable	Not applicable
EU PAS register number	EUPAS34319
Active substance	L01XC18, monoclonal antibody, pembrolizumab L01XE17, Protein-kinase inhibitors, axitinib
Medicinal product	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)	MSD K.K.
Joint PASS	No
Research question and objectives	The specific aim of this research study was 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 received treatment with pembrolizumab in combination with axitinib and to describe treatment and resolution of these adverse events in real-world clinical practice.
Country of study	Japan
Author	PPD Associate Director, Drug Safety Drug Safety Operations

	PPD Associate Director, Drug Safety Drug Safety Operations MSD K.K. 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo, Japan
Sponsor Final Repository (REDS) Date	08-JUL-2024

MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	Merck Sharp and Dohme (MSD) KK 1-13-12 Kudan-kita, Chiyoda-ku, Tokyo, Japan
MAH contact person	PPD Associate Director, Drug Safety Drug Safety Operations PPD Associate Director, Drug Safety Drug Safety Operations

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 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

Keywords

Renal cell carcinoma, Japan, pembrolizumab, axitinib

Rationale and 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 patients with previously untreated advanced renal cell carcinoma (RCC).

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. In the clinical study KN426, the incidence of hepatic adverse reactions such as ALT and AST elevations of all grades occurred in 26.8% and 26.1% of patients, respectively in the pembrolizumab/axitinib group [Ref. 5.4: 05706K].

As part of the Japan risk management plan (J-RMP), the Japanese health authority (Pharmaceutical and Medical Devices Agency [PMDA]) requested 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 and objectives

The specific aim of this research study was 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 received treatment with pembrolizumab in combination with axitinib and to describe treatment and resolution of these adverse events in real-world clinical practice.

Study design

The approach of a prospective, open-label, multicentre, observational, Phase 4 study, conducted in Japan via central registry as a DURS was utilized.

Setting

Healthcare practitioners within Japan were surveyed for information related to treatment with pembrolizumab in combination with axitinib as used in routine clinical practice for patients with radically unresectable or metastatic renal cell carcinoma who received treatment with pembrolizumab in combination with axitinib.

Subjects and study size, including dropouts

Planned sample size: 150 patients (registration was planned to end when the number of registered patients had reached the planned sample size [180 registered patients].

Actual safety analysis set: 193 patients

Variables and data sources

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) were also collected.

Results

This survey started on March 30, 2020, and contracts were made with 138 sites. There were 196 registered patients, and survey forms for 196 patients were collected (last patient started treatment on January 31, 2022). Of the 196 patients with collected survey forms, 193 patients were included in the safety analysis set. The 3 patients excluded from the safety analysis set were "Patients who did not register within 14 days from the start of administration" (2 patients) and "Patients who have previously received pembrolizumab or axitinib" (1 patient).

In the 193 patients in the safety analysis set, hepatic adverse events occurred in 60 patients (31.09%) and hepatic adverse reactions of pembrolizumab occurred in 49 patients (25.39%). Serious hepatic adverse reactions were reported in 15.03% of patients and Grade ≥ 3 hepatic adverse reactions were reported in 12.44% of patients. The outcome of hepatic adverse reactions was resolved or resolving in most of the patients (93.88%). No deaths from hepatic adverse reactions were reported.

Discussion

There are methodological limitations to this study. Direct comparison between the results from this survey and the findings from other studies is limited due to differences in study design, sample size, patient background, observation period, etc. However, the incidence of hepatic events in this study was in line with what has been previously reported in patients with RCC.

In conclusion, the results presented do not suggest new safety concern about hepatic adverse reaction with the combination of pembrolizumab plus axitinib in this patient population.

No changes in the benefit-risk profile of pembrolizumab were observed in the specified indication. It was determined that it was not necessary to take any particular measures such as revising the indications, dosage and administration or precautions for pembrolizumab as specified at the time of approval based on these results. No additional risk minimization measures were deemed warranted.

Marketing Authorisation Holder(s)

MSD K.K.

Names and affiliations of principal investigators

Contact details for the designees (such as contract research organization [CRO]) are available upon request.

2 LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
CI	Confidence Interval
COVID	Coronavirus Disease
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
γ-GTP	Gamma-glutamyl transpeptidase
HCP	Healthcare Practitioner
HR	Hazard Ratio
IDF	Iyakuhinmei Data File
IMDC	International Metastatic RCC Database Consortium
IRB/ERC	Institutional Review Board/ Ethics Review Committee
J-RMP	Japan Risk Management Plan
JPSUR	Japan Periodic Safety Update Report
KN	KEYNOTE
MAH	Marketing Authorization Holder
MHLW	Ministry of Health, Labour and Welfare
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

3 INVESTIGATORS

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

4 OTHER RESPONSIBLE PARTIES

Not applicable

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	1Q 2020	29-Jul-2020	COVID pandemic impacted study start
End of data collection	2Q 2023	26-Apr-2023	COVID pandemic impacted enrolment rate
Registration in the EU PAS register	Study will be registered within 35 days of PMDA approval of the protocol.	07-Apr-2020	
Final report of all safety event study results	4Q 2023	08-JUL-2024	COVID pandemic impacted time for study completion

6 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) [Ref. 5.4: 05706K]. 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 (44 in the pembrolizumab plus axitinib arm and 49 in the sunitinib arm).

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., favourable, 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 overall and 11% (5/44) of Japanese patients [Ref. 5.4: 08LXSH] in KN426 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 United States, Europe (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 requested a drug-use results survey (DURS), or more specifically a specific use results survey, to collect information on hepatic disorders in Japanese patients who received 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 was 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 Marketing Authorization Holder (MAH) considers this a voluntary EU 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 [Ref. 5.4: 05DQYW]. 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 was 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 was conducted.

7 RESEARCH QUESTION AND OBJECTIVES

The study is exploratory and descriptive in nature. The specific aim of this research study was 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 received treatment with pembrolizumab in combination with axitinib, and to describe the treatment and resolution of these adverse events in real-world clinical practice. There was no formal hypothesis testing. These research aims were assessed with the following specific study objectives.

7.1 Primary Objectives

Among Japanese patients with radically unresectable or metastatic RCC who received 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.

7.2 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 were to be conducted for drug-related adverse events, based on investigator assessed causality.

8 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1v1	04-Nov-2020	Cover Page 4 Milestones 7.3.1 Exposure 7.4.1 Study Procedures	Amendment	Protocol information updated to reflect Amendment 1 id and dates, as well as include EU PAS Registrar id. Dates of milestones met have been added. Exposure amended to also include 400 mg dose every 6 weeks and clinic visits at a 6 week interval. Site visit timing amended to also include 6 week interval.
2v1	23-Dec-2020	Cover Page 4 Milestones 7.2 Study Setting	Amendment	Protocol information updated to reflect Amendment 2 id and dates. Anticipated date of end of data collection milestone has been updated.

Number	Date	Section of study protocol	Amendment or update	Reason
				Updated anticipated data collection endpoint to 2Q2022.
3v1	27-Apr-2021	Cover Page 4 Milestones 7.2 Study Setting 12.4 Annex 4 Qualified Person for Pharmaco-Vigilance (QPPV)	Amendment	Protocol information updated to reflect Amendment 03 ID and dates. Anticipated dates of end of data collection and final report of study results milestones have been updated. Updated anticipated data collection endpoint to 2Q2023. Replaced page with updated template.
4v1	20-Dec-2022	Cover Page 12.3 Annex 3 Administrative and Regulatory Details 12.4 Annex 4 Qualified Person for PharmacoVigilance (QPPV)	Amendment	Protocol information updated to reflect Amendment 04 ID and dates. Updated Sponsor address and name. Updated Sponsor name
4v2	24-Oct-2023	Cover Page 2 Abstract 12.4 Annex 4 Global Qualified Person for PharmacoVigilance (GQPPV)	Update	Protocol information updated to reflect Update 04v2 ID and dates Updated Name of Sponsor Author throughout. Updated title of Global Qualified Person for Pharmacovigilance office

9 RESEARCH METHODS

9.1 Study design

The approach of a prospective, open-label, multicentre, observational, Phase 4 study, conducted in Japan via central registry as a DURS was utilized.

9.2 Setting

Healthcare practitioners within Japan were surveyed for information related to treatment with pembrolizumab in combination with axitinib as used in routine clinical practice for patients with radically unresectable or metastatic renal cell carcinoma treated who received treatment with pembrolizumab in combination with axitinib.

9.3 Subjects

Japanese patients with radically unresectable or metastatic RCC treated with pembrolizumab in combination with axitinib were eligible for study participation. Given the rare nature of RCC in paediatric patients, it was expected that most study participants would be adult patients. There were no exclusion criteria for inclusion in this study. Patient registration was performed for patients who started the 1st dose of pembrolizumab after the site concluded the contract. Necessary information (e.g., patient identification number, sex, starting date of drug administration) at the initiation of pembrolizumab was entered to the patient registration screen of the Electronic Data Capture (EDC) and sent for registration within 14 days of the starting date of administration of pembrolizumab (Day 0).

9.4 Variables

In principle, the duration of treatment was from the start date of administration of pembrolizumab in combination with axitinib to the end date of administration. The observation period was 9 months from the starting date of administration. The observation period may be shortened by drop out or may be longer than 9 months (e.g., date of patient visit, follow-up date of adverse event outcome.). Therefore, not all data collected may uniformly include 9 months of follow-up for all cases.

The definitions of terms are specified as follows in Table 1:.

Table 1. Definition of study terms

Disease duration	Calculated as the period from the diagnosis date on the survey form to the initiation date of administration of pembrolizumab.
Disease stage	Tabulated based on the reported disease stage classification at the start of administration of pembrolizumab.
Observation period	Calculated from the initiation date of administration of pembrolizumab and the end date of the observation period (the last observation date, completion date/discontinuation date, outcome date of adverse event, initiation date of administration, and the latest measurement date of laboratory test values)
Adverse event	Any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease that occurred within 9 months after the initiation of administration of pembrolizumab from the starting date of administration of pembrolizumab regardless of the causal relationship to pembrolizumab. This survey was designed to collect hepatic AEs only, and thereby the tabulation targets hepatic AEs only.
Adverse reaction	AEs other than those for which a causal relationship by physician with pembrolizumab or axitinib "can be ruled out." In this report, adverse reaction of pembrolizumab was described as "adverse reaction". The adverse drug reaction of both drugs (pembrolizumab or axitinib) was described as "adverse drug reaction of pembrolizumab or axitinib".
Seriousness	Events meeting the following criteria were considered serious. Events that the physician considered non-serious but were treated as serious based on the company's decision were also included. 1. Events resulting in death 2. Events that were life-threatening 3. Events requiring inpatient hospitalization or prolongation of existing hospitalization 4. Events resulting in permanent or significant disability/incapacitation 5. Events that were congenital anomalies/birth defects 6. Other events or reactions determined to be medically significant conditions

9.4.1 Exposure

The study is non-interventional and there was no assignment of drug. Patients receiving pembrolizumab in combination with axitinib was part of their routinely administered healthcare and consent to study participation followed. The study did not include collection of data on any comparator drug or drug combination. Information on pembrolizumab and axitinib exposure were as described below and were collected via survey from HCPs. The Iyakuhinmei Data File (IDF) coding system, which is used in Japan when reporting medication safety data to PMDA, was used.

- Pembrolizumab treatment status: Starting date of administration, dosing, last observation date (end or discontinuation date), treatment status on the last observation day, reason for discontinuation of administration

- Axitinib treatment status: Daily dose and duration of treatment (start and end dates of treatment)

- Combination therapy (except for axitinib) after initiation of pembrolizumab treatment for RCC: Use/no use of concomitant therapy, name of concomitant therapy (surgical procedure, radiation therapy, other), duration or date of treatment, total dose of radiation, and location (for radiation therapy)

9.4.2 Outcome

Health outcomes of interest include hepatic adverse clinical events and other abnormal changes in laboratory values related to liver dysfunction. The following were collected regarding the occurrence of hepatic adverse events: Presence or absence of hepatic AEs, name of hepatic AEs, date of onset, seriousness, worst grade based on Common Terminology Criteria for Adverse Events v5.0 – Japanese Clinical Oncology Group (CTCAE v5.0-JCOG), outcome, date of outcome, pembrolizumab and axitinib administration after the date of onset, presence or absence of resolution of symptoms after discontinuation of pembrolizumab or axitinib, presence or absence of relapse on pembrolizumab or axitinib rechallenge, causality to pembrolizumab and axitinib, factors other than pembrolizumab or axitinib, treatment status for hepatic adverse events, and changes in laboratory values related to hepatic adverse events.

9.4.3 Covariates

The following patient characteristics and reason for use were collected: patient identification number, sex, date of birth (or age at the start of treatment), inpatient/outpatient category, reason for use of pembrolizumab, pregnancy status (female only), height, weight, allergy history and details, smoking history and details, drinking habits, amount of drinking per day, medical history and details, history of viral hepatitis, history of hepatobiliary diseases other than viral hepatitis, drug-induced liver dysfunction (including immunotherapy-induced liver dysfunction), status of renal cell carcinoma (date of diagnosis, onset information, treatment site, IMDC risk, type of disease, stage of disease, presence/absence and site of metastasis), Karnofsky performance status, presence or absence of complications and details, and Child-Pugh Classifications. Additionally, status of renal cell carcinoma treatment (surgical treatment, radiotherapy, chemotherapy, and immunotherapy) prior to initiation of pembrolizumab administration were collected.

9.5 Data sources and measurement

Study-specific case report forms (CRFs) were completed by healthcare providers (HCPs) and submitted using an electronic data capture (EDC) system. As patient data was to be sourced from the patient's medical records, there was not independent source data verification (SDV) of the data submitted by each site.

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

The MAH is the controller of data collected from the clinical sites.

9.5.1 Study Procedures

Patients were observed from initiation of pembrolizumab plus axitinib (index drugs) until the end of observation due to withdrawal of consent, loss to follow-up, death, or until end of the study period. Visits did not occur according to a set schedule and were driven by clinical management of patients at each site. However, it was expected that site visits would occur

approximately every 3 weeks or 6 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 were recruited for the study and enrolled if consent to study participation, in accordance with local ethics committee requirements, was provided. As a general rule, patients were to be registered within 14 days from the starting day of the index drugs. Sites completed and submitted a patient registration CRF using an EDC system, and that CRF include some baseline information. The remaining data were collected via additional CRFs that were to be collected and submitted at the end of the 9-month observational period for each patient. Additional information on the schedule for completion/submission of case report forms can be found in the protocol.

9.6 Bias

Information bias due to missing data, misclassification errors, or transcription errors was a concern for this study. Quality control and data handling procedures were therefore implemented to help mitigate this potential form of bias. Given the inability to perform source data verification, this bias could not be fully mitigated.

9.7 Study size

Statistical analyses were of an explorative and descriptive nature. The study was not aimed to confirm or reject pre-defined hypotheses, and therefore no formal power calculation was performed.

The goal was to collect complete data on approximately 150 patients, as agreed to with the PMDA. With data on 150 patients, some information on treatment patterns, interruption, treatment, and re-administration would be available from this study given what was observed in KN426.

- 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 alanine aminotransferase (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 was therefore determined to 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%

9.8 Data transformation

9.8.1 Data management

All data were collected, processed, and stored centrally via an EDC system (CCI [redacted]). The EDC system is a secure web application for building and managing online databases. The database for the study was developed with built into logic and consistency checks, intended to minimize data errors at the point of entry. As received, the MAH designee reviewed the CRF entries and, as needed, the clinical site was asked by the designee to add, correct, or confirm conflicting or unclear entries through the EDC system. Additional data management steps are outlined below.

For handling cases, the safety evaluation criteria were as follows:

- Seriousness of adverse events (serious, non-serious)
- Worst grade of adverse events (CTCAE v5.0-JCOG Grade classification 1, 2, 3, 4, 5 and unknown)
- Outcome of adverse events (resolved, resolving, resolved with sequelae, not resolved, fatal, unknown)
- Causal relationship with pembrolizumab or axitinib (related [cannot be ruled out], not related [can be ruled out])

The criteria for exclusion from the safety analysis dataset were as follows.

- Patients outside the contract period
- Patients exceeding the contract number of patients
- Patients registered outside the registration period
- Patients administered outside the registration period
- Patients not registered within 14 days of the initiation of treatment
- Unregistered patients
- Duplicate patients
- Patients who did not make a repeat visit after the initial prescription
- Patients with a history of using pembrolizumab and/or axitinib in the past
- Patients with no records of presence/absence of adverse events and details of adverse events
- Patients not administered pembrolizumab

The criteria for handling duplicate patients were as follows.

- Patients at the same site with the same abbreviated patient name, sex and calculated age

If the criteria for a duplicate patient were met, a query was sent to the physician of the corresponding case to confirm whether it was the same patient or not.

Similarly, if any hepatic adverse event was confirmed by information other than survey forms (such as spontaneous report and literature etc.), it was included in the data of this survey.

9.9 Statistical methods

Statistical analyses were of an exploratory and descriptive nature. Descriptive statistics are 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 was 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 could be used, as relevant, depending on the data distributions and normality assumptions.

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

The method of counting adverse events and the like is specified in Table 3. In addition, in this survey, the observation period was set to be 9 months from the start of treatment with pembrolizumab and axitinib, and events that occurred after 9 months from the start date of treatment with pembrolizumab and axitinib were excluded from tabulations. However, events for which the onset date could not be specified were included in the tabulations.

Table 3. Analytic definitions

	Item name	Details of definition
1	Number of patients in the safety analysis set	The number of patients in the safety analysis set in the general drug use-results survey were tabulated.
2	Number of patients with AEs	The number of patients in whom AEs occurred.
3	Number of occurrences of AEs	If the same events (PT) occurred multiple times in the same patient, these were tabulated as 1 event. If the same PT but different grade (severity or CTCAE v5.0-JCOG grade), the highest grade is shown.
4	Incidence of AEs (%)	Number of patients with AEs/Number of patients in the safety analysis set × 100%
5	Type of AEs: System organ class (SOC)	If multiple patients report events (PT) in the same SOC, number of patients by the SOC is tabulated as 1 patient.

9.10 Quality control

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

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

10 RESULTS

10.1 Participants

This survey started on March 30, 2020, and contracts were made with 138 sites. There were 196 patients registered, and survey forms for 196 patients were collected. Enrolment was completed on January 31, 2022 (196 patients, started treatment on). Data collection was completed on April 26, 2023.

The disposition of patients collected during the survey is shown in Figure 1. Of the 196 patients with collected survey forms, 193 patients were included in the safety analysis set.

The 3 patients excluded from the safety analysis set were “Patients who did not register within 14 days from the start of administration (2 patients) “and “Patients who have previously received pembrolizumab or axitinib (1 patient)".

Of the 3 patients excluded from the safety analysis set, hepatic adverse event was reported in 1 patient. The event was immune-mediated hepatic disorder (Grade 3, Outcome: resolved) for which a causal relationship could not be ruled out.

Hepatic adverse reactions in patients who were excluded from the safety analysis set and backgrounds of patients with Grade ≥3 hepatic adverse reactions are shown in Table 4 and Table 5.

Figure 1. Disposition of patients

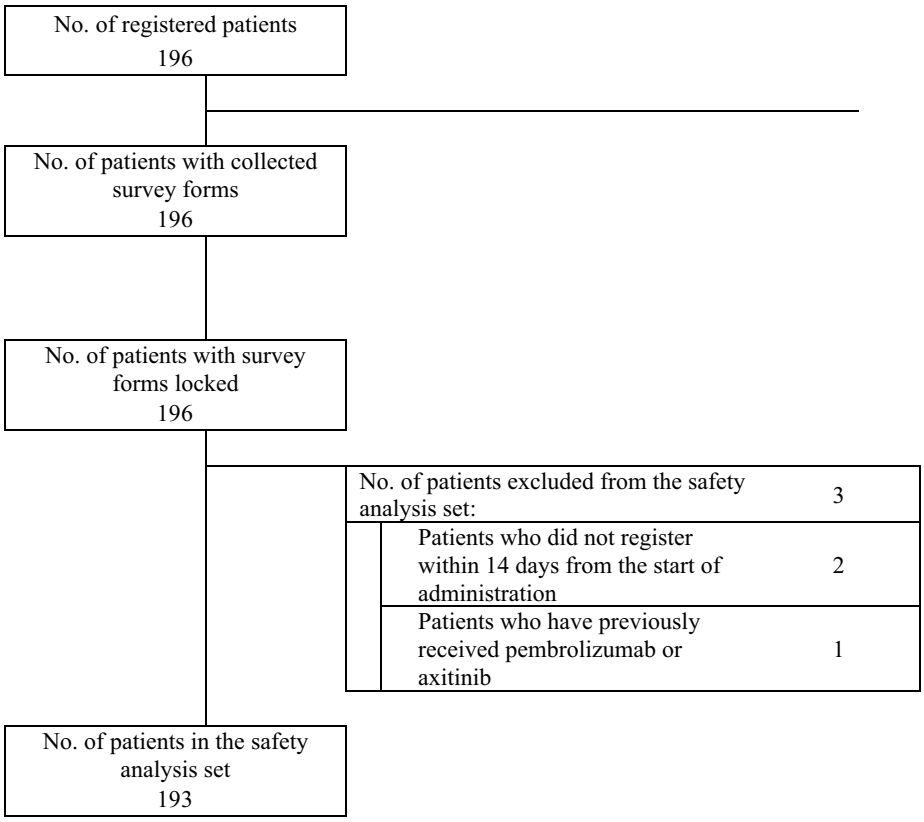


Table 4. Incidences of hepatic adverse reactions in patients who were excluded from safety analysis set

Number of patients surveyed	3	
Number of subjects with adverse reactions	1	
Number of Events	1	
Incidence of adverse reactions	33.33%	
Type of adverse reactions	Patients with events (number of events)	Incidence (%)
Hepatobiliary disorders	1	(33.33)
Immune-mediated hepatic disorder	1	(33.33)

MedDRA/J version (26.0)

Table 5. List of backgrounds of patients with Grade ≥3 hepatic adverse reactions in patients who were excluded from safety analysis set

No	Sex	Age at initiation of treatment	Adverse reaction term (PT)	History of hepatobiliary disease	Other medical history	Metastases to liver	Complication: Hepatic function disorder	Drinking habits	Action for adverse reaction
1	[redacted]	[redacted]	Immune-mediated hepatic disorder	No	Cataract	No	No	Unknown	Resumed after interruption

M: male, F: female

10.1.1 Protection of Human Subjects

The physician in charge at each respective site was to 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 had to be documented with 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, was to be given to the patient or legally acceptable representative prior to participation in the study.

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

10.2 Descriptive data

Basic statistics for the 193 patients in the safety analysis set and numbers and percentages of patients by patient background are shown in Table 6 and Table 7.

The mean age was 67.6 years, and the percentage of elderly patients aged ≥ 65 years was 63.27%. There were 81 male patients (82.65%) and 17 female patients (17.35%), and the mean disease duration was 1.69 years. The percentages of initial and recurrent disease were 69.39% with initial disease and 30.61% with recurrent disease, and initial disease included patients

with a history of other chemotherapy for cancer in whom disease progressed without remission ever occurring. The sites of disease were metastasis site in 74 patients and primary site in 24 patients. The disease stage at the initiation of pembrolizumab was Stage IV in 95.92% of patients. The mean hepatic laboratory test values before initiation of pembrolizumab were aspartate aminotransferase (AST) 20.2 IU/L, ALT 18.5 IU/L, total bilirubin 0.56 mg/dL, alkaline phosphatase (ALP) 247.5 IU/mL, and gamma-glutamyl transpeptidase (γ-GTP) 51.7 IU/L.

Table 6. Basic statistics

Item	No. of patients	Mean	SD	Min	Median	Max
Age (years)	193	68.6	9.7	39	70.0	94
BMI (kg/m^2)	187	22.56	4.19	13.4	22.27	36.4
Disease duration (years)	186	1.82	3.27	0.0	0.21	23.2
Duration of treatment (weeks)	193	22.19	13.78	0.1	27.14	36.0
Observation period (weeks)	193	31.22	16.62	0.1	36.00	86.3
No. of doses of pembrolizumab	193	6.5	3.7	1	6.0	12
Initial dose of pembrolizumab (mg)	193	208.3	40.0	200	200	400
Maximum dose of pembrolizumab (mg)	193	232.1	73.6	200	200	400
Mean dose of pembrolizumab at a time (mg)	193	220.15	52.31	200	200	400
Duration of axitinib treatment (days)	193	144.5	84.3	3	157	257
Initial daily dose of axitinib (mg)	193	9.6	1.9	4	10	20
Maximum daily dose of axitinib (mg)	193	9.9	2.3	5	10	20
Mean daily dose of axitinib (mg)	193	8.48	2.47	3.0	8.89	20.0
Total dose/daily dose (Gy) (previous therapy)	15	39.667	24.082	20.00	35.000	117.00
SD: standard deviation, Min: minimum, Max: maximum						

Table 7. Number and percentage of patients by patient background

Background factor	Category	No. of patients (%)	
Safety analysis set	-	193	
Sex	Male	147	(76.17)
	Female	46	(23.83)
Pregnancy	No	46	(100.00)
(females only)	Yes	0	(0.00)
Age category 1	< 65	63	(32.64)
	≥ 65	130	(67.36)
Age category 2	< 75	144	(74.61)
	≥ 75	49	(25.39)
Inpatient/outpatient	Inpatient	156	(80.83)
	Outpatient	37	(19.17)
BMI	< 25.0	140	(72.54)
	≥ 25.0	47	(24.35)
	Unknown	6	(3.11)
History of allergy	No	171	(88.60)
	Yes	18	(9.33)
	Unknown	4	(2.07)
Smoking	No	73	(37.82)
	Yes (ongoing)	20	(10.36)

Background factor	Category	No. of patients (%)	
	Yes (past)	76	(39.38)
	Unknown	24	(12.44)
Brinkman index	No	73	(37.82)
No. of cigarettes/day × years of smoking	< 400	26	(13.47)
	≥ 400 to < 600	14	(7.25)
	≥ 600 to < 1,200	30	(15.54)
	≥ 1,200	11	(5.70)
	Unknown	39	(20.21)
Medical history†	No	102	(52.85)
	Yes	91	(47.15)
Alcohol consumption	No	85	(44.04)
	Yes	65	(33.68)
	Unknown	43	(22.28)
Drinking habits (n=65)	Every day	31	(47.69)
	Occasionally	32	(49.23)
	Rarely (cannot drink)	2	(3.08)
Amount of drinking per day	< 1	20	(30.77)
(cups) (n=65)	1 to < 2	26	(40.00)
	2 to < 3	7	(10.77)
	≥ 3	1	(1.54)
	Unknown	11	(16.92)
Disease duration (years)	< 1	128	(66.32)
	1 to < 3	19	(9.84)
	≥ 3	39	(20.21)
	Unknown	7	(3.63)
Initial or recurrent	Initial	128	(66.32)
	Recurrent	65	(33.68)
	1	55	(84.62)
	2	5	(7.69)
	3	4	(6.15)
	Other	1	(1.54)
Target site of pembrolizumab treatment	Primary	48	(24.87)
	Metastasis	145	(75.13)
Stage of disease	Stage III	10	(5.18)
	Stage IV	183	(94.82)
	Other	0	(0.00)
IMDC risk	Favourable	39	(20.21)
	Intermediate	113	(58.55)
	Poor	38	(19.69)
	Unknown	3	(1.55)
Type of disease	Clear cell	149	(77.20)
	Non-clear cell	16	(8.29)
	Unknown	28	(14.51)
Metastases to other sites	No	8	(4.15)
	Yes	185	(95.85)
Site of metastasis††	Liver	18	—
(n=185)	Regional lymph nodes	34	—
	Distance lymph nodes (other than regional lymph nodes)	26	—
	Lung	123	—
	Bone	47	—
	Bone marrow	0	—
	Pleura	6	—
	Peritoneum	3	—
	Adrenal gland	19	—
	Intestinal tract	0	—
	Brain	10	—

Background factor	Category		No. of patients (%)	
	Skin		7	—
	Other		30	—
Metastases to regional or distance lymph nodes (no metastases to other sites)	Metastases to regional lymph nodes only		6	(3.11)
	Metastases to distance lymph nodes only		5	(2.59)
	Not applicable		182	(94.30)
Metastases to lung	No		70	(36.27)
	Yes		123	(63.73)
Metastases to liver	No		175	(90.67)
	Yes		18	(9.33)
Metastases to bone	No		146	(75.65)
	Yes		47	(24.35)
Karnofsky performance status (KPS)	0% to 40%		3	(1.55)
	50% to 70%		26	(13.47)
	80% to 100%		151	(78.24)
	Unknown		13	(6.74)
Complications	No		46	(23.83)
	Yes		146	(75.65)
	Unknown		1	(0.52)
Complication (renal function disorder)	No		71	(36.79)
	Yes		121	(62.69)
	Unknown		1	(0.52)
Complication (hepatic function disorder)	No		186	(96.37)
	Yes		6	(3.11)
	Child-Pugh classifications			
		Grade A	5	(83.33)
		Grade B	0	(0.00)
		Grade C	0	(0.00)
		Unknown	1	(16.67)
	Unknown		1	(0.52)
Complication (autoimmune disease)	No		189	(97.93)
	Yes		3	(1.55)
	Unknown		1	(0.52)
Complication (interstitial lung disease)	No		190	(98.45)
	Yes		2	(1.04)
	Unknown		1	(0.52)
Complication (endocrine disorder)	No		184	(95.34)
	Yes		8	(4.15)
	Unknown		1	(0.52)
Complication (other)	No		124	(64.25)
	Yes		65	(33.68)
	Unknown		4	(2.07)
Complication or medical history (hepatic function disorder)	No		185	(95.85)
	Yes		7	(3.63)
	Unknown		1	(0.52)
Previous therapy (surgery)	No		90	(46.63)
	Yes		102	(52.85)
	Unknown		1	(0.52)
Previous therapy (radiotherapy)	No		175	(90.67)
	Yes		17	(8.81)
	Unknown		1	(0.52)
Previous therapy (anti-cancer drugs)	No		187	(96.89)
	Yes		4	(2.07)
	Unknown		2	(1.04)
ALT (IU/L)	< 40		182	(94.30)
	≥ 40		11	(5.70)
AST (IU/L)	< 40		181	(93.78)
	≥ 40		12	(6.22)

Background factor	Category	No. of patients (%)	
Total bilirubin (mg/dL)	< 1.5	188	(97.41)
	≥ 1.5	4	(2.07)
	Unknown	1	(0.52)
ALP (IU/mL)	< 350	175	(90.67)
	≥ 350	17	(8.81)
	Unknown	1	(0.52)
γ-GTP (IU/L)	≤ 100	165	(85.49)
	> 100	21	(10.88)
	Unknown	7	(3.63)

†: Medical history in the past of viral hepatitis (e.g., HBV, HCV, EBV, CMV), hepatobiliary diseases other than viral hepatitis, drug-induced liver dysfunction (including immunotherapy-induced liver dysfunction), or any other condition reported by physician.
††: Overlapping tabulation

10.3 Main results and outcome data

10.3.1 Incidence of hepatic adverse reactions

In the safety analysis set, there were 49 patients with 53 hepatic adverse drug reactions (ADRs) reported. The incidence of hepatic ADRs with pembrolizumab was 25.39% (49/193 patients). The breakdown of hepatic ADRs is shown in Table 8. The most common hepatic ADRs (≥ 5.0%) were hepatic function abnormal in 8.81% (17/193 patients) and immune-mediated hepatic disorder in 8.29% (16/193 patients).

The incidences of hepatic adverse reactions that were observed in this survey and are included within the safety specifications of the Japan risk management plan (J-RMP) of pembrolizumab are shown in Table 8. Of the hepatic adverse reactions included in the safety specification, serious adverse reactions occurred in 15.03% (29/193 patients). The most common serious hepatic adverse reactions (>4.0 %) were immune-mediated hepatic disorder in 8.29% (16/193 patients) and drug-induced liver injury in 4.15% (8/193 patients).

Table 8. Incidences of hepatic adverse reactions included in the safety specification

No. of patients in the safety analysis set		193					
Safety specification		Serious		Non-serious		Total	
		No. of patients with events† (incidence)		No. of patients with events† (incidence)		No. of patients with events† (incidence)	
Important identified risks		-		-		-	
Hepatic function disorder†		29	(15.03%)	22	(11.40%)	49	(25.39%)
	Ascites	1	(0.52)	0	(0.00%)	1	(0.52)
	Hepatic function abnormal	2	(1.04)	15	(7.77)	17	(8.81)
	Hepatomegaly	0	(0.00%)	1	(0.52)	1	(0.52)
	Liver disorder	2	(1.04)	0	(0.00%)	2	(1.04)
	Drug-induced liver injury	8	(4.15)	0	(0.00%)	8	(4.15)
	Immune-mediated hepatitis	1	(0.52)	0	(0.00%)	1	(0.52)
	Immune-mediated hepatic disorder	16	(8.29)	0	(0.00%)	16	(8.29)

	Congestive hepatopathy	1	(0.52)	0	(0.00%)	1	(0.52)
	Aspartate aminotransferase increased	0	(0.00%)	1	(0.52)	1	(0.52)
	Transaminases increased	0	(0.00%)	2	(1.04)	2	(1.04)
	Hepatic enzyme increased	0	(0.00%)	3	(1.55)	3	(1.55)
						MedDRA/J version (26.0)	
†: Each patient was counted for the “no. of patients” for “total”, “serious”, “non-serious” of each adverse reaction.							

The dosing regimen of pembrolizumab was 200 mg administered every 3 weeks. On August 21, 2020, a dosing regimen of 400 mg administered every 6 weeks was added as an inclusion criterion within the study protocol. The incidence of hepatic adverse reactions at 400 mg was 16.13% (5/31) (see Table 9). The reported events were immune-mediated hepatic disorder in 6.45% (2/31 patients), hepatic function abnormal and drug-induced liver injury each in 3.23% (1/31 patients).

The incidences and outcomes of hepatic adverse reactions by grade are shown in Table 10. Time to onset of hepatic adverse reactions by worst grade is shown in Table 11. Duration of treatment and number of doses before onset of adverse reaction are shown in Figure 2 and Figure 3. A list of backgrounds of patients with Grade ≥3 hepatic adverse reactions is shown in Table 12.

Most [93.88% (46/49 patients)] hepatic adverse reactions with pembrolizumab were reported as resolved or resolving. No deaths due to hepatic adverse reactions were reported. Three patients with outcome of "not resolved" discontinued treatment for reasons other than hepatic adverse reaction, and the outcome of hepatic adverse reaction at the time of discontinuation was "not resolved." The outcomes of Grade ≥ 3 hepatic adverse reactions of pembrolizumab were reported as resolved or resolving in 95.83% (23/ 24 patients).

Patients with multiple events of the same adverse drug reaction were each counted in sub-category of Figure 2 and Figure 3.

Of the 59 events of hepatic adverse reactions of pembrolizumab, the event occurred within 3 months in 67.80% (40/59 events), and by the 3rd dose after the initiation of administration in 71.19% (42/59 events). Hepatic adverse reactions also occurred in patients who continued treatment with the 4th dose and onward. The overall median time to onset of hepatic adverse reactions was 64.0 days, and the median time to onset of Grade ≥3 hepatic adverse reactions was 57.0 days.

Table 9. Incidences of hepatic adverse reactions included in the safety specification (400 mg)

	Status in the post-marketing surveillance
No. of patients in the safety analysis set (400 mg)	31
No. of patients with adverse reactions (400 mg)	5
Incidence of adverse reactions	16.13%
Type of adverse reactions	No. of patients by type of adverse reactions (Incidence)
Hepatobiliary disorders	4 (12.90%)
Hepatic function abnormal	1 (4.76%)
Drug-induced liver injury	1 (4.76%)
Immune-mediated hepatic disorder	2 (9.52%)
Investigations	1 (3.23%)
Transaminases increased	1 (3.23%)

MedDRA/J version (26.0)

Table 10. Incidences and outcomes of hepatic adverse reactions by grade

Grade	Incidence of adverse reaction (%)	No. of patients	Outcome		
			Resolved	Resolving	Not resolved
Overall†	25.39	49	33(67.35%)	13(26.53%)	3(6.12%)
1	4.66	9	9(100.00%)	0(0.00%)	0(0.00%)
2	7.77	15	8(53.33%)	6(40.00%)	1(6.67%)
3	9.84	19	12(63.16%)	6(31.58%)	1(5.26%)
4	2.59	5	4(80.00%)	1(20.00%)	0(0.00%)
5	0.00	0	—	—	—
Grade≤ 2	12.44	24	17(70.83%)	6(25.00%)	1(4.17%)
Grade ≥ 3	12.44	24	16(66.67%)	7(29.17%)	1(4.17%)

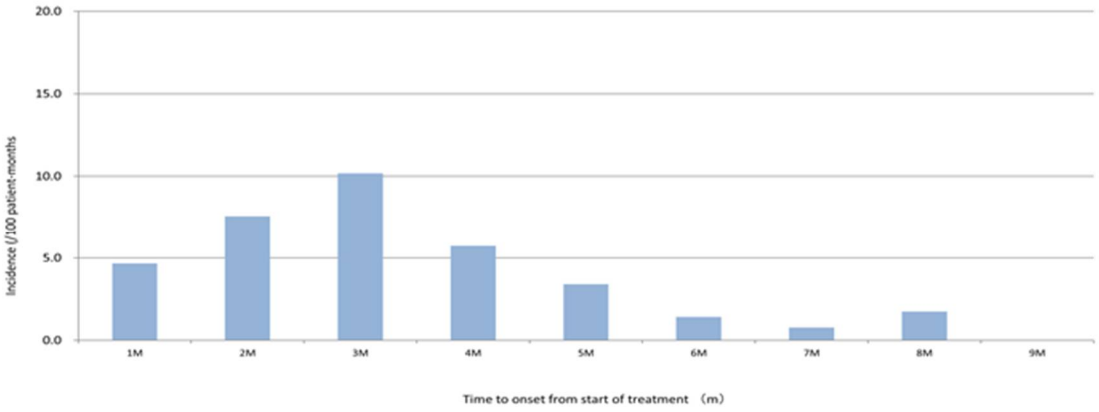
† : Including 1 patient with Grade unknown (outcome not recovered).

Table 11. Time (days) to onset of hepatic adverse reactions by worst grade

Grade	No. of patients	Mean	SD	Min	Median	Max
Overall	48†	64.6	40.5	1	64.0	197
1	8	89.9	64.2	8	94.5	197
2	15	70.6	35.8	4	71.0	161
3	19	51.7	24.8	5	50.0	120
4	5	68.2	39.6	5	85.0	102
5	0	—	—	—	—	—
Grade≤ 2	23	77.3	47.1	4	76.0	197
Grade ≥ 3	24	55.2	28.3	5	57.0	120

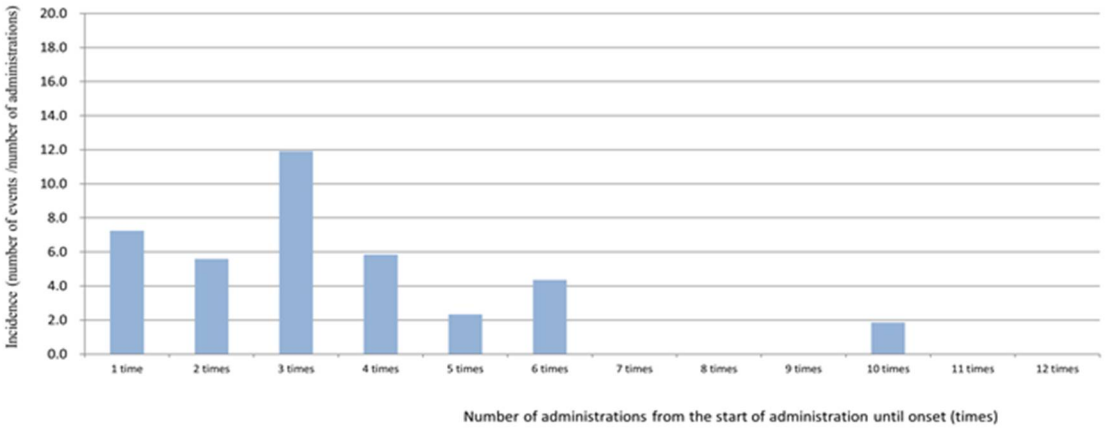
† : Excluding 1 patient with an unknown date of onset.

Figure 2. Incidences of hepatic adverse reactions by duration of treatment before onset†



† : Patients with multiple events of the same adverse drug reaction were each counted in that category.

Figure 3. Incidences of hepatic adverse reactions by number of doses before onset†



† : Number of doses were including patients receiving 400mg/dose.

Patients with multiple events of the same adverse drug reaction were each counted in that category.

Table 12. List of backgrounds of patients with Grade ≥ 3 hepatic adverse reactions

No	Sex	Age at treatment initiation	Adverse reaction term (PT)	History of hepatobiliary disease	Other medical history	Metastases to liver	Complication : Hepatic function disorder	Drinking habits	Action for adverse reaction
1	PPD		Immune-mediated hepatic disorder	No	Type 2 diabetes mellitus, gout, glaucoma	No	No	Unknown	Administration of steroids
2			Immune-mediated hepatitis	HBV	No	No	No	Unknown	Administration of steroids
3			Immune-mediated hepatic disorder	No	Amputation of right thigh (road traffic accident)	No	No	Occasionally (< 1 cup)	Administration of steroids: (Pulse therapy)
4			Hepatic function abnormal	No	No	No	No	Occasionally (1 to < 2 cups)	Administration of steroids, glycyrrhizin agents
5			Liver disorder	No	No	No	No	No	Administration of steroids, ursodeoxycholic acid, glycyrrhizin agents
6			Immune-mediated hepatic disorder	No	No	No	No	Occasionally (< 1 cup)	Administration of steroids
7			Hepatic function abnormal	No	Internal carotid artery thrombosis, hypercholesterolaemia	No	No	Unknown	No
8			Hepatic enzyme increased	No	No	Yes	No	No	No
9			Hepatic function abnormal	No	Pyloric stenosis	No	No	No	Administration of steroids, ursodeoxycholic acid, glycyrrhizin agents
10			Drug-induced liver injury	No	Hypertension, hyperlipidaemia	No	No	Occasionally (amount unknown)	No
11			Immune-mediated hepatic disorder	HBV	Hypertension	No	No	Unknown	No
12			Hepatic function abnormal	No	No	No	No	No	No
13			Immune-mediated hepatic disorder	No	Appendicitis	No	No	Every day (1 to < 2 cups)	Administration of steroids
14			Immune-mediated hepatic disorder	No	No	No	No	No	No
15			Drug-induced liver injury	No	No	No	No	Every day (< 1 cup)	No
16			Immune-mediated hepatic disorder	No	No	No	No	Every day (1 to < 2 cups)	No
17			Immune-mediated hepatic disorder	No	No	No	No	No	Administration of steroids
18			Immune-mediated hepatic disorder	No	No	No	No	Occasionally (< 1 cup)	No
19			Hepatic function abnormal	No	No	No	No	Every day (amount unknown)	No
20			Immune-mediated hepatic disorder	No	No	No	No	Every day	Administration of steroids

No	Sex	Age at treatment initiation	Adverse reaction term (PT)	History of hepatobiliary disease	Other medical history	Metastases to liver	Complication : Hepatic function disorder	Drinking habits	Action for adverse reaction
								(1 to < 2 cups)	
21	PPD		Hepatic function abnormal, Immune-mediated hepatic disorder	No	No	No	No	Every day (2 to < 3 cups)	Administration of steroids
22			Immune-mediated hepatic disorder	No	No	No	No	No	Administration of ursodeoxycholic acid, glycyrrhizin agents
23			Liver disorder	No	No	No	No	Occasionally (amount unknown)	No

M: male, F: female

10.3.2 Occurrence of hepatic adverse reactions by patient background

For hepatic adverse reactions (N=49), a logistic regression analysis (univariate analysis) was performed using patient background as a factor, and the crude odds ratio (OR) and its asymptotic 95% CI were calculated Table 13.

Brinkman index [OR: 3.867 in those sub-group of ≥400 to < 600] was the only background item that met the criteria for which the lower limit of the 95% CI met the fixed criterion (>1) and which had an OR ≥2. There was no consistent trend between the Brinkman Index and the OR.

Table 13. Incidence of hepatic adverse reaction by patient background

Item	Category	No. of patients	Patients with hepatic adverse reaction		Odds ratio	95% CI	
			No. of patients	Incidence (%)		Lower limit	Upper limit
Safety analysis set		193	49	25.39			
Sex	Male	147	41	27.89	1.837	0.791	4.270
	Female	46	8	17.39			
Pregnancy (female only)	No	46	8	17.39			
	Yes	0	0	—	-	-	-
Age category 1	< 65	63	21	33.33			
	≥ 65	130	28	21.54	0.549	0.281	1.073
Age category 2	< 75	144	36	25.00			
	≥ 75	49	13	26.53	1.083	0.518	2.266
Inpatient/ outpatient	Inpatient	156	39	25.00	0.900	0.400	2.025
	Outpatient	37	10	27.03			
BMI	< 25.0	140	34	24.29			
	≥ 25.0	47	14	29.79	1.323	0.634	2.758
	Unknown	6	1	16.67			
History of allergy	No	171	42	24.56			
	Yes	18	6	33.33	1.536	0.543	4.346
	Unknown	4	1	25.00			

Item	Category	No. of patients	Patients with hepatic adverse reaction		Odds ratio	95% CI	
			No. of patients	Incidence (%)		Lower limit	Upper limit
Safety analysis set		193	49	25.39			
Smoking	No	73	15	20.55			
	Yes (ongoing)	20	7	35.00	2.082	0.707	6.132
	Yes (past)	76	22	28.95	1.575	0.741	3.347
	Unknown	24	5	20.83			
Brinkman index No. of cigarettes/day × years of smoking	No	73	15	20.55			
	< 400	26	7	26.92	1.425	0.506	4.014
	≥ 400 to < 600	14	7	50.00	3.867	1.174	12.730
	≥ 600 to < 1,200	30	8	26.67	1.406	0.523	3.778
	≥ 1,200	11	2	18.18	0.859	0.168	4.403
	Unknown	39	10	25.64			
Medical history	No	102	33	32.35			
	Yes	91	16	17.58	0.446	0.226	0.881
Drinking	No	85	17	20.00			
	Yes	65	20	30.77	1.778	0.841	3.757
	Unknown	43	12	27.91			
Drinking habits (n=65)	Every day	31	9	29.03			
	Occasionally	32	11	34.38	1.280	0.442	3.713
	Rarely (cannot drink)	2	0	0.00	<0.001	<0.001	>999.999
Amount of drinking per day (cups) (n=65)	< 1	20	5	25.00			
	1 to < 2	26	8	30.77	1.333	0.360	4.945
	2 to < 3	7	3	42.86	2.250	0.369	13.707
	≥ 3	1	0	0.00	<0.001	<0.001	>999.999
	Unknown	11	4	36.36			
Disease duration (years)	< 1	128	31	24.22			
	1 to < 3	19	7	36.84	1.825	0.661	5.042
	≥ 3	39	9	23.08	0.939	0.402	2.191
	Unknown	7	2	28.57			
Initial or recurrent	Initial	128	34	26.56			
	Recurrent	65	15	23.08	0.829	0.413	1.666
Target site of pembrolizumab treatment	Primary	48	9	18.75	0.606	0.269	1.363
	Metastasis	145	40	27.59			
Stage of disease	Stage III	10	1	10.00	0.313	0.039	2.532
	Stage IV	183	48	26.23			
	Other	0	0	—	-	-	-
IMDC risk	Favourable	39	14	35.90			
	Intermediate	113	24	21.24	0.482	0.218	1.066
	Poor	38	9	23.68	0.554	0.205	1.497
	Unknown	3	2	66.67			
Type of disease	Clear cell	149	36	24.16			
	Non-clear cell	16	4	25.00	1.047	0.318	3.448
	Unknown	28	9	32.14			
Metastases to other sites	No	8	0	0.00			
	Yes	185	49	26.49	>999.999	<0.001	>999.999

Item	Category	No. of patients	Patients with hepatic adverse reaction		Odds ratio	95% CI	
			No. of patients	Incidence (%)		Lower limit	Upper limit
Safety analysis set		193	49	25.39			
Metastases to regional lymph nodes only	Applicable	6	1	16.67	0.579	0.066	5.082
	Not applicable	187	48	25.67			
Metastases to distance lymph nodes only	Applicable	5	1	20.00	0.729	0.080	6.685
	Not applicable	188	48	25.53			
Metastases to reginal or distance lymph nodes (no metastases to other sites)	Applicable	11	2	18.18	0.639	0.133	3.062
	Not applicable	182	47	25.82			
Metastases to lung	No	70	13	18.57			
	Yes	123	36	29.27	1.814	0.886	3.715
Metastases to liver	No	175	44	25.14			
	Yes	18	5	27.78	1.145	0.386	3.394
Metastases to bone	No	146	40	27.40			
	Yes	47	9	19.15	0.628	0.279	1.415
Karnofsky performance status (KPS)	0% to 40%	3	1	33.33	1.388	0.122	15.723
	50% to 70%	26	5	19.23	0.661	0.234	1.870
	80% to 100%	151	40	26.49			
	Unknown	13	3	23.08			
Complications	No	46	16	34.78			
	Yes	146	33	22.60	0.547	0.266	1.125
	Unknown	1	0	0.00			
Complication (renal function disorder)	No	71	22	30.99			
	Yes	121	27	22.31	0.640	0.331	1.238
	Unknown	1	0	0.00			
Complication (hepatic function disorder)	No	186	47	25.27			
	Yes	6	2	33.33	1.479	0.262	8.336
	Child-Pugh classifications						
	Grade A	5	1	20.00			
	Grade B	0	0	—			
	Grade C	0	0	—			
	Unknown	1	1	100.00			
	Unknown	1	0	0.00			
Complication (autoimmune disease)	No	189	49	25.93			
	Yes	3	0	0.00	<0.001	<0.001	>999.999
	Unknown	1	0	0.00			
Complication (interstitial lung disease)	No	190	49	25.79			
	Yes	2	0	0.00	<0.001	<0.001	>999.999
	Unknown	1	0	0.00			
Complication (endocrine disorder)	No	184	49	26.63			
	Yes	8	0	0.00	<0.001	<0.001	>999.999
	Unknown	1	0	0.00			
Complication (other)	No	124	38	30.65			
	Yes	65	9	13.85	0.364	0.163	0.810

Item	Category	No. of patients	Patients with hepatic adverse reaction		Odds ratio	95% CI	
			No. of patients	Incidence (%)		Lower limit	Upper limit
Safety analysis set		193	49	25.39			
	Unknown	4	2	50.00			
Complication or medical history (hepatic function disorder)	No	185	47	25.41			
	Yes	7	2	28.57	1.174	0.220	6.257
	Unknown	1	0	0.00			
Previous therapy (surgery)	No	90	23	25.56			
	Yes	102	26	25.49	0.997	0.520	1.909
	Unknown	1	0	0.00			
Previous therapy (radiotherapy)	No	175	43	24.57			
	Yes	17	6	35.29	1.675	0.585	4.799
	Unknown	1	0	0.00			
Previous therapy (anti-cancer drugs)	No	187	47	25.13			
	Yes	4	2	50.00	2.979	0.408	21.739
	Unknown	2	0	0.00			
ALT (IU/L)	< 40	182	44	24.18			
	≥ 40	11	5	45.45	2.615	0.761	8.985
AST (IU/L)	< 40	181	45	24.86			
	≥ 40	12	4	33.33	1.511	0.434	5.258
Total bilirubin (mg/dL)	< 1.5	188	46	24.47			
	≥ 1.5	4	2	50.00	3.087	0.423	22.537
	Unknown	1	1	100.00			
ALP (IU/mL)	< 350	175	45	25.71			
	≥ 350	17	4	23.53	0.889	0.276	2.866
	Unknown	1	0	0.00			
γ-GTP (IU/L)	≤ 100	165	42	25.45			
	> 100	21	4	19.05	0.689	0.220	2.164
	Unknown	7	3	42.86			

10.3.3 Laboratory test data for patients with hepatic adverse events

In this survey, laboratory test data related to liver function were collected from patients with hepatic adverse events. For patients without hepatic adverse events, only laboratory test data of the liver function before the start of treatment was collected.

Summary statistics of laboratory test data at: a) Before the start of treatment, b) At the onset of liver-related adverse events, c) Worst value, d) Improved / Resolving value, e) At the time of consultation, and f) At treatment resumption, in patients with hepatic adverse reactions are shown in Table 14.

Table 14. Summary statistics by test variable in hepatic adverse reaction cases

Test variable	N	Mean	Standard deviation	Minimum	Median	Maximum
Before the start of treatment						
AST(IU/L)	49	24.1	14.9	6	20.0	78
ALT(IU/L)	49	21.6	15.7	4	17.0	83
Total bilirubin(mg/dL)	48	0.61	0.35	0.0	0.50	1.9
ALP (IU/mL)	49	206.4	247.9	37	125.0	1644
γ-GTP(IU/L)	46	49.3	38.8	12	37.5	219
At the onset of liver-related adverse events						
AST(IU/L)	47	253.1	349.4	31	139.0	2030
ALT(IU/L)	47	295.8	365.4	31	133.0	1483
Total bilirubin(mg/dL)	46	1.42	2.10	0.3	0.85	13.1
ALP (IU/mL)	47	276.7	381.9	37	158.0	1985
γ-GTP(IU/L)	44	97.3	114.4	21	56.0	644
Worst value						
AST(IU/L)	47	336.1	422.3	25	170.0	2030
ALT(IU/L)	47	406.0	428.9	31	239.0	1483
Total bilirubin(mg/dL)	46	1.45	2.09	0.3	0.90	13.1
ALP (IU/mL)	47	291.4	386.6	37	166.0	1985
γ-GTP(IU/L)	45	108.4	109.5	21	76.0	644
Improved / Resolving value						
AST(IU/L)	46	28.8	13.8	15	26.5	106
ALT(IU/L)	46	34.6	20.6	12	30.5	132
Total bilirubin(mg/dL)	44	0.72	0.32	0.2	0.70	2.2
ALP (IU/mL)	46	183.8	169.8	35	127.5	988
γ-GTP(IU/L)	45	65.3	54.5	17	52.0	319
At the time of consultation						
AST(IU/L)	16	443.4	271.6	81	362.0	965
ALT(IU/L)	16	565.6	366.8	110	586.5	1430
Total bilirubin(mg/dL)	16	1.84	3.03	0.3	1.10	13.1
ALP (IU/mL)	16	259.3	145.2	69	212.5	535
γ-GTP(IU/L)	15	149.6	159.5	23	113.0	644
At treatment resumption						
AST(IU/L)	31	30.2	12.0	10	27.0	61
ALT(IU/L)	31	40.2	35.7	3	31.0	213
Total bilirubin(mg/dL)	31	0.68	0.23	0.3	0.70	1.2
ALP (IU/mL)	31	204.5	186.9	38	162.0	988
γ-GTP(IU/L)	30	66.2	50.3	20	55.5	249

Collected laboratory test data was not reassessed: assessment of the presence / absence of onset of adverse drug reaction for which certain criteria have been set, seriousness, etc.

Although it is necessary to consider that the reported laboratory test data was measured in daily medical practice (unmeasured values in some cases), considering liver-related laboratory test data, re-administration of the drug was considered to have been performed almost appropriately.

10.3.4 Causality to pembrolizumab and axitinib

In this section, the occurrence status of AEs is described for AEs reported in the survey form.

The causal relationship between the pembrolizumab and axitinib for 58 patients with hepatic adverse event excluding 2 patients (only causal relationship with pembrolizumab has been determined) with "adverse drug reaction assessment outside the survey form", is presented in Table 15.

Table 15. The causal relationship between pembrolizumab and/or axitinib for 58 patients with hepatic adverse event

		Causality to axitinib	
		Yes	No
Causality to pembrolizumab	Yes	41cases	6 cases
	No	8 cases	3 cases

"Yes": Causal relationship with the drug cannot be ruled out.

In the hepatic adverse events reported in the safety analysis set, the causality to pembrolizumab or axitinib was not ruled out (hepatic adverse reaction of pembrolizumab or axitinib) in 28.50% (55/193 patients). The causality to pembrolizumab was not ruled out in 24.35% (47/193 patients), the causality to axitinib was not ruled out in 25.39% (49/193 patients), and the causality to both pembrolizumab and axitinib was not ruled out in 21.24% (41/193 patients). The causality to both pembrolizumab and axitinib of hepatic adverse event were ruled out in 3 patients.

10.3.5 Actions to pembrolizumab or axitinib at onset of hepatic adverse reactions

For hepatic adverse reactions which the causality to pembrolizumab or axitinib cannot be ruled out, actions taken to pembrolizumab or axitinib at the onset of hepatic adverse reactions are shown by grade in Table 16, the disposition of discontinuation is shown in Table 18, and the disposition of resumption after washout is shown in Table 19.

Patients who did not receive pembrolizumab or axitinib again after the interruption were defined as "discontinued", and patients who received pembrolizumab or axitinib again after the interruption were defined as "resumed after the interruption".

After the onset of hepatic adverse reaction of both drugs, both pembrolizumab and axitinib were continued in 7.27% (4/55) of patients, only pembrolizumab was continued in 9.09% (5/55) of patients, only axitinib was continued in 5.45% (3/55) of patients, and both pembrolizumab and axitinib were interrupted in 69.09% (38/55) of patients.

In Grade ≥ 3 adverse reactions, pembrolizumab was not continued in any patient, axitinib alone was continued in 3.70% (1/27 patients), and both pembrolizumab and axitinib were interrupted in 81.48% (22/27 patients).

Table 16. Actions to pembrolizumab or axitinib at onset of hepatic adverse reactions by grade

Grade	No. of patients	Action after onset††			
		pembrolizumab (Continued) axitinib (Continued)	pembrolizumab (Continued) axitinib (Interruption)	pembrolizumab (Interruption) axitinib (Continued)	pembrolizumab (Interruption) axitinib (Interruption)
Overall	55	4(7.27%)	5(9.09%)	3(5.45%)	38(69.09%)
1	9	3(33.33%)	2(22.22%)	1(11.11%)	3(33.33%)
2	18	0(0.00%)	3(16.67%)	1(5.56%)	13(72.22%)
3	23	0(0.00%)	0(0.00%)	1(4.35%)	18(78.26%)
4	4	0(0.00%)	0(0.00%)	0(0.00%)	4(100.00%)
5	0	—	—	—	—
≤2	27	3(11.11%)	5(18.52%)	2(7.41%)	16(59.26%)
≥3	27	0(0.00%)	0(0.00%)	1(3.70%)	22(81.48%)

† : Including 1 patient with Grade unknown.
†† : Excluding 5 patients who discontinued pembrolizumab or axitinib at the first onset of hepatic adverse reaction.

Of the patients who continued pembrolizumab, no patients had a dose reduction. Of the patients who continued axitinib treatment, 2 patients shown in Table 17 continued axitinib treatment at a reduced dose.

Table 17. Handling of axitinib in cases of hepatic adverse reaction（continuing at a reduced dose

	Adverse drug reaction name	Grade	Daily dose of axitinib		
			At onset	Re-administration	Final dosing
1	Hepatic function abnormal	2	10mg	5mg	6mg
2	Hepatic function abnormal	1	10mg	6mg	4mg

The time (mean ±SD) from the onset of the hepatic adverse drug reaction to treatment interruption was 3.9 ± 11.2 days [≤ Grade 2: 5.4 ± 9.7 days; ≥ Grade 3: 2.5 ± 12.4 days].

For hepatic adverse reaction of pembrolizumab or axitinib, pembrolizumab was discontinued in 34.55% (19/55) of patients, axitinib was discontinued in 25.45% (14/55) of patients, and both pembrolizumab and axitinib were discontinued in 18.18% (10/55) of patients. For adverse reaction of Grade ≥ 3, pembrolizumab was discontinued in 51.85% (14/27) of patients, axitinib was discontinued in 37.04% (10/27) of patients, and both pembrolizumab and axitinib were discontinued in 29.63% (8/27) of patients.

Table 18. Actions taken with pembrolizumab or axitinib for hepatic adverse reaction by Grade (discontinuation)

Grade	No. of patients	Action after onset (discontinuation)		
		Pembrolizumab	Axitinib	Pembrolizumab and axitinib
Overall†	55	19(34.55%)	14(25.45%)	10(18.18%)
1	9	1(11.11%)	2(22.22%)	0(0.00%)
2	18	4(22.22%)	2(11.11%)	2(11.11%)
3	23	11(47.83%)	7(30.43%)	6(26.09%)
4	4	3(75.00%)	3(75.00%)	2(50.00%)
5	0	-	-	-
≤ 2	27	5(18.52%)	4(14.81%)	2(7.41%)
≥ 3	27	14(51.85%)	10(37.04%)	8(29.63%)

†: Including 1 patient with Grade unknown.

For Grade ≥ 3 hepatic adverse reaction, pembrolizumab was resumed after interruption in 43.64% (24/55) of patients, axitinib was resumed after interruption in 58.18% (32/55) of patients, and both pembrolizumab and axitinib were resumed after interruption in 30.91% (17/55) of patients. For Grade ≥ 3 hepatic adverse reaction, the pembrolizumab was resumed after interruption in 40.74% (11/27) of patients, axitinib was resumed after interruption in 51.85% (14/27) of patients, and both pembrolizumab and axitinib were resumed after interruption in 25.93% (7/27) of patients.

Table 19. Actions taken with the pembrolizumab or axitinib for hepatic adverse reaction by Grade (resumed after interruption)

Grade	No. of patients	Action after onset (resumed after interruption)		
		Pembrolizumab	Axitinib	Pembrolizumab and axitinib
Overall†	55	24(43.64%)	32(58.18%)	17(30.91%)
1	9	3(33.33%)	3(33.33%)	1(11.11%)
2	18	10(55.56%)	15(83.33%)	9(50.00%)
3	23	10(43.48%)	13(56.52%)	7(30.43%)
4	4	1(25.00%)	1(25.00%)	0(0.00%)
5	0	-	-	-
≤ 2	27	13(48.15%)	18(66.67%)	10(37.04%)
≥ 3	27	11(40.74%)	14(51.85%)	7(25.93%)

†: Including 1 patient with Grade unknown.

Of the 16 patients who received re-treatment with pembrolizumab, no patients had a dose reduction of pembrolizumab at the time of re-treatment. Of the 16 patients who received re-treatment with axitinib, 16 patients had a dose reduction of axitinib at the time of re-treatment. Of the 16 patients who received re-treatment with axitinib at a reduced dose, 6 patients had had a hepatic adverse reaction of ≥ Grade 3, and the daily dose of axitinib at the time of occurrence of the adverse reaction was 10 mg in 1 patient and 6 mg in 4 patients, and the daily dose of axitinib was being interrupted (the dose was 10 mg before interruption) in 1 patient at data cut-off. An overview of the patients who had a dose reduction during re-treatment with

axitinib, including the number of days from the onset of hepatic adverse reaction to re-treatment with axitinib at a reduced dose, is shown in Table 20.

Table 20. Dose handling of axitinib in cases of hepatic adverse reaction (re-administration at reduced dose)

	Adverse drug reaction name	Grade	Axitinib Daily Dose			Axitinib Treatment (Number of days from date of onset of adverse drug reaction)	
			At onset Daily Dose	Re-administration Daily Dose	Final dosing Daily Dose	Number of days until suspension / discontinuation	Days to dose reduction
1	Drug-induced liver injury	**3**	10mg	6mg	6mg	1	10
2	Immune-mediated liver injury	**3**	During drug cessation (10 mg before interruption)	8mg	4mg	-29	47
3	Hepatic function abnormal	1	10mg	6mg	6mg	2	8
4	Drug-induced liver injury	2	4mg	2mg	2mg	2	15
5	Hepatic function abnormal	2	10mg	6mg	-	2	29
	Hepatic function abnormal	2	During drug cessation (6 mg before interruption)	6mg	-	-19	-
	Hepatic function abnormal	2	6mg	Continuous treatment	6mg	-	-
6	Immune-mediated liver injury	**3**	6mg	2mg	-	1	48
	Congestive liver disorder	Not listed	During drug cessation (6 mg before interruption)	2mg	-	-	-
	Immune-mediated liver injury	1	2mg	Continuous treatment	2mg	-	-
7	Drug-induced liver injury	2	10mg	6mg	6mg	2	10
8	Hepatic function abnormal	**3**	6mg	4mg	4mg	1	22
9	Liver disorder	2	10mg	6mg	6mg	2	43
10	Hepatic function abnormal	2	10mg	6mg	4mg	22	29
11	Aspartate aminotransferase increased	2	6mg	4mg	4mg	2	31
12	Hepatic function abnormal	2	6mg	4mg	6mg	2	11
13	Immune-mediated liver injury	2	6mg	6mg	-	1	-
	Hepatic function abnormal	**3**	6mg	4mg	4mg	1	60
14	Immune-mediated liver injury	2	8mg	6mg	6mg	2	99
15	Hepatic function abnormal	2	10mg	6mg	-	2	50

	Adverse drug reaction name	Grade	Axitinib Daily Dose			Axitinib Treatment (Number of days from date of onset of adverse drug reaction)	
			At onset Daily Dose	Re-administration Daily Dose	Final dosing Daily Dose	Number of days until suspension / discontinuation	Days to dose reduction
	Hepatic function abnormal	2	6mg	Discontinuation of treatment	Discontinuation of treatment	1	-
16	Immune-mediated liver injury	**3**	6mg	4mg	-	2	15
	Hepatic function abnormal	2	4mg	2mg	2mg	2	38

The mean (±standard deviation) time to restart of axitinib was 38.6 ± 26.3 days (≤ Grade 2: 38.8 ± 28.9 days; ≥ Grade 3: 38.2 ± 23.5 days).

Table 21 shows the status of interruption of pembrolizumab or axitinib at the onset of hepatic adverse reaction by Grade in 9 recurrent cases out of 55 cases with hepatic adverse reaction of the pembrolizumab or axitinib for which causal relationship with axitinib could not be ruled out, and Table 22 shows the breakdown of discontinuation and Table 23 shows the breakdown of retreatment after interruption.

In the 9 patients with recurrent hepatic adverse reaction of both pembrolizumab or axitinib, pembrolizumab was interrupted in 33.33% (3/9) of patients, axitinib was interrupted in 66.67% (6/9) of patients, and both pembrolizumab and axitinib were interrupted in 22.22% (2/9) of patients; for hepatic adverse reaction of Grade ≥ 3, pembrolizumab was interrupted in 33.33% (1/3) of patients, axitinib was interrupted in 33.33% (1/3) of patients, and both pembrolizumab and axitinib were not discontinued in any patient.

Table 21. Action taken with pembrolizumab or axitinib after onset of hepatic adverse reaction (recurrent) by Grade (interruptions)

Grade	No. of patients	Treatment after recurrence (drug interruption)		
		Pembrolizumab	Axitinib	Pembrolizumab and axitinib
Overall†	9	3(33.33)	6(66.67)	2(22.22)
1	0	-	-	-
2	5	2(40.00)	4(80.00)	2(40.00)
3	3	1(33.33)	2(66.67)	0(0.00)
4	0	-	-	-
5	0	-	-	-
≤ 2	5	2(40.00)	4(80.00)	2(40.00)
≥ 3	3	1(33.33)	2(66.67)	0(0.00)

†: Including 1 patient with Grade unknown.

In the following sections, events occurring after interruption of pembrolizumab or axitinib in patients with recurrent hepatic adverse reaction are described separately as "discontinued" and "resumed after interruption."

In 9 patients with recurrent hepatic adverse reactions, 4 patients discontinued treatment (2 patients (22.2%) discontinued pembrolizumab and axitinib, each). None of the patients discontinued both pembrolizumab and axitinib. For Grade ≥ 3 hepatic adverse reaction, the pembrolizumab was discontinued in 33.33% (1/3) of patients, axitinib was discontinued in 66.66% (1/3) of patients, and both pembrolizumab and axitinib were not discontinued in any patient.

Table 22. Actions taken with pembrolizumab or axitinib after onset of hepatic adverse reaction (recurrent) by Grade (discontinuation)

Grade	No. of patients	Treatment after recurrence (discontinuation)		
		Pembrolizumab	Axitinib	Pembrolizumab and axitinib
Overall†	9	2(22.22)	2(22.22)	0(0.00)
1	0	-	-	-
2	5	1(20.00)	1(20.00)	0(0.00)
3	3	1(33.33)	1(33.33)	0(0.00)
4	0	-	-	-
5	0	-	-	-
≤ 2	5	1(20.00)	1(20.00)	0(0.00)
≥ 3	3	1(33.33)	1(33.33)	0(0.00)

†: Including 1 patient with Grade unknown.

In the 9 patients with recurrent hepatic adverse reaction of both pembrolizumab and axitinib, pembrolizumab was interrupted and re-administered in 11.11% (1/9 patients), axitinib was interrupted and re-administered in 55.56% (4/9 patients), and both pembrolizumab and axitinib were interrupted and re-administered in 11.11% (1/9 patients); for hepatic adverse reaction of Grade ≥ 3, pembrolizumab was not interrupted and re-administered in 33.33% (1/3 patients), and both pembrolizumab and axitinib were not interrupted and re-administered in any patient.

Table 23. Actions taken with pembrolizumab or axitinib after onset of hepatic adverse reaction (recurrent) by Grade (resumed after interruption)

Grade	No. of patients	Treatment after recurrence (resumed after interruption)		
		Pembrolizumab	Axitinib	Pembrolizumab and axitinib
Overall†	9	1(11.11)	4(44.44)	1(11.11)
1	0	-	-	-
2	5	1(20.00)	3(60.00)	1(20.00)
3	3	0(0.00)	1(33.33)	0(0.00)
4	0	-	-	-
5	0	-	-	-
≤ 2	5	1(20.00)	1(20.00)	0(0.00)
≥ 3	3	1(33.33)	1(33.33)	0(0.00)

†: Including 1 patient with Grade unknown.

10.3.6 Administration of steroids or other drugs for hepatic adverse reactions

In this section, treatments for hepatic adverse reaction are described separately for “adverse reaction of pembrolizumab” and “adverse reaction of axitinib”.

Basic statistics of patients who received steroids as treatment for hepatic adverse reactions of pembrolizumab are shown in Table 24, outcome by use/no use of steroids is shown in Table 25, and status of administration of steroids or non-steroidal drugs for hepatic adverse reactions is shown in Table 26.

Steroids were administered for treatment of hepatic adverse reactions in 26.53% (13/40 patients) of patients with hepatic adverse reactions of pembrolizumab. All these events were resolved or resolving. The administration of treatment with steroids or other drugs for hepatic adverse reactions was unknown in one patient, and the outcome was “not resolved”. Time to administration of steroids after the date of onset was 11.0 ± 9.2 days. 11 patients received steroid at a daily dose of ≥ 40 mg (in prednisolone equivalent), 2 patients received steroid at a daily dose of <40 mg, and 7.69% (1/13 patients) received steroid pulse therapy. Except for 1 patient with unknown onset date of adverse reaction, the initial doses (daily doses in prednisolone equivalent) were 30 mg, 40 mg, and 60 mg in 2 patients each, 65 mg in 1 patient, 70 mg in 2 patients, and 125 mg, 156.25 mg, and 160 mg in 1 patient each.

Of the 24 patients with Grade ≤ 3 hepatic adverse reaction of pembrolizumab, 11 patients received steroids as treatment. The proportion of patients who received steroid pulse therapy was 9.09% in (1/11).

One patient who received steroid pulse therapy (No. 3 case in Table 12) developed immune-mediated liver disorder (Grade 4) on Day 5 of treatment with pembrolizumab, discontinued pembrolizumab and axitinib, received steroid pulse therapy, and recovered 264 days after onset.

Non-steroidal drugs were administered in 18.37% (9/49 patients), ursodeoxycholic acid was administered in 14.29% (7/49 patients), and glycyrrhizin agents were administered in 12.24% (6/49 patients). Hepatic adverse reactions were improved (resolved or resolving) after administration of drugs in all patients. No patients received mycophenolate mofetil or other immunosuppressants.

Of 24 patients with Grade ≤ 3 hepatic adverse reaction of pembrolizumab, 16.67% (4/ 24 patients) received non-steroid medications, 12.50% (3 / 24 patients) received ursodeoxycholic acid, and 16.67% (4 / 24 patients) received glycyrrhizin.

The outcomes of 49 patients with the hepatic adverse reaction in this survey regardless of the use of steroids or other drugs were "recovered" in 33 patients, "recovering" in 13 patients, and "not recovered" in 3 patients.

In one of the 3 patients with an outcome of "not resolved", the implementation of drug therapy status of steroids, etc. was unknown as described above.

Two of the 3 patients did not receive steroids or other drugs for hepatic adverse reactions.

All of the 3 patients with an outcome of "not resolved" discontinued treatment for reasons other than hepatic adverse reaction, and the outcome of hepatic adverse reaction at the time of discontinuation was "not resolved".

Of the 49 patients with hepatic adverse reaction of axitinib, 41 patients had events for which causal relationship of both pembrolizumab and axitinib could not be ruled out, and thus, included in the above-mentioned cases with hepatic adverse reaction of pembrolizumab; thus, 8 cases for which causal relationship of pembrolizumab drug was ruled out and causal relationship of axitinib alone could not be ruled out were described. The outcomes of these events in these 8 patients (Grade ≤ 2 events in 5 patients, Grade ≥ 3 events in 3 patients) were all reported as resolved or resolving.

The status of treatment with therapeutic drugs such as steroids was checked in 8 patients; no patients received steroids as treatment. Of the 8 patients, 37.50% (3/8 patients) received ursodeoxycholic acid. The treatment status by Grade was ≤ Grade 2 in 20.00% (1/5 patients) and ≥ Grade 3 in 66.67% (2/3 patients).

Table 24. Basic statistics for administration of steroids in patients with hepatic adverse reactions

Patients with hepatic adverse reactions		No. of patients	49
Patients who received steroids for treatment of adverse reactions		No. of patients	13
Time (days) to administration of steroids after onset		No. of patients†	12
		Mean	11.0
		SD	9.2
		Min	1
		Median	8.5
		Max	31
Total dose (mg)		No. of patients†	12
		Mean	5,309.979
		SD	5,435.050
		Min	70.00
		Median	3,149.250
		Max	1,6945.00
Total duration of treatment (days)		No. of patients†	12
		Mean	109.3
		SD	76.0
		Min	1
		Median	95.5
		Max	242
Initial Dose（mg）	30	No. of patients†	2
	40		2
	60		2
	65		1
	70		2
	125		1
	156.25		1
	160		1
†: Excluding 1 patient with an unknown date of onset			

Table 25. Outcome by use/no use of steroids in patients with hepatic adverse reactions

Administration of steroids	No. of patients	Outcome					
		Resolved	Resolving	Not resolved	Resolved with sequelae	Fatal	Unknown
No	34	24(70.59%)	8(23.53%)	2(5.88%)	0(0.00%)	0(0.00%)	0(0.00%)
Yes	13	9(69.23%)	4(30.77%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Pulse therapy	1	1(100.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)	0(0.00%)

Table 26. Status of administration of steroids or non-steroidal drugs for hepatic adverse reactions

Grade	No. of patients	Steroids				Non-steroidal drugs		
		Patients treated with steroids	Administration of daily steroid dose of ≥40 mg (prednisolone equivalent) (max dose, including pulse)	Administration of daily steroid dose of < 40 mg (prednisolone equivalent) (max dose)	Pulse therapy	Patients treated with non-steroidal drugs	Ursodeoxycholic acid	Glycyrrhizin agents
Overall	49	13(26.53%)	11(22.45%)	2(4.08%)	1(2.04%)	9(18.37%)	7(14.29%)	6(12.24%)
1	9	1(11.11%)	0(0.00%)	1(11.11%)	0(0.00%)	1(11.11%)	1(11.11%)	0(0.00%)
2	15	1(6.67%)	1(6.67%)	0(0.00%)	0(0.00%)	4(26.67%)	3(20.00%)	2(13.33%)
3	19	9(47.37%)	8(42.11%)	1(5.26%)	0(0.00%)	3(15.79%)	2(10.53%)	3(15.79%)
4	5	2(40.00%)	2(40.00%)	0(0.00%)	1(20.00%)	1(20.00%)	1(20.00%)	1(20.00%)
5	0	—	—	—	—	—	—	—
≤ 2	24	2(8.33%)	1(4.17%)	1(4.17%)	0(0.00%)	5(20.83%)	4(16.67%)	2(8.33%)
≥ 3	24	11(45.83%)	10(41.67%)	1(4.17%)	1(4.17%)	4(16.67%)	3(12.50%)	4(16.67%)

10.3.7 Pembrolizumab or axitinib treatment for hepatic adverse reaction (non-drug treatment)

For hepatic adverse reaction for which causal relationship with pembrolizumab or axitinib could not be ruled out, treatment other than drug therapy was not performed in any patients.

10.3.8 Consultation to medical specialists

Among adverse reactions reported in patients whose survey forms were locked during this survey unit period, events that completed data cleaning are tabulated in this section.

The status of consultation to medical specialists concerning hepatic adverse reactions which the causality to pembrolizumab or axitinib cannot be ruled out is shown in Table 27. In overall, 32.73% (18/55 patients) consulted to medical specialists, 62.96% (17/27 patients) consulted medical specialists for Grade ≥ 3 adverse reactions.

Table 27. Consultation to medical specialists after onset of hepatic adverse reactions

Grade	No. of patients	Consultation to medical specialist	
		No	Yes
Overall	55	37(67.27%)	18(32.73%)
1	9	9(100.00%)	0(0.00%)
2	18	17(94.44%)	1(5.56%)
3	23	9(39.13%)	14(60.87%)
4	4	1(25.00%)	3(75.00%)
5	0	—	—
≤ 2	27	26(96.30%)	1(3.70%)
≥ 3	27	10(37.04%)	17(62.96%)

10.4 Patients with specific backgrounds

In the 193 patients in the safety analysis set of the drug use-results survey, there were no paediatric patients or pregnant women, there were 130 (67.36%) elderly patients, 121 patients (62.69%) with renal function disorder, and 6 patients (3.11%) with hepatic function disorder.

10.4.1 Paediatric patients

In the 98 patients in the safety analysis set, cases of use in paediatric patients were not collected.

10.4.2 Elderly patients

In the 193 patients in the safety analysis set, there were 130 elderly patients aged ≥ 65 years, and the incidence of hepatic adverse reactions was 21.54% (28/130 patients) in these patients. The incidence of hepatic adverse reactions in non-elderly patients was 33.33% (21/63 patients), and no statistically significant difference was found (OR: 0.549; 95% CI: 0.281-1.037).

10.4.3 Pregnant women

In the 193 patients in the safety analysis set, cases of use in pregnant women were not collected.

10.4.4 Patients with renal function disorder

In the 193 patients in the safety analysis set, there were 121 patients with renal function disorder, and the incidence of hepatic adverse reactions was 22.31% (27/121 patients). The incidence of hepatic adverse reactions in patients without renal function disorder was 30.99% (22/71 patients), and no statistically significant difference was found (OR: 0.640; 95% CI: 0.331-1.238).

10.4.5 Patients with hepatic function disorder

In the 193 patients in the safety analysis set, there were 6 patients with hepatic function disorder, and the incidence of hepatic adverse reactions was 33.33% (2/6 patients). The incidence of hepatic adverse reaction in patients without hepatic function disorder was 25.27% (47/186 patients), and no statistically significant difference was found (OR: 1.479; 95% CI: 0.262-8.336).

10.5 Adverse events/adverse reactions

Information on non-hepatic adverse drug reactions (320 total of which 115 were categorized as serious and 205 were categorized as non-serious) were collected and are summarized in Table 28. Occurrence rates are calculated as the number of cases in safety analysis set (n=193). Medical Dictionary for Regulatory Activities (MedDRA) terminology were used for coding the adverse reaction terms, the PT level and SOC are presented in the summary tabulations. The table is organised by MedDRA SOC and listed in the internationally agreed order.

Table 28. Incidence of non-hepatic adverse drug reactions (ADRs)†

Preferred term (PT)	PT code	Serious ADR (115 total)		Non-serious ADR (205 total)		All ADR (320 total)	
		# of cases	Occurrence rate	# of cases	Occurrence rate	# of cases	Occurrence rate
1 - Infections and infestations (10021881)							
Meningitis	10027199	1	0.52%	0	0.00%	1	0.52%
Pericoronitis	10034504	0	0.00%	1	0.52%	1	0.52%
Pneumonia	10035664	2	1.04%	0	0.00%	2	1.04%
Pneumonia aspiration	10035669	2	1.04%	0	0.00%	2	1.04%
Septic shock	10040070	1	0.52%	0	0.00%	1	0.52%
Urinary tract infection	10046571	0	0.00%	1	0.52%	1	0.52%
Pneumonia bacterial	10060946	1	0.52%	0	0.00%	1	0.52%
COVID-19	10084268	0	0.00%	1	0.52%	1	0.52%
2 - Neoplasms benign, malignant and unspecified (incl cysts and polyps) (10029104)							
Malignant pleural effusion	10026673	1	0.52%	0	0.00%	1	0.52%
Malignant neoplasm progression	10051398	7	3.63%	0	0.00%	7	3.63%
3 - Blood and lymphatic system disorders (10005329)							
Anaemia	10002034	0	0.00%	1	0.52%	1	0.52%
Thrombocytopenia	10043554	1	0.52%	0	0.00%	1	0.52%
4 - Immune system disorders (10021428)							
Cytokine release syndrome	10052015	1	0.52%	0	0.00%	1	0.52%
5 – Endocrine disorders (10014698)							
Adrenal insufficiency	10001367	3	1.55%	0	0.00%	3	1.55%
Adrenocortical insufficiency acute	10001389	2	1.04%	0	0.00%	2	1.04%
Graves' disease	10018706	1	0.52%	0	0.00%	1	0.52%
Hyperthyroidism	10020850	3	1.55%	0	0.00%	3	1.55%
Hypopituitarism	10021067	0	0.00%	1	0.52%	1	0.52%
Hypothyroidism	10021114	13	6.74%	0	0.00%	13	6.74%
Secondary adrenocortical insufficiency	10039807	0	0.00%	2	1.04%	2	1.04%
Thyroiditis	10043778	2	1.04%	1	0.52%	3	1.55%
Adrenocorticotropic hormone deficiency	10073179	2	1.04%	1	0.52%	3	1.55%

Preferred term (PT)	PT code	Serious ADR (115 total)		Non-serious ADR (205 total)		All ADR (320 total)	
		# of cases	Occurrence rate	# of cases	Occurrence rate	# of cases	Occurrence rate
Silent thyroiditis	10079012	0	0.00%	2	1.04%	2	1.04%
Immune-mediated thyroiditis	10083071	2	1.04%	0	0.00%	2	1.04%
Immune-mediated hypothyroidism	10083075	12	6.22%	0	0.00%	12	6.22%
Immune-mediated hyperthyroidism	10083517	1	0.52%	0	0.00%	1	0.52%
Immune-mediated adrenal insufficiency	10085547	2	1.04%	0	0.00%	2	1.04%
6 - Metabolism and nutrition disorders (10027433)							
Dehydration	10012174	1	0.52%	2	1.04%	3	1.55%
Diabetes mellitus	10012601	1	0.52%	0	0.00%	1	0.52%
Hypercalcaemia	10020583	0	0.00%	1	0.52%	1	0.52%
Hyperglycaemia	10020635	0	0.00%	1	0.52%	1	0.52%
Hyponatraemia	10021036	1	0.52%	1	0.52%	2	1.04%
Decreased appetite	10061428	4	2.07%	18	9.33%	22	11.40%
7 – Psychiatric disorders (10037175)							
Disorientation	10013395	0	0.00%	1	0.52%	1	0.52%
Depressive symptom	10054089	0	0.00%	1	0.52%	1	0.52%
8 - Nervous system disorders (10029205)							
Altered state of consciousness	10001854	1	0.52%	0	0.00%	1	0.52%
Cerebral infarction	10008118	2	1.04%	0	0.00%	2	1.04%
Dizziness	10013573	0	0.00%	1	0.52%	1	0.52%
Headache	10019211	0	0.00%	2	1.04%	2	1.04%
Hypoaesthesia	10020937	0	0.00%	1	0.52%	1	0.52%
Myasthenia gravis	10028417	1	0.52%	0	0.00%	1	0.52%
Taste disorder	10082490	1	0.52%	2	1.04%	3	1.55%
9 – Eye disorders (10015919)							
Visual acuity reduced	10047531	1	0.52%	0	0.00%	1	0.52%
11 – Cardiac disorders (10007541)							
Atrial fibrillation	10003658	1	0.52%	0	0.00%	1	0.52%
Immune-mediated myocarditis	10082606	2	1.04%	0	0.00%	2	1.04%
12 – Vascular disorders (10047065)							
Hypertension	10020772	0	0.00%	12	6.22%	12	6.22%
Vasculitis	10047115	1	0.52%	0	0.00%	1	0.52%
13 - Respiratory, thoracic and mediastinal disorders (10038738)							
Dysphonia	10013952	0	0.00%	10	5.18%	10	5.18%
Dyspnoea	10013968	1	0.52%	0	0.00%	1	0.52%
Epistaxis	10015090	0	0.00%	2	1.04%	2	1.04%
Interstitial lung disease	10022611	6	3.11%	0	0.00%	6	3.11%
Pleural effusion	10035598	1	0.52%	0	0.00%	1	0.52%

Preferred term (PT)	PT code	Serious ADR (115 total)		Non-serious ADR (205 total)		All ADR (320 total)	
		# of cases	Occurrence rate	# of cases	Occurrence rate	# of cases	Occurrence rate
Pneumothorax	10035759	1	0.52%	0	0.00%	1	0.52%
Pulmonary embolism	10037377	1	0.52%	0	0.00%	1	0.52%
Pulmonary oedema	10037423	1	0.52%	0	0.00%	1	0.52%
Lung opacity	10081792	0	0.00%	1	0.52%	1	0.52%
14 - Gastrointestinal disorders (10017947)							
Abdominal pain	10000081	0	0.00%	2	1.04%	2	1.04%
Abdominal pain upper	10000087	0	0.00%	1	0.52%	1	0.52%
Colitis	10009887	0	0.00%	2	1.04%	2	1.04%
Colitis ischaemic	10009895	1	0.52%	0	0.00%	1	0.52%
Colitis ulcerative	10009900	1	0.52%	0	0.00%	1	0.52%
Constipation	10010774	0	0.00%	3	1.55%	3	1.55%
Diarrhoea	10012735	2	1.04%	19	9.84%	21	10.88%
Duodenal ulcer	10013836	1	0.52%	0	0.00%	1	0.52%
Duodenitis	10013864	0	0.00%	1	0.52%	1	0.52%
Gingival pain	10018286	0	0.00%	1	0.52%	1	0.52%
Haematemesis	10018830	1	0.52%	0	0.00%	1	0.52%
Ileus	10021328	1	0.52%	0	0.00%	1	0.52%
Nausea	10028813	0	0.00%	1	0.52%	1	0.52%
Oesophagitis	10030216	0	0.00%	1	0.52%	1	0.52%
Stomatitis	10042128	0	0.00%	6	3.11%	6	3.11%
Toothache	10044055	0	0.00%	1	0.52%	1	0.52%
Upper gastrointestinal haemorrhage	10046274	1	0.52%	0	0.00%	1	0.52%
Vomiting	10047700	0	0.00%	2	1.04%	2	1.04%
Immune-mediated enterocolitis	10078961	5	2.59%	0	0.00%	5	2.59%
15 - Hepatobiliary disorders (10019805)							
Bile duct stone	10004637	1	0.52%	0	0.00%	1	0.52%
Cholecystitis acute	10008614	1	0.52%	0	0.00%	1	0.52%
Jaundice	10023126	0	0.00%	1	0.52%	1	0.52%
Gallbladder polyp	10049704	0	0.00%	1	0.52%	1	0.52%
16 - Skin and subcutaneous tissue disorders (10040785)							
Drug eruption	10013687	0	0.00%	1	0.52%	1	0.52%
Erythema multiforme	10015218	1	0.52%	0	0.00%	1	0.52%
Palmar-plantar erythrodysaesthesia syndrome	10033553	0	0.00%	13	6.74%	13	6.74%
Rash	10037844	0	0.00%	7	3.63%	7	3.63%
Skin ulcer	10040943	1	0.52%	0	0.00%	1	0.52%
17 - Musculoskeletal and connective tissue disorders (10028395)							
Arthralgia	10003239	0	0.00%	2	1.04%	2	1.04%
Back pain	10003988	0	0.00%	1	0.52%	1	0.52%

Preferred term (PT)	PT code	Serious ADR (115 total)		Non-serious ADR (205 total)		All ADR (320 total)	
		# of cases	Occurrence rate	# of cases	Occurrence rate	# of cases	Occurrence rate
Muscular weakness	10028372	0	0.00%	2	1.04%	2	1.04%
Musculoskeletal stiffness	10052904	0	0.00%	2	1.04%	2	1.04%
18 - Renal and urinary disorders (10038359)							
Nephrotic syndrome	10029164	1	0.52%	0	0.00%	1	0.52%
Proteinuria	10037032	0	0.00%	16	8.29%	16	8.29%
Kidney enlargement	10048469	0	0.00%	1	0.52%	1	0.52%
Renal impairment	10062237	4	2.07%	0	0.00%	4	2.07%
Acute kidney injury	10069339	1	0.52%	0	0.00%	1	0.52%
20 - Reproductive system and breast disorders (10038604)							
Prostatomegaly	10051482	0	0.00%	1	0.52%	1	0.52%
22 - General disorders and administration site conditions (10018065)							
Asthenia	10003549	0	0.00%	1	0.52%	1	0.52%
Death	10011906	2	1.04%	0	0.00%	2	1.04%
Malaise	10025482	0	0.00%	15	7.77%	15	7.77%
Oedema	10030095	0	0.00%	2	1.04%	2	1.04%
Oedema peripheral	10030124	0	0.00%	2	1.04%	2	1.04%
Pain	10033371	0	0.00%	1	0.52%	1	0.52%
Pyrexia	10037660	0	0.00%	2	1.04%	2	1.04%
General physical health deterioration	10049438	0	0.00%	2	1.04%	2	1.04%
Physical deconditioning	10051588	0	0.00%	1	0.52%	1	0.52%
Adverse event	10060933	0	0.00%	1	0.52%	1	0.52%
Inflammation	10061218	0	0.00%	1	0.52%	1	0.52%
Multiple organ dysfunction syndrome	10077361	1	0.52%	0	0.00%	1	0.52%
23 – Investigations (10022891)							
Blood corticotrophin increased	10005453	0	0.00%	2	1.04%	2	1.04%
Blood creatine phosphokinase increased	10005470	0	0.00%	1	0.52%	1	0.52%
Blood creatinine increased	10005483	0	0.00%	2	1.04%	2	1.04%
Blood thyroid stimulating hormone decreased	10005832	0	0.00%	1	0.52%	1	0.52%
Blood thyroid stimulating hormone increased	10005833	0	0.00%	1	0.52%	1	0.52%
C-reactive protein increased	10006825	0	0.00%	1	0.52%	1	0.52%
Platelet count decreased	10035528	0	0.00%	3	1.55%	3	1.55%
Protein urine	10037018	0	0.00%	1	0.52%	1	0.52%
Weight decreased	10047895	0	0.00%	2	1.04%	2	1.04%

Preferred term (PT)	PT code	Serious ADR (115 total)		Non-serious ADR (205 total)		All ADR (320 total)	
		# of cases	Occurrence rate	# of cases	Occurrence rate	# of cases	Occurrence rate
White blood cell count decreased	10047942	0	0.00%	1	0.52%	1	0.52%
White blood cell count increased	10047943	0	0.00%	1	0.52%	1	0.52%
Tumour marker increased	10048621	0	0.00%	1	0.52%	1	0.52%
Protein urine present	10053123	0	0.00%	1	0.52%	1	0.52%
24 - Injury, poisoning and procedural complications (10022117)							
Fall	10016173	0	0.00%	3	1.55%	3	1.55%
Femur fracture	10016454	1	0.52%	0	0.00%	1	0.52%
Fracture	10017076	0	0.00%	1	0.52%	1	0.52%
†In the calculation of the aggregate results for non-hepatic ADR, each unique case of the same event (PT) occurring multiple times is counted as a single instance. SOC are per international agreement order							

11 DISCUSSION

11.1 Key results

In the renal cell carcinoma population, the incidence of hepatic adverse events reported varies across treatments and lines of therapy. A population-based study in Japan reported an incidence of events of hepatic disfunction of 17% in patients who received sorafenib as first line treatment due to unresectable or metastatic renal cell carcinoma [Ref. 5.4: 08LL3G]. An incidence rate of 9.1 per 100 person-years and 11 per 100 person-years of events of hepatitis were reported with tyrosine kinase (TK) inhibitors/ vascular endothelial growth factor (VEGF) inhibitors therapy and mTOR inhibitor, respectively in a claim-based study of patients with metastatic renal cell carcinoma in the U.S. [Ref. 5.4: 08LL3J].

In the clinical study KN426, the incidence of hepatic adverse reactions such as ALT and AST elevations of all grades occurred in 26.8% and 26.1% of patients, respectively in the pembrolizumab/axitinib group [Ref. 5.4: 05706K]. In a controlled clinical study with axitinib for the treatment of patients with renal cell carcinoma, ALT and AST elevations of all grades occurred in 22% and 20% of patients, respectively [Ref. 5.4: 08LL4R].

This DUR survey started on March 30, 2020, and contracts were made with 138 sites. A cumulative total of 196 patients were registered since the start of the survey, and survey forms for 196 patients were collected.

In the 193 patients in the safety analysis set, the incidence of hepatic adverse reactions with pembrolizumab was 25.39% (49/193 patients). The most common hepatic adverse reactions (≥ 5.0%) were hepatic function abnormal in 8.81% (17/193 patients) and immune-mediated hepatic disorder in 8.29% (16/193 patients). Most of the hepatic adverse reactions (67.80%) occurred within 3 months of starting therapy with pembrolizumab. The overall median time to onset of hepatic adverse reactions was 64.0 days.

Serious hepatic adverse reactions were reported in 15.03% of patients and Grade ≥ 3 hepatic adverse reactions were reported in 12.44% of patients.

The outcome of hepatic adverse reactions was resolved or resolving in most of the patients (93.88%). No deaths from hepatic adverse reactions were reported.

For hepatic adverse reactions, a logistic regression analysis (univariate analysis) was performed using patient background as a factor, and the crude OR and its asymptotic 95% CI were calculated, only Brinkman index [sub-group: ≤400 to <600] for which the lower limit of the 95% CI met the fixed criterion (>1) and which had an OR ≥2. There was no consistent trend between the Brinkman Index and the OR. When interpreting the results of this survey, it is necessary to consider the limitations of this survey, such as small sample size, confounding potential of background factors, and short observation period (9 months).

After onset of hepatic adverse reactions of pembrolizumab or axitinib, both pembrolizumab and axitinib were continued in 7.27% (4/55 patients), only pembrolizumab was continued in 9.09% (5/55 patients), only axitinib was continued in 5.45% (3/55 patients), and both pembrolizumab and axitinib were suspended in 69.09% (38/55 patients).

Due to hepatic adverse reactions of pembrolizumab or axitinib. pembrolizumab was discontinued in 34.55% (19/55 patients), axitinib was discontinued in 25.45% (14/55 patients), and both pembrolizumab and axitinib were discontinued in 18.18% (10/55 patients).

After onset of hepatic adverse reactions of pembrolizumab or axitinib. pembrolizumab was resumed in 43.64% (24/55 patients), axitinib was resumed in 58.18% (32/55 patients), and both pembrolizumab and axitinib were resumed in 30.91% (17/55 patients).

Steroids were administered for treatment of hepatic adverse reactions of pembrolizumab in 26.53% (13/49 patients), non-steroidal drugs were administered in 18.37% (9/49 patients), ursodeoxycholic acid was administered in 14.29% (7/49 patients), and glycyrrhizin agents were administered in 12.24% (6/49 patients). All these events resolved or were resolving after administration of steroids or other drugs. No patients received mycophenolate mofetil or other immunosuppressants. Hepatic adverse reactions improved (resolved or resolving) after administration of drugs in all patients.

There was no patient who received treatment other than drug therapy for hepatic adverse reactions of pembrolizumab or axitinib.

32.73% (18/55 patients) of patients were consulted by medical specialists for hepatic adverse reactions of pembrolizumab or axitinib.

Actions after the onset of the hepatic adverse reaction are summarized in Table 29 and Table 30.

Table 29. Actions at onset of hepatic adverse reactions of pembrolizumab or axitinib

Grade	Overall	Grade≤ 2	Grade³3
Hepatic adverse reactions of Pembrolizumab and Axitinib	55†	27	27
	No. of patients (%)		
Pembrolizumab was discontinued	19 (34.55%)	5 (18.52%)	14 (51.85%)
Axitinib was discontinued	14 (25.45%)	4 (14.81%)	10 (37.04%)
Both drugs (Pembrolizumab and Axitinib) were discontinued	10 (18.18%)	2 (7.41%)	8 (29.63%)
Pembrolizumab was resumed	24 (43.64%)	13 (48.15%)	11 (40.74%)
Axitinib was resumed	32 (58.18%)	18 (66.67%)	14 (51.85%)
Both drugs (Pembrolizumab and Axitinib) were resumed	17 (30.91%)	10 (37.04%)	7 (25.93%)
Consultation to medical specialist "Yes"	18 (32.73%)	1 (3.70%)	17 (62.96%)

† : Including 1 patient with Grade unknown

Table 30. Status of administration of treatment drugs for hepatic adverse reactions of Pembrolizumab

Grade	Overall	Grade≤ 2	Grade ≥3
Hepatic adverse reactions of Pembrolizumab	49†	24	24
	No. of patients (%)		
Patients treated with steroid	13 (26.53%)	2 (8.33%)	11 (45.83%)
Pulse therapy	1 (2.04%)	0 (0.00%)	1 (4.17%)
Patients treated with non-steroidal drugs	9 (8.37%)	5 (20.83%)	4 (16.67%)

† : Including 1 patient with Grade unknown.

In the results of this survey, a small proportion (N=23/193, 11.92%) of patients discontinued treatment with pembrolizumab or axitinib due to the development of hepatic adverse reaction, while 30.5% of patients in KN426 discontinued either drug due to any adverse event [Ref. 5.4: 05706K]; For most in this survey (N=39/55,70.90%), the hepatic adverse reaction resolved or was resolving after interruption of pembrolizumab or axitinib, and treatment could be resumed after dose interruption, including dose reduction of axitinib.

Steroids were used as therapeutic drugs in 13 patients (N=13/49, 26.53%), and pulse therapy was performed in only 1 of these patients.

No patients received immunosuppressant products and the observed hepatic adverse reaction was generally manageable.

Regarding patients with specific backgrounds, there were no paediatric patients or pregnant women in this study. No safety signals were observed for patients with renal function disorder or patients with hepatic function disorder.

11.2 Limitations

Given its observational nature, the study is prone to potential forms of 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 is likely some degree of selection bias given the index drugs are commercially available and patient consent to study participation was necessary. The descriptive baseline demographic and medical history for patients included in this study are qualitatively compared with other trial and real-world 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 channelling of newly marketed drugs to more severe cases. This may result in channelling 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 was done to help in identifying the potential degree of channelling 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 were implemented to help mitigate this potential form of bias. Given the inability to perform SDV, this bias is also another notable limitation of this study.

Lastly, the study was not designed to appropriately power statistical tests and no correction was performed for multiple testing. These exploratory and descriptive results should be interpreted with caution.

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

11.3 Interpretation

No changes in the benefit-risk profile of pembrolizumab was observed in the specified indication. It was determined that it is not necessary to take any particular measures such as

revising the indications, dosage and administration or precautions for pembrolizumab as specified at the time of approval. No additional risk minimization measures were deemed warranted.

11.4 Generalisability

The demographic characteristics of the patients in this survey [gender composition ratio (Male: 76.17%, Female: 23.83% and age (median:70.0years)] were generally consistent with what has been reported in patients with RCC in the general population.

12 OTHER INFORMATION

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., PMS studies in Japan and PASS in Europe [Ref. 5.4: 05DQYW]. 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 GPSP, which generally allows for five potential designs noted above. The GPSP also does not recognize the need to collect data on a comparator drug and does not allow for SDV at participating clinical sites. These and other limitations of GPP does not allow for an unbiased assessment of treatment causality.

Although sufficient rigor was applied to the 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 was conducted.

13 CONCLUSION

In conclusion, the results presented above do not suggest new safety concern about hepatic adverse reaction with the combination of pembrolizumab plus axitinib in this patient population.

REFERENCES

[Ref. 5.4: 05706K] 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.

[Ref. 5.4: 05DQYW] 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.

[Ref. 5.4: 08LL3G] Akaza H, Oya M, Iijima M, Hyodo I, Gemma A, Itoh H, et al. A large-scale prospective registration study of the safety and efficacy of sorafenib tosylate in unresectable or metastatic renal cell carcinoma in Japan: results of over 3200 consecutive cases in post-marketing all-patient surveillance. Jpn J Clin Oncol. 2015;45(10):953-62.

[Ref. 5.4: 08LL3J] Pal S, Gong J, Mhatre SK, Lin SW, Surinach A, Ogale S, et al. Real-world treatment patterns and adverse events in metastatic renal cell carcinoma from a large US claims database. BMC Cancer. 2019;19:548.

[Ref. 5.4: 08LL4R] U.S. Prescribing Information: INLYTA (axitinib) tablets for oral administration: Aug 2018.

[Ref. 5.4: 08LXSH] Tamada S, Kondoh C, Matsubara N, Mizuno R, Kimura G, Anai S, et al. Pembrolizumab plus axitinib versus sunitinib in metastatic renal cell carcinoma: outcomes of Japanese patients enrolled in the randomized, phase III, open-label KEYNOTE-426 study. Int J Clin Oncol. 2022;27:154-64.