Report on the Deliberation Results

September 12, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Bavencio Injection 200 mg
Non-proprietary Name	Avelumab (Genetical Recombination) (JAN*)
Applicant	Merck Serono Co., Ltd.
Date of Application	March 7, 2017

Results of Deliberation

In its meeting held on September 8, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 10 years. The drug product and its drug substance are both classified as powerful drugs.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a drug use-results survey, covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

Review Report

August 31, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Bavencio Injection 200 mg
Non-proprietary Name	Avelumab (Genetical Recombination)
Applicant	Merck Serono Co., Ltd.
Date of Application	March 7, 2017
Dosage Form/Strength	Injection: Each 10 mL vial contains 200 mg of Avelumab (Genetical Recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Avelumab is a recombinant human IgG1 monoclonal antibody against human programmed cell death-ligand 1 (PD-L1). Avelumab is produced in Chinese hamster ovary cells. Avelumab is a glycoprotein (molecular weight: ca. 147,000) composed of 2 H-chains (γ1-chains) consisting of 450 amino acid residues each and 2 L-chains (λ-chains) consisting of 216 amino acid residues each.

Structure

Amino acid sequence:

L chain

QSALTQPASV SGSPGQSITI SCTGTSSDVG GYNYVSWYQQ HPGKAPKLMI

YDVSNRPSGV SNRFSGSKSG NTASLTISGL QAEDEADYYC SSYTSSSTRV

FGTGTKVTVL GQPKANPTVT LFPPSSEELQ ANKATLVCLI SDFYPGAVTV

AWKADGSPVK AGVETTKPSK QSNNKYAASS YLSLTPEQWK SHRSYSCQVT

HEGSTVEKTV APTECS

H chain

EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYIMMWVRQA PGKGLEWVSS

IYPSGGITFY ADTVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCARIK

LGTVTTVDYW GQGTLVTVSS ASTKGPSVFP LAPSSKSTSG GTAALGCLVK

DYFPEPVTVS WNSGALTSGV HTFPAVLQSS GLYSLSSVVT VPSSSLGTQT

YICNVNHKPS NTKVDKKVEP KSCDKTHTCP PCPAPELLGG PSVFLFPPKP

KDTLMISRTP EVTCVVVDVS HEDPEVKFNW YVDGVEVHNA KTKPREEQYN

STYRVVSVLT VLHQDWLNGK EYKCKVSNKA LPAPIEKTIS KAKGQPREPQ

VYTLPPSRDE LTKNQVSLTC LVKGFYPSDI AVEWESNGQP ENNYKTTPPV

LDSDGSFFLY SKLTVDKSRW QQGNVFSCSV MHEALHNHYT QKSLSLSPGK

Intrachain disulfide bonds: Shown in solid lines

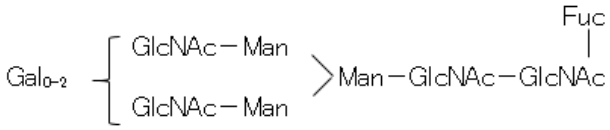
Interchain disulfide bonds: C215 in L chain - C223 in H chain, C229 in H chain - C229 in H chain, C232 in H chain - C232 in H chain

Pyroglutamate formation (partial): Q1 in L chain

Glycosylation site: N300 in H chain

Partial processing: K450 in H chain

Estimated structure of main carbohydrate chain



Gal, Galactose; GlcNAc, *N*-acetylglucosamine; Man, Mannose; Fuc, Fucose

Molecular formula: $C_{6374}H_{9898}N_{1694}O_{2010}S_{44}$ (protein portion)

Molecular weight: ca. 147,000

Items Warranting Special Mention

Orphan drug (Orphan Drug Designation No. 394 of 2016 [*28 yaku*]; PSEHB/PED Notification No. 1221-1 dated December 21, 2016, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, MHLW)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the product has a certain level of efficacy in the treatment of unresectable Merkel cell carcinoma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. Further investigations in the post-marketing surveillance are required on interstitial lung disease, hepatic dysfunction, colitis/severe diarrhoea, thyroid dysfunction, adrenal dysfunction, type 1 diabetes mellitus, myocarditis, nerve disorder (including Guillain-Barre syndrome), renal disorder, myositis/rhabdomyolysis, infusion reaction, encephalitis/meningitis, embryo-fetal toxicity, and on patients with history of organ transplantation (including history of haematopoietic stem cell transplant).

Indication

Unresectable Merkel cell carcinoma

Dosage and Administration

The usual adult dosage is 10 mg/kg (body weight) of avelumab (genetical recombination) intravenously infused over 1 hour or more once every 2 weeks.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a drug use-results survey covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.

Attachment

Review Report (1)

July 21, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Bavencio Injection 200 mg
Non-proprietary Name	Avelumab (Genetical Recombination)
Applicant	Merck Serono Co., Ltd.
Date of Application	March 7, 2017
Dosage Form/Strength	Injection: Each 10 mL vial contains 200 mg of Avelumab (Genetical Recombination).
Proposed Indication	Unresectable Merkel cell carcinoma

Proposed Dosage and Administration

The usual adult dosage is 10 mg/kg (body weight) of avelumab (genetical recombination) intravenously infused once every 2 weeks.

Table of Contents

List of Abbreviations

ADCC	antibody dependent cell mediated cytotoxicity
[redacted]	[redacted]
ALT	alanine aminotransferase
Anti-avelumab antibody	antibody against avelumab (genetical recombination)
Application	marketing application
ARDS	acute respiratory distress syndrome
ASGM1	asialoganglioside ganliotetraosylceramide
Asn	asparagine
AST	aspartate aminotransferase
AUC_{ss}	area under the serum concentration-time curve at steady state
Avelumab	avelumab (genetical recombination)
C1q	subcomponent of complement C1
CAL	cells at the limit of *in vitro* cell age
CDC	complement dependent cytotoxicity
C_{eoi}	serum concentration at the end of the infusion
CE-SDS	capillary gel electrophoresis with sodium dodecyl sulfate
CHO cells	Chinese hamster ovary cells
CI	confidence interval
$C_{max,ss}$	maximum serum concentration observed postdose at steady state
CPK	creatine phosphokinase
CQA	critical quality attribute
CR	complete response
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough,ss}$	serum concentration at the end of the dosing interval at steady state
DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
EC_{50}	half maximal effective concentration
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
eGFR	estimated glomerular filtration rate
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
Fab	fragment antigen binding
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FcγR	Fc γ receptor
FDA	Food and Drug Administration
GGT	gamma-glutamyl transferase
GM-CSF	granulocyte macrophage colony-stimulating factor
HCP	host cell protein
HLGT	high level group term
HLT	high level term
HRP	horseradish peroxidase
iCIEF	imaged capillary isoelectric focusing
IERC	Independent Endpoint Review Committee
IEX	ion exchange liquid chromatography
IFN-γ	interferon-γ
Ig	Immunoglobulin
IL-10	interleukin-10
IL-1β	interleukin-1β
IL-2	interleukin-2
IL-6	interleukin-6
IL-8	interleukin-8

ILD	interstitial lung disease
Japanese clinical practice guideline	Clinical practice guideline for dermal malignancies, 2nd edition (Japanese Skin Cancer Society, ed.)
K_D	dissociation constant
MCB	master cell bank
MCC	Merkel cell carcinoma
MCP-1	monocyte chemotactic protein-1
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
[redacted]	[redacted]
[redacted]	[redacted]
MTD	maximum tolerated dose
NCCN Guideline	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Merkel cell carcinoma
NCI	National Cancer Institute
NE	not evaluable
NEC	not elsewhere classified
nivolumab	nivolumab (genetical recombination)
NK	natural killer
NSCLC	non-small cell lung cancer
OS	overall survival
OVA	ovalbumin
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death-1
PDE	permitted daily exposure
PD-L1	programmed cell death ligand-1
PD-L1-Fc recombinant fusion protein	recombinant protein comprising human PD-L1 conjugated with Fc portion of human IgG1
PDQ	Physician Data Query
pembrolizumab	pembrolizumab (genetical recombination)
PFS	progression-free survival
PHA	phytohemagglutinin
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PR	partial response
PS	performance status
Q	intercompartmental clearance
Q2W	quaque 2 weeks
QbD	quality by design
QTcF	QT interval corrected using Fredericia equation
QTcP	QT interval corrected for heart rate by the secondary correction factor specific to the study population
QW	quaque 1 week
RECIST	Response Evaluation Criteria in Solid Tumors
SD	stable disease
SEA	*Staphylococcal* enterotoxin A
SEC	size exclusion chromatography
Ser	Serine
SMQ	standardised MedDRA queries
SOC	system organ class
SPR	surface plasmon resonance
Study 001	Study EMR100070-001
Study 002	Study EMR100070-002

Study 003	Study EMR100070-003
TLS	tumor lysis syndrome
TNF-α	tumor necrosis factor-α
V1	central volume of distribution
V2	peripheral volume of distribution
WCB	working cell bank
ΔQTcF	change in QTcF from baseline
ΔQTcP	change in QTcP from baseline

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Overview of the product submitted for registration

CD274 (programmed cell death ligand-1 [PD-L1]) is expressed on antigen-presenting cells, etc., in the body, and is considered to down-regulate immune response by binding to CD279 (programmed cell death-1 [PD-1]) and CD80 (B7-1) expressed on activated lymphocytes (T cells, B cells, and natural killer T cells), etc. (*Ann NY Acad Sci*. 2011;1217:45-59). PD-L1 is also reported to be expressed on various tumor cells (*Int Immunol*. 2007;19:813-24). Based on these findings, it is considered that the pathway mediated by PD-L1 and PD-1 is a mechanism for tumor cells to evade the attack by antigen-specific T cells.

Avelumab (genetical recombination) (hereinafter referred to as avelumab) is a human-type monoclonal antibody of IgG1 subclass against human PD-L1, discovered by Merck KGaA (Germany), EMD Serono (US), and Pfizer (US). It is supposed that avelumab suppresses tumor growth by binding to the extracellular domain of PD-L1, thereby inhibiting the binding of PD-L1 with PD-1, leading to enhanced cytotoxic activity of T cells specific to tumor antigens.

1.2 Development history, etc.

In foreign countries, a phase I study (Study EMR100070-001 [Study 001]) in patients with advanced solid cancer was initiated in January 2013 by Merck KGaA (Germany) and by EMD Serono (US). Subsequently, a phase II study (Study EMR100070-003 [Study 003]) was initiated in July 2014 involving patients with metastatic, unresectable Merkel cell carcinoma (MCC) by Merck KgaA, EMD Serono, and the applicant.

In the US and EU, an application for avelumab was submitted in September 2016 and in October 2016, respectively, based on the pivotal data from Study 003. In the US, avelumab received accelerated approval for the following indication in March 2017: “BAVENCIO is a programmed death ligand-1 (PD-L1) blocking antibody indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC). This indication is approved under accelerated approval. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.” In the EU, avelumab is currently under review.

As of May 2017, avelumab is approved for indication for MCC in the US only.

In Japan, a phase I study (Study EMR100070-002 [Study 002]) in patients with advanced solid cancer was initiated in September 2013 by the applicant. Also, enrollment of patients in Study 003 above was started from [redacted] 20[redacted].

Now, an application for avelumab was submitted based on the results of Study 003 as the pivotal data.

Avelumab was designated as an orphan drug with the expected indication of “Merkel cell carcinoma” in December 2016 (Designation No. 394 of 2016 [*28 yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Preparation and control of cell substrate

A nucleotide sequence of fragment antigen binding (Fab) antibody with an affinity to PD-L1 was selected by screening of Fab antibodies using the phage display method. The gene sequences encoding heavy- and light-chain variable regions thus obtained were joined to the gene fragments encoding the constant region of the heavy- and light-chain of immunoglobulin (Ig) G1, respectively, to prepare gene fragments encoding heavy and light chains, which were then subjected to codon optimization. These gene fragments were inserted to an expression vector to prepare an expression construct for avelumab. The construct was introduced into Chinese hamster ovary (CHO) cells, and, from among cell lines obtained, the optimal clone for avelumab production was selected and used for the preparation of master cell bank (MCB) and working cell bank (WCB).

Characterization and purity testing on MCB, WCB, and cells at the limit of in vitro cell age (CAL) were performed according to ICH Q5A (R1), Q5B, and Q5D Guidelines. Results confirmed that they are genetically stable throughout the manufacturing period and that, within the range of the tests performed, no viral or non-viral adventitious agents were detected except endogenous retrovirus-like particles commonly observed in rodent-derived cell lines.

MCB and WCB are stored in the gaseous phase of liquid nitrogen. There is no plan to regenerate MCB, while WCB is regenerated on an as-needed basis.

2.1.2 Manufacturing process

The manufacturing process of the drug substance comprises cell culture (seed culture, expanded culture, proliferative culture, and production culture), harvesting and clarification, [redacted] chromatography, [redacted] virus inactivation, [redacted], virus filtration, [redacted] chromatography, ultrafiltration/diafiltration, preparation, filling, storage, and testing processes.

The [redacted], [redacted] virus inactivation, [redacted], virus filtration, and [redacted] chromatography are defined as critical steps.

The manufacturing process of the drug substance is subjected to process validation on production scale.

2.1.3 Safety evaluation of adventitious agents

In the manufacturing process of the drug substance, no raw materials of biological origin are used except the host cells which are derived from a CHO cell line.

MCB, WCB, and CAL have been subjected to purity tests [see Section "2.1.1 Preparation and control of cell substrate"]. Unpurified bulks obtained before harvest from the commercial-scale culture were subjected to bioburden test, mycoplasma test, *in vitro* virus test, test for specific adventitious viruses, test for infectious retroviruses, and transmission electron microscopy. As a result, infection by viral or non-viral adventitious agents was not observed within the range of the tests performed. The following

tests on unpurified bulk before harvest are defined as in-process control tests: Bioburden test, mycoplasma test, *in vitro* virus test, and test for specific adventitious viruses.

The purification process was subjected to viral clearance study using model viruses, and results demonstrated a sufficient level of viral-clearance performance (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Viral clearance factor (log_{10})				
	Xenotropic murine leukemia virus	Pseudorabies virus	Parainfluenza virus type 3	Reovirus type 3	Minute virus of mice
[redacted] virus inactivation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus filtration	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>19.04	>19.05	>13.99	>16.57	>16.45

2.1.4 Manufacturing process development

The following changes were made during the development process of the drug substance: Manufacturing site, production scale, culture conditions ([redacted], [redacted]), [redacted], [redacted], and [redacted] in the purification process, [redacted], drug substance formulation, [redacted] of the drug substance, etc. The manufacturing process of the drug substance was changed at the same time when the manufacturing process of the drug product was changed [see Section "2.2.3 Manufacturing process development"] (the manufacturing processes for the drug substance and the drug product before and after the change are referred to as "the initial manufacturing process" and "the proposed manufacturing process," respectively).

The drug product manufactured using the drug substance prepared by the initial manufacturing process was used in Study 001, in the dose titration part and the extension part of Study 002, and in Part A of Study 003. The drug product manufactured using the drug substance prepared by the proposed manufacturing process was used in Study 001, in the extension part of Study 002, and in Part B of Study 003.

Comparability assessment of quality attributes was performed before and after the change of the manufacturing process, which confirmed the comparability of the drug substance.

The quality by design (QbD) approach was used in the development of the manufacturing process [see Section "2.3 QbD"].

2.1.5 Characterization

2.1.5.1 Structure and characteristics

The drug substance was subjected to characterization tests described in Table 2.

Table 2. Parameters evaluated in characterization tests

Primary structure	Amino acid sequence, N-terminal amino acid sequence, structural variants ([redacted], [redacted], [redacted], [redacted])
Higher order structures	Secondary structure, tertiary structure, disulfide bond, free thiol group, heat stability
Physicochemical properties	Molecular weight, isoelectric point, extinction coefficient, [redacted] (Related Substance A, Related Substance B, [redacted])
Carbohydrate structure	Monosaccharide composition analysis, sialic acid analysis, analysis of glycosylation sites, N-linked oligosaccharide, non-glycosylated heavy chains
Biological properties	PD-L1 binding activity
	FcγR binding activity ([redacted], [redacted], [redacted], [redacted]), FcRn binding activity, C1q binding activity
	ADCC activity, CDC activity

As for biological properties, PD-L1-binding activity was confirmed by the surface plasmon resonance (SPR) method and by the test system using recombinant [redacted] introduced with human PD-L1. Fragment crystallizable (Fc) receptor-binding activity was evaluated by the SPR method, which confirmed binding activity characteristic to IgG1. Antibody dependent cell mediated cytotoxicity (ADCC) activity was confirmed by an *in vitro* test using peripheral blood mononuclear cell (PBMC) as the effector cells or by [redacted]. Subcomponent of complement C1 (C1q) binding activity was confirmed by [redacted]. Complement dependent cytotoxicity (CDC) activity was evaluated by the test system of a human tumor-derived cell line in the presence of complement. Results showed no CDC activity. The inhibitory activity against the binding of PD-L1 and PD-1 was evaluated by the activity of avelumab to competitively inhibit the binding of ^{125}I-labeled PD-L1 to immobilized PD-1 [see Section "3.1.2 Inhibitory effect against binding of PD-L1with PD-1 and B7-1"].

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of the characterization described in Section "2.1.5.1 Structure and characteristics," [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as product-related substances. Related Substance A and Related Substance B were identified as product-related impurities. The product-related impurities are appropriately controlled by the specifications for the drug substance and the drug product.

2.1.5.3 Process-related impurities

[redacted], [redacted], [redacted], [redacted], [redacted], [redacted], and [redacted] were identified as process-related impurities. All process-related impurities have been shown to be completely removed during the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include description, identification (size exclusion chromatography [SEC], imaged capillary isoelectric focusing [iCIEF]), pH, charge variants (iCIEF), carbohydrate profile, purity (Related Substance A [SEC], [redacted] [capillary gel electrophoresis with sodium dodecyl sulfate (CE-SDS) (reduced)], Related Substance B [CE-SDS (non-reduced)], [redacted] [peptide mapping], [redacted] [ion exchange liquid chromatography (IEX)], host cell protein [HCP] [enzyme-linked immunosorbent assay (ELISA)]), bacterial endotoxin, microbial limit, biological activity [PD-L1-binding activity]), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

Table 3 shows the main stability studies for the drug substance.

Table 3. Outline of main stability studies for drug substance

	Number of batches[*1]	Storage conditions	Test period	Storage form
Long-term testing	3	5 ± 3ºC	24 months[*2]	Low-density polyethylene bag
Accelerated testing	3	25 ± 2ºC/60 ± 5%RH	6 months	
Stress testing	2	40 ± 2ºC/75 ± 5%RH	3 months	

[*1] The drug substance was manufactured by the proposed manufacturing process; [*2] The stability test is ongoing up to [redacted] months.

The long-term testing showed no clear change in the quality attributes throughout the test period.

The accelerated testing showed a tendency of increase in [redacted] and a decrease in [redacted] in [redacted], a tendency of increase in Related Substance B, and a tendency of increases in [redacted] and [redacted].

The stress testing showed a tendency of decrease in [redacted] in [redacted] in addition to changes observed in the accelerated testing which were more marked in the stress testing.

Based on the above, a shelf life of 24 months has been proposed for the drug substance when stored at 2°C to 8°C in a low-density polyethylene bag.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an injection containing 200 mg of avelumab in each glass vial (10 mL). The drug product contains, as excipients, D-mannitol, glacial acetic acid, polysorbate 20, sodium hydroxide, and water for injection.

2.2.2 Manufacturing process

The manufacturing process for the drug product comprises pooling and mixing of the drug substance, sterile filtration and filling, clamping, labeling, packaging, storage, and testing processes.

Sterile filtration and filling processes are defined as critical steps.

The manufacturing process of the drug product is subjected to process validation on a production scale.

2.2.3 Manufacturing process development

The following changes were made during the process of the development of the drug product: Changes in the formulation, [redacted] system, manufacturing site, production scale, etc. The manufacturing process of the drug product was changed at the same time when the manufacturing process of the drug substance was changed [see Section “2.1.4 Manufacturing process development”]. The formulation change is included in the preparation process of the drug substance [see Section “2.1.2 Manufacturing process”].

The drug product manufactured by the initial manufacturing process was used in Study 001, in the dose titration part and the extension part of Study 002, and in Part A of Study 003. The drug product manufactured by the proposed manufacturing process was used in Study 001, in the extension part of Study 002, and in Part B of Study 003.

Comparability assessment of quality attributes was performed before and after the change of the manufacturing process, which confirmed the comparability of the drug product.

The QbD approach was used in the development of the manufacturing process [see Section "2.3 QbD"].

2.2.4 Control of drug product

The proposed specifications for the drug product include description, identification (SEC, iCIEF), osmotic pressure, charge variants (iCIEF), pH, purity (Related Substance A [SEC], [redacted] (CE-SDS [reduced]), Related Substance B (CE-SDS [non-reduced]), [redacted] [peptide mapping], [redacted] [IEX]), bacterial endotoxin, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, [redacted], biological activity (PD-L1-binding activity), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

Table 4 shows the main stability studies for the drug product.

Table 4. Outline of main stability studies for drug product

	Number of batches[*1]	Storage conditions	Test period	Storage form
Long-term testing	3	5 ± 3ºC	24 months[*2]	Glass vial with butyl rubber stopper
Accelerated testing	3	25 ± 2ºC/60 ± 5%RH	6 months	
Stress testing	1	40 ± 2ºC/75 ± 5%RH	3 months	
Photostability testing	1	25 ± 2ºC, overall illuminance of ≥1.2 million lux·hr, integrated near ultraviolet energy of ≥200 W·h/m^2		

[*1] The drug substance and the drug product were manufactured by the proposed manufacturing process; [*2] The stability test is ongoing up to [redacted] months.

The long-term testing showed no clear change in the quality attributes throughout the test period.

The accelerated testing showed a tendency of increase in [redacted] and decrease in [redacted] in [redacted], a tendency of increase in Related Substance B, and a tendency of increases in [redacted] and [redacted].

The stress testing showed a tendency of decrease in [redacted] in [redacted] in addition to changes observed in the accelerated testing which were more marked in the stress testing.

The photostability testing showed that the drug product is unstable to light.

Based on the above, a shelf life of 24 months has been proposed for the drug product when stored at 2°C to 8°C in butyl rubber-stoppered glass vials protected from light in a paperboard box.

2.3 QbD

In the development of the manufacturing process of the drug substance and the drug product, the QbD approach was used and applied to the development of the quality control strategy based on the following investigations.

- Identification of critical quality attribute (CQA):
  From among the quality attributes related to product-related substances, process-related impurities, and drug product formulation, the following CQAs were identified based on the information obtained during the process of avelumab development and related findings.
  - [redacted] ([redacted], [redacted], [redacted], [redacted], [redacted]), [redacted] ([redacted], [redacted], [redacted], [redacted], [redacted], [redacted]), [redacted] ([redacted], [redacted], [redacted]), [redacted] (adventitious agents), [redacted] ([redacted], [redacted]), [redacted] (HCP, [redacted], residual deoxyribonucleic acid [DNA], [redacted], [redacted]), [redacted] (polysorbate concentration, protein concentration), and [redacted] ([redacted], [redacted], [redacted], [redacted])

- Process characterization:
  Process parameters were identified based on the effect on quality attributes, and the acceptable control range for each process parameter was determined.

- Establishment of the control method:
  Based on the process knowledge including the process characterization described above, the control method for the quality attributes of avelumab was established by the combination of process parameter control, in-process control, and specifications.

2.R Outline of the review conducted by PMDA

Based on the submitted data and on the results of the following reviews, PMDA has concluded that, in order to appropriately control the quality of the drug substance and the drug product, it is necessary to appropriately control the activity to inhibit the interaction between PD-L1 and PD-1 and the amino acid-substituted analogs of avelumab, and to add peptide mapping to identification tests. The applicant's responses to these issues will be reported in the Review Report (2).

2.R.1 Test for biological activity

In the specifications for the drug product proposed at the application, evaluation of the binding capacity of avelumab to PD-L1 was included in the test for biological activity [see Section "2.2.4 Control of drug product"].

PMDA's view:

The critical mechanism of action of avelumab is inhibition of the binding of PD-L1 to PD-1 as a result of the binding of avelumab to PD-L1. It is thus difficult to control the inhibitory effect of avelumab against the binding of PD-L1 and PD-1 simply by evaluating the binding of avelumab to PD-L1.

Therefore, a test that evaluates the inhibitory effect of avelumab against the interaction of PD-L1 and PD-1 should be included in the specifications for the drug product.

2.R.2 Amino acid-substituted analogs

The applicant's explanation:

After the change of the manufacturing process of the drug substance, it was confirmed that the amount of amino acid-substituted analogs (change from asparagine [Asn] to serine [Ser] at [redacted] sites) increased. However, the content of the amino acid-substituted analogs is controllable by maintaining, within the proven acceptable range, the parameters of cell culture process that are identified as the process parameters affecting amino acid substitution.

PMDA's view:

Since there is only limited experience of avelumab production after the change in the manufacturing process, it cannot be concluded that the control strategy by the process parameters is sufficiently robust against changes in the content of amino acid-substituted analogs. Therefore, an in-process control test should be established for monitoring variations in the extent of amino acid substitutions.

2.R.3 Identification

In the specifications for the drug substance and the drug product proposed at the application, SEC and iCIEF were included in identification tests, but peptide mapping was not [see Sections "2.1.6 Control of drug substance" and "2.2.4 Control of drug product"].

PMDA's view:

The identification test for avelumab should be highly specific to the target substance and be capable of detecting changes in the primary structure. Therefore, peptide mapping should be included in the identification of the specifications for the drug substance and the drug product.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Binding to PD-L1

3.1.1.1 *In vitro* (CTD 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.5, 4.2.1.1.6)

Binding of avelumab to PD-L1 (recombinant protein) of humans, mice, cynomolgus monkeys, dogs, rats, and rabbits was investigated by SPR. Table 5 shows dissociation constant (K_D) of avelumab to each PD-L1, determined by SPR.

Table 5. Binding of avelumab to PD-L1

Animal species	K_D (nmol/L)	Animal species	K_D (nmol/L)
Humans	0.7 ± 0.09	Dogs	4.5 ± 0.4
Mice	1.1 ± 0.02	Rats	66.8 ± 8.8
Cynomolgus monkeys	0.9 ± 0.04	Rabbits	105.4 ± 11.2

Mean ± standard deviation (SD), n = 3

Binding of Optimized F02[1)] to human PD-L1, PD-L2, B7-1, B7-2, B7-H2, and B7-H3 (recombinant protein) was investigated by SPR. K_D of Optimized F02 to human PD-L1 was 0.5 nmol/L (n = 1), whereas binding of Optimized F02 (1 μmol/L) to human PD-L2, B7-1, B7-2, B7-H2, and B7-H3 was not detected.

Using human epidermoid carcinoma-derived A431 cell line with enhanced PD-L1 expression induced by interferon-γ (IFN-γ), human non-small cell lung cancer-derived A549 cell line, human pancreatic carcinoma-derived BxPC3 cell line, human colorectal cancer-derived HCT116 cell line, human malignant melanoma-derived M24 cell line, human prostate cancer-derived PC3mm2 cell line, human glioblastoma-derived U-87 MG cell line, and human PBMC expressing PD-L1 induced by phytohemagglutinin (PHA) stimulation, binding of avelumab to each cell line was investigated by flow cytometry. As a result, avelumab bound to PD-L1 expressed on all tumor-derived cells and on PBMC.

Using HEK293 cell line expressing PD-L1 of humans, mice, or cynomolgus monkeys, binding of avelumab or MSB0010608H[2)] to PD-L1 was investigated by flow cytometry. Half maximal effective concentration (EC_{50}) (mean ± standard deviation [SD]) of avelumab to human and mouse PD-L1 was 0.3 ± 0.02 nmol/L (n = 12) and 0.34 ± 0.08 nmol/L (n = 3), respectively, and EC_{50} (mean ± SD) of MSB0010608H to cynomolgus monkey PD-L1 was 0.94 ± 0.015 nmol/L (n = 3).

The occupancy rate of avelumab for PD-L1 expressed on human CD3-positive T cells was investigated by flow cytometry. EC_{50}[3)] (mean ± SD, n = 8) of avelumab was 0.122 ± 0.042 nmol/L, and the occupancy rate of avelumab was ≥95% at 1 μg/mL.

3.1.1.2 *In vivo* (CTD 4.2.1.1.10)

A single dose of avelumab (25, 50, 100, 200, 400 μg) was administered intravenously to mice (n = 5/group), and occupancy rates of avelumab for PD-L1 expressed on peripheral blood-derived white blood cells and on spleen-derived white blood cells were calculated. The PD-L1 occupancy rate of avelumab on 2 days after avelumab administration was 75% to 100% in both cell populations.

3.1.2 Inhibitory effect against binding of PD-L1 with PD-1 and B7-1 (CTD 4.2.1.1.5)

The activity of avelumab to competitively inhibit the binding of ^{125}I-labeled PD-L1 and immobilized PD-1 was investigated. IC_{50} (n = 2) of avelumab was 0.06108 and 0.08018 nmol/L.

Using HEK293 cell line expressing PD-L1, the competitive inhibitory effect of avelumab against binding of PD-L1 and fluorescence-labeled B7-1 was investigated by flow cytometry. IC_{50} (n = 2) of avelumab was 0.1917 and 0.0979 nmol/L.

3.1.3 Effect on immune system (CTD 4.2.1.1.5)

Using ovalbumin (OVA)-specific CD8-positive T cells, the effect of MSB0010608H[2)] on antigen-specific activation of CD8-positive T cells was investigated by ELISA under cocultivation with mouse

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1) Anti- PD-L1 antibodies in which 3 amino acid residues in the constant region are different from those in avelumab
2) Anti- PD-L1 antibody that is produced by HEK293 cell line and has the same amino acid sequence as avelumab
3) Concentration at which 50% of PD-L1 on the cell membrane is occupied

lymphoma-derived EL4 cell line overexpressing mouse PD-L1, with OVA-derived peptide-induced IFN-γ production as the index. EC_{50} (mean ± SD, n = 3) of avelumab was 0.28 ± 0.1 nmol/L.

Using human PBMC, the effect of avelumab on the activation of CD4-positive T cells was investigated by ELISA, with *Staphylococcal* enterotoxin A (SEA)-stimulated interleukin-2 (IL-2) production as the index. EC_{50} (mean ± SD, n = 3) of avelumab was 0.08 ± 0.03 nmol/L.

3.1.4 ADCC and CDC activities (CTD 4.2.1.1.3, 4.2.1.1.4)

Using ^{51}Cr-labeled A431 and A549 cell lines with enhanced PD-L1 expression by IFN-γ stimulation, ADCC activity of avelumab against tumor cells was investigated by the chromium release method, with human PBMC as effector cells. ADCC activity was observed in both cell lines.

Using ^{51}Cr-labeled A431, A549, and human malignant melanoma-derived M21 cell lines, CDC activity of avelumab against tumor cells was investigated by the chromium release method in the presence of human complement. CDC activity was not observed in any of the cell lines investigated.

3.1.5 Growth inhibitory effect against malignant tumor-derived cell lines (CTD 4.2.1.1.7, 4.2.1.1.8, 4.2.1.1.9, 4.3.60)

The tumor growth-suppressive effect of avelumab was investigated using mice (n = 14/group) subcutaneously transplanted with mouse colorectal cancer-derived MC38 cell line expressing PD-L1. When the mean tumor volume reached approximately 50 mm^3, the mice were randomized and, on Days 0, 3, and 6 after randomization, avelumab (100, 200, 400, 800 μg) was administered intravenously, and tumor volume was calculated on Day 22. As a result, a statistically significant tumor growth-suppressive effect was observed in all avelumab groups compared to the control (isotype antibody) group (P < 0.0001, two-way analysis of variance [ANOVA]).

Using mice (n = 8/group) subcutaneously transplanted with MC38 cell line, the tumor growth-suppressive effect of MSB0010294[4)] was investigated under depletion of CD8-positive T cells. When the mean tumor volume reached approximately 60 mm^3, the animals were randomized, followed by intraperitoneal administration of MSB0010294 (400 μg) on Days 0, 3, and 6 after randomization and of anti-CD8 antibody (100 μg) on Days 0, 5, 10, 15, and 20, and tumor volume was calculated on Day 22. In mice not receiving anti-CD8-antibody, a statistically significant tumor growth-suppressive effect was observed in the MSB0010294 group compared with the control (isotype antibody) group (P = 0.0074, one-way ANOVA). In mice receiving anti-CD8 antibody, in contrast, the tumor growth-suppressive effect of MSB0010294 was not observed.

Using mice (n = 8/group) subcutaneously transplanted with MC38 cell line, the tumor growth-suppressive effect of intact avelumab and deglycosylated avelumab (with a resultant loss of the binding capacity to Fc γ receptor [FcγR]) was investigated. When the mean tumor volume reached approximately 60 mm^3, the animals were randomized and, on Days 0, 3, and 6 after randomization, avelumab or deglycosylated avelumab (400 μg) was administered intraperitoneally, and tumor volume

4) Anti-PD-L1 antibody in which 5 amino acid residues in the variable region are different from those in avelumab

was calculated on Day 17. In the deglycosylated avelumab group, a statistically significant attenuation of the tumor growth-suppressive effect was observed compared with the avelumab group (P = 0.001, two-way ANOVA).

Using mice (n = 8/group) subcutaneously transplanted with MC38 cell line, the tumor growth-suppressive effect of avelumab was investigated under the condition of natural killer (NK) cell depletion. When the mean tumor volume reached approximately 60 mm^3, the animals were randomized, and avelumab (400 μg) was administered intraperitoneally on Days 0, 3, and 6 after randomization, and anti-asialoganglioside ganliotetraosylceramide (ASGM1) serum (50 μL) was administered on Days 0, 7, and 14 with the purpose of removing NK cells. Tumor volume was calculated on Day 17. A statistically significant attenuation of the tumor growth-suppressive effect was observed in mice in the avelumab group receiving anti-ASGM1 serum compared with mice in the avelumab group not receiving anti-ASGM1 serum (P = 0.001, two-way ANOVA).

3.2 Secondary pharmacodynamics (CTD 4.2.1.2.1)

Using human PBMC expressing PD-L1 induced by anti-CD3 antibody with CD3 agonist activity, ADCC activity of avelumab against immune cell subsets among human PBMC was investigated by flow cytometry, with intracellular uptake of propidium iodide as the index. Avelumab did not show ADCC activity against CD3, CD4, CD8, CD14, CD19, or CD56-positive subsets among human PBMC.

3.3 Safety pharmacology

In 4- and 13-week repeated-dose toxicity studies in cynomolgus monkeys, the effect of avelumab (140 mg/kg) on heart rate, electrocardiogram, arterial pressure, respiratory rate, clinical signs, behavior, and rectal temperature was investigated [see Section “5.2 Repeated-dose toxicity”]. Avelumab had no effect on these parameters.

3.R Outline of the review conducted by PMDA

Based on the submitted data and on the results of the following reviews, PMDA has concluded that avelumab is expected to be effective against MCC.

3.R.1 Mechanism of action of avelumab and its efficacy against MCC

The applicant’s explanation on the mechanism of action of avelumab and its efficacy against MCC:
PD-L1 is expressed on antigen-presenting cells, etc., in the body, and considered to down-regulate immune response by combining with PD-1 and B7-1 expressed on activated lymphocytes (e.g., T cells, B cells, natural killer T cells), etc. (*Ann NY Acad Sci.* 2011;1217:45-59). PD-L1 is also reported to be expressed on various tumor cells (*Int Immunol.* 2007;19:813-24), and it is considered that PD-L1 expressed on tumor cells suppresses immune response against tumor.

Avelumab is a human-type monoclonal antibody of IgG1 subclass against human PD-L1. Avelumab binds to the extracellular region of PD-L1, thereby inhibiting the binding of PD-L1 with PD-1 and B7-1 [see Sections “3.1.1 Binding to PD-L1” and “3.1.2 Inhibitory effect against binding of PD-L1 with PD-1 and B7-1”], which is considered to enhance the cytotoxic activity of antigen-specific T cells, leading to suppression of tumor growth [see Section “3.1.5 Growth inhibitory effect against malignant tumor-derived cell lines”]. Also, avelumab showed ADCC activity against tumor-derived cell lines [see

Section “3.1.4 ADCC and CDC activities”], which suggests that the ADCC activity also contributes to the tumor growth-suppressive effect of avelumab.

Although no nonclinical study was conducted on the growth-inhibitory effect of avelumab against any human MCC-derived cell line, taking account of the mechanism of action of avelumab and of the observations that avelumab suppressed the growth of MC38 cell line expressing PD-L1 [see Section “3.1.5 Growth inhibitory effect against malignant tumor-derived cell lines”] and that PD-L1 is expressed on MCC (*Cancer Immunol Res.* 2013;1:54-63 and *Clin Cancer Res*. 2013;19:5351-60), avelumab is expected to be effective against MCC.

The applicant’s explanation on the difference in pharmacological characteristics between avelumab, the antibody drug against PD-L1, and nivolumab (nivolumab [genetical recombination]) and pembrolizumab (pembrolizumab [genetical recombination]) which are antibody drugs against PD-1:
Avelumab, nivolumab, and pembrolizumab all inhibit the binding of PD-L1 with PD-1, thereby inhibiting their interaction, which results in the enhancement of immune response against tumors, leading to tumor growth suppression. Thus, the above action is similar among these drugs.

On the other hand, both nivolumab and pembrolizumab inhibit the binding of PD-L2 with PD-1 (*Cancer Immunol Res.* 2014;2:846-56 and *Onco Targets Ther*. 2015;8:2535-43), whereas avelumab inhibits the binding of PD-L1 and B7-1, indicating a difference in the action between these two groups of drugs. Another difference is that since PD-1 is a molecule expressed on immune cells in the body, neither nivolumab nor pembrolizumab is expected to have ADCC activity against tumor cells, whereas since PD-L1 is expressed on various tumor cells as well, avelumab is expected to have ADCC activity against tumor cells [see Section “3.1.4 ADCC and CDC activities”].

PMDA’s view:
The applicant’s explanation on the expected efficacy of avelumab against MCC is understandable from the point of view of the mechanism of action of avelumab. However, questions still remain regarding the following: (a) The extent to which PD-L1/B7-1 binding inhibition or ADCC activity contributes to the tumor growth-suppressive effect of avelumab, (b) relationship between PD-L1 expression and the efficacy of avelumab, and (c) whether the pharmacological characteristics of avelumab are the same as those of nivolumab and pembrolizumab. Since the above information may be useful for selecting appropriate patients in the clinical use of avelumab, the relevant information should be collected continuously, and when new findings become available, the information should be provided to healthcare professionals in an appropriate manner.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Pharmacokinetics (PK) of avelumab in animals was investigated using mice, rats, and monkeys.

4.1 Analytical methods

4.1.1 Assay for avelumab

For the quantitation of avelumab in (a) mouse or rat plasma and (b) monkey serum, the plasma or serum sample was added to immobilized streptavidin and biotin-labeled PD-L1-Fc recombinant fusion protein (recombinant protein comprising human PD-L1 conjugated with Fc portion of human IgG1), and the

amount of avelumab was measured using (a) ruthenium-labeled PD-L1-Fc recombinant fusion protein or (b) fluorescence-labeled PD-L1-Fc recombinant fusion protein, respectively.

4.1.2 Assay for anti-avelumab antibody

Anti-avelumab antibody (antibody against avelumab [genetical recombination]) in (a) mouse or rat plasma and (b) monkey serum was quantified by (a) SPR and by (b) ELISA using immobilized avelumab, biotin-labeled avelumab, and horseradish peroxidase (HRP)-labeled streptavidin, respectively.

4.2 Absorption

4.2.1 Single-dose administration

Avelumab (1.25, 2.5, 5, 10, 20 mg/kg) was administered intravenously in a single dose to female mice, and plasma avelumab concentration was investigated (Table 6). AUC_{288h} of avelumab increased more than proportionally to dose within the dose range investigated. Regarding the above observation, the applicant explained that, with the increase in dose, the elimination pathway mediated by binding to PD-L1 became saturated, resulting in a decrease in CL.

Table 6. PK parameters of avelumab* (female mice, single intravenous administration)

Dose (mg/kg)	AUC_{288h} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_z (mL/kg)
1.25	880	15.8	1.42	32.2
2.5	2000	14.1	1.25	25.4
5	5640	11.9	0.887	15.3
10	12,300	18.4	0.814	21.6
20	30,900	39.7	0.644	36.9

* Calculated based on the mean plasma avelumab concentration at each measuring time point (n = 5)

4.2.2 Repeated-dose administration

Avelumab (20, 40, 140 mg/kg) was administered intravenously quaque 1 week (QW) for 5 weeks to male and female mice and rats, and plasma avelumab concentration was investigated (Table 7). In both mice and rats, AUC_{168h} of avelumab increased roughly in proportion to dose within the dose range investigated. No clear sex difference was observed in PK parameters of avelumab. Repeated administration did not have any clear effect on AUC_{168h}.

After avelumab administration, anti-avelumab antibody was detected in 5 of 12 mice in the 20 mg/kg group, in 7 of 13 mice in the 40 mg/kg group, and in 3 of 12 mice in the 140 mg/kg group; and in 4 of 12 rats in the 20 mg/kg group, in 2 of 12 rats in the 40 mg/kg group, and in 3 of 12 rats in the 140 mg/kg group.

Table 7. PK parameters of avelumab* (mice and rats, 5-week repeated intravenous administration)

Animal species	Day of measurement	Dose (mg/kg)	Sex	AUC_{168h} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_{ss} (mL/kg)
Mice	1	20	Male	20,100	78.5	0.771	87.6
			Female	21,800	71.4	0.755	76.2
		40	Male	33,800	66.4	0.976	94.4
			Female	38,900	91.2	0.734	98.0
		140	Male	124,000	59.1	0.965	83.1
			Female	120,000	64.5	0.946	91.1
	29	20	Male	20,700	73.7	0.763	81.9
			Female	22,600	45.3	0.841	57.0
		40	Male	30,000	48.7	1.20	84.4
			Female	38,600	59.3	0.857	76.2
		140	Male	111,000	59.3	1.07	92.9
			Female	117,000	75.9	0.883	103
Rats	1	20	Male	31,605	144	0.375	71.6
			Female	25,284	116	0.517	82.4
		40	Male	48,376	107	0.593	80.7
			Female	40,953	112	0.668	99.3
		140	Male	252,210	132	0.346	61.0
			Female	169,579	92.9	0.578	79.3
	29	20	Male	39,236	111	0.510	72.1
			Female	52,209	144	0.383	73.4
		40	Male	100,600	94.1	0.398	51.7
			Female	89,748	112	0.446	71.5
		140	Male	333,865	102	0.419	66.4
			Female	274,237	137	0.511	95.3

* Calculated based on the mean plasma avelumab concentration (n = 3) at each measuring time point

Avelumab (20, 60, 140 mg/kg) was administered intravenously QW for 13 weeks to male and female monkeys, and serum avelumab concentration was investigated (Table 8). C_{max} and AUC_{168h} of avelumab increased roughly in proportion to dose within the dose range investigated. No clear sex difference was observed in PK parameters of avelumab. Repeated administration did not have any clear effect on C_{max} or AUC_{168h}.

Anti-avelumab antibody was not detected in any of the dose groups.

Table 8. PK parameters of avelumab
(male and female monkeys, 13-week repeated intravenous administration)

Day of measurement	Dose (mg/kg)	Sex	n	C_{max} (μg/mL)	t_{max}* (h)	AUC_{168h} (μg·h/mL)
1	20	Male	3	496 ± 79.7	1.5 (1.5, 1.5)	24,015 ± 793
		Female	3	431 ± 52.4	1.5 (1.5, 6)	24,379 ± 4060
	60	Male	3	1502 ± 247	1.5 (1.5, 1.5)	74,280 ± 14,209
		Female	3	1854 ± 855	6 (1.5, 6)	82,476 ± 12,377
	140	Male	5	4660 ± 89.2	1.5 (1.5, 24)	274,427 ± 32,794
		Female	5	4197 ± 586	1.5 (1.5, 1.5)	223,285 ± 48,175
29	20	Male	3	564 ± 91.7	1.5 (1.5, 6)	30,921 ± 7861
		Female	3	596 ± 84.6	1.5 (1.5, 1.5)	33,341 ± 7544
	60	Male	3	2447 ± 719	1.5 (1.5, 6)	117,728 ± 66,121
		Female	3	1941 ± 184	1.5 (1.5, 1.5)	128,030 ± 25,941
	140	Male	5	4445 ± 428	1.5 (1.5, 6)	315,140 ± 77,498
		Female	5	4349 ± 784	1.5 (1.5, 1.5)	275,122 ± 82,831
85	20	Male	3	562 ± 15.4	1.5 (1.5, 6)	33,785 ± 8902
		Female	3	610 ± 89.8	1.5 (1.5, 1.5)	33,980 ± 9275
	60	Male	3	2210 ± 93.2	1.5 (1.5, 1.5)	110,702 ± 26,708
		Female	3	2183 ± 68.3	1.5 (1.5, 6)	140,645 ± 32,878
	140	Male	5	4700 ± 0	1.5 (1.5, 1.5)	356,514 ± 80,009
		Female	5	4618 ± 184	1.5 (1.5, 1.5)	303,662 ± 80,272

Arithmetic mean ± SD; * Median (range)

4.3 Distribution

Following a 4-week repeated intravenous QW administration of avelumab (20, 60, 140 mg/kg) to male and female monkeys, V_{ss} of avelumab on Day 22 (58.6, 40.8, and 47.7 mL/kg, respectively[5)]) was similar to the plasma volume (44.8 mL/kg) in monkeys (*Pharm Res*. 1993;10:1093-5). The applicant explained that since this finding suggests that avelumab is distributed mainly in the circulating blood, tissue distribution of avelumab was not investigated.

As for placental and fetal transfer of avelumab, it is reported that human IgG crosses the placenta by neonatal Fc receptor (FcRn)-mediated transcytosis and is distributed in fetuses (*J Reprod Immunol*. 1997;37:1-23). The applicant explained that avelumab, a human-type antibody of IgG1 subclass, may therefore cross the placenta and be distributed in fetuses.

4.4 Metabolism and excretion

The applicant explained that since avelumab is an antibody drug and it is considered to be eliminated through the protein degradation pathway, no study on metabolism or excretion of avelumab was conducted according to "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

As for excretion of avelumab in milk, the applicant explained that, taking account of the report that human IgG is excreted in milk (*Nutrients*. 2011;3:442-74), avelumab, a human-type antibody of IgG1 subclass, may also be excreted in milk.

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's discussions on the absorption, distribution, metabolism, and excretion of avelumab are acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

Taking account of the observations that avelumab caused serious anaphylactic reactions, including death, in the 4-week repeated intravenous dose toxicity study in mice, that avelumab has only a low binding affinity to PD-L1 of rats [see Section "3.1.1.1 *In vitro*"], and that avelumab has a similar affinity to monkey PD-L1 as to human PD-L1 [see Section "3.1.1.1 *In vitro*"], toxicity of avelumab was evaluated based on studies in monkeys.

In this section, vehicle used in *in vivo* studies was a solution (pH 5.5) containing 280 mmol/L mannitol, 10 mmol/L sodium acetate, 1.4 mmol/L methionine, and 0.05% polysorbate 20, unless otherwise specified.

5.1 Single-dose toxicity

No single-dose toxicity study was conducted. Instead, acute toxicity of avelumab was evaluated based on the results of the first dose in the repeated intravenous dose toxicity studies in monkeys [see Section

5) Since no clear sex difference was observed in PK parameters, mean values were calculated from combined data of males and females.

"5.2 Repeated-dose toxicity"]. No avelumab-related changes in clinical signs or death were observed even after administration of the maximum dose (140 mg/kg) of avelumab.

Based on the above, the approximate lethal dose was determined to be >140 mg/kg.

5.2 Repeated-dose toxicity

5.2.1 Four-week repeated intravenous dose toxicity study in monkeys

Avelumab (0 [vehicle], 20, 60, 140 mg/kg) was administered intravenously QW for 4 weeks to cynomolgus monkeys (n = 2/sex/group). Immunophenotyping of peripheral blood and measurement of serum chemokine and cytokine concentrations[6)] were also performed.

No avelumab-related death was observed. Animals in the 140 mg/kg group showed decreased total lymphocyte count, changes in subcutaneous site, perivascular site, and blood vessels at the injection site (haemorrhage, mixed inflammatory cell infiltration, fibroblast growth, and hypertrophy and necrosis of vascular endothelium). The applicant explained that since the final avelumab concentration in the 60 mg/kg group, in the 140 mg/kg group, and in clinical use (body weight 40-120 kg) is 4, 9.3, and 1.5 to 3.9 mg/mL, respectively, avelumab is unlikely to cause changes at the injection site in clinical use.

Immunophenotyping of peripheral blood by flow cytometry showed decreases in total lymphocyte count, NK cell count, and NK cell ratio in the 140 mg/kg group. However, since all of the changes were within the range of historical data, and no such changes were observed in the 13-week repeated intravenous dose toxicity study [see Section "5.2.2 Thirteen-week repeated intravenous dose toxicity study in monkeys"], the observed changes were considered to be unlikely related to avelumab. Avelumab did not affect serum chemokine or cytokine concentrations.

Based on the above, local and systemic no observed adverse effect levels (NOAELs) in this study were determined to be 60 and 140 mg/kg/week, respectively.

5.2.2 Thirteen-week repeated intravenous dose toxicity study in monkeys

Avelumab (0 [vehicle[7)]], 20, 60, 140 mg/kg) was administered intravenously QW for 13 weeks to cynomolgus monkeys (n = 3-5/sex/group). In the control group and in the 140 mg/kg group, 2 each of males and females underwent an 8-week recovery period after the end of the administration period to assess reversibility. Immunophenotyping of peripheral blood[8)] and measurement of serum chemokine and cytokine concentrations were also performed.

No avelumab-related death was observed. Animals in the ≥20 mg/kg groups showed subcutaneous reddening, subcutaneous haemorrhage, and subcutaneous fibroblast growth at the injection site, animals in the 60 mg/kg group showed subcutaneous mononuclear cell infiltration at the injection site, and animals in the 140 mg/kg group showed decreased adrenal weight. These injection site changes were all mild and not considered to be toxicities. Decreased adrenal weight was not accompanied by

6) Immunophenotyping and measurement of chemokine and cytokine concentrations were carried out under non-GLP conditions.
7) Polysorbate 20 content of vehicle used up to Week 8 was 0.0025%.
8) Immunophenotyping was conducted under non-GLP conditions.

histopathological findings, and was therefore considered to have little toxicological significance. All findings were reversible after an 8-week recovery period.

Based on the above, the local and systemic NOAELs in this study were both determined to be 140 mg/kg/week. $AUC_{0\text{-}168h}$ of avelumab at the NOAELs (330,088 μg·h/mL) was approximately 16 times the clinical exposure.[9)]

5.3 Genotoxicity

Since avelumab is an antibody drug, it is considered not to directly interact with DNA or other chromosomal components. Therefore, no genotoxicity study was conducted.

5.4 Carcinogenicity

Since avelumab is an antineoplastic agent intended to be used for the treatment of patients with advanced cancer, no carcinogenicity study was conducted.

5.5 Reproductive and developmental toxicity

Since avelumab is an antineoplastic agent intended to be used for the treatment of patients with advanced cancer and it is expected to affect embryo-fetal development, such as abortion and fetal death, from its pharmacological action, no reproductive and developmental toxicity study was conducted.

5.5.1 Effect on fertility

The applicant's explanation on the effect of avelumab on fertility:

In the repeated intravenous dose toxicity studies in monkeys [see Section "5.2 Repeated-dose toxicity"], no avelumab-related histopathological findings were observed in the reproductive organ among sexually matured animals receiving avelumab (17 females and 1 male). Also, it is reported that mice with *PD-1* or *PD-L1* gene deletion are both fertile (*J Exp Med*. 2005;202:231-7 and *Int Immunol*. 1998;10:1563-72). These findings suggest that avelumab is unlikely to affect the fertility of male or female animals.

5.5.2 Effect on embryo-fetal development and administration in pregnant women

The applicant's explanation on the effect of avelumab on embryo-fetal development and administration in pregnant women:

In light of the following reports, avelumab may possibly be transferred from the mother to the fetus, suggesting the possibility that administration of avelumab to pregnant women may increase the incidences of abortion and stillbirth.

- Inhibition of interaction between PD-L1 and PD-1 markedly increases the risk of abortion during pregnancy and of neonatal death by suppressing the immune tolerance of the pregnant maternal body (*J Exp Med*. 2005;202:231-7, etc.).
- Human IgG1 cross the placenta (*British J Pharma.* 2009;157:220-3).

Therefore, avelumab should not be administered to pregnant women as a general rule. However, taking account of the facts that MCC is a disease with poor prognosis and that there are only extremely limited

9) In Study 002 in Japanese patients with advanced solid cancer, $AUC_{0\text{-}336h}$ of avelumab following the first intravenous dose of avelumab (10 mg/kg) was 20,131 μg·h/mL.

treatment options for MCC, clinical use of avelumab in these patients is acceptable if the expected therapeutic benefits outweigh the possible risks associated with treatment, under the condition that the avelumab-induced risk of abortion, etc., is explained in the package insert for precautions.

5.6 Other studies

5.6.1 Study on cytokine release by human PBMC (Reference data)

After stimulation of human PBMC with PHA, avelumab (2-2000 μg/mL) was added to PBMC and cytokine release was investigated. Exposure to ≥2 μg/mL of avelumab induced release of interleukin-6 (IL-6), monocyte chemotactic protein-1 (MCP-1), tumor necrosis factor-α (TNF-α), granulocyte macrophage colony-stimulating factor (GM-CSF), interleukin-10 (IL-10), interleukin-8 (IL-8), and interleukin-1β (IL-1β) from human PBMC.

The applicant explained that since the median C_{max} in clinical use of avelumab is 224 μg/mL, the above results suggest that cytokines may be released by avelumab administration, given the above findings. Avelumab-induced infusion reaction will be discussed in Section "7.R.3.6 Infusion reaction."

5.6.2 Tissue cross-reactivity study using normal tissues of cynomolgus monkeys

A tissue cross-reactivity study of avelumab was conducted using normal tissue slices of cynomolgus monkeys. Results showed staining of the following cells and tissues by avelumab: Epithelial cells of various tissues, mesothelial cells, smooth muscle cells of small intestine, pancreatic islet cells, parafollicular cells of thyroid gland, membrane of decidual cells of placenta, neurofilaments and cell processes (spinal cord and optic nerve) of nerve cells, etc.

5.6.3 Tissue cross-reactivity study using human normal tissues

A tissue cross-reactivity study of avelumab was conducted using human normal tissue slices. Results showed staining by avelumab of the following cells and tissues that are reported to express PD-L1 (*Clin Cancer Res.* 2008;14:4800-8, *J Immunol.* 2003;170:1257-66, etc.): Adipose cells, epithelial cells of various tissues, mononuclear white blood cells, alveolar macrophages, smooth muscle cells, pancreatic islet cells, membrane of decidual cells of placenta, neurofilament and cell processes of nerve cells (cerebellum, cerebral cortex, spinal cord, plexuses of colon and small intestine, neurohypophysis). In addition, the following cells and cell components that are not reported to express PD-L1 were also stained with avelumab: Mesothelial cells of various tissues, parafollicular cells of thyroid gland, granulosa cells of ovary, membrane and cytoplasm of interstitial cells of testis, and megakaryocytes in the bone marrow, etc.

Regarding the tissues that showed staining of cytoplasm only, the applicant explained that avelumab is unlikely to directly bind to these tissues and have effects because antibody does not directly bind to the components of cellular cytoplasm in the body (*MAbs*. 2011;3:3-16).

The applicant's explanation on the tissues that showed staining of cell membrane with avelumab:
Tissues that showed the binding of avelumab to cell membrane in the tissue cross-reactivity study in cynomolgus monkeys [see Section "5.6.2 Tissue cross-reactivity study using normal tissues of cynomolgus monkeys"] did not show any toxicity findings in the repeated intravenous dose toxicity

study in monkeys [see Section "5.2 Repeated-dose toxicity"], which suggests that avelumab is not toxic to these tissues. As for ovarian granulosa cells and testicular interstitial cells that showed no cross-reactivity in monkeys, avelumab is also unlikely to be toxic to these cells because clinical studies (Studies 001, 002, and 003 [785 males and 795 females in total]) did not show any adverse events suggestive of abnormalities in sex hormone secretion associated with the effect on these cells.

5.6.4 Safety evaluation of impurities

Impurities 1, 2, and 3 which may be dissolved into the drug product from the container or the stopper do not have genotoxicity, and the exposure in clinical use is below permitted daily exposure (PDE). The applicant explained that the above results have confirmed the safety of these impurities.

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that non-clinical toxicity data do not pose any problems about clinical use of avelumab.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical methods

6.1.1.1 Assay of avelumab

Avelumab in human serum samples was quantified by the assay method using immobilized streptavidin, biotin-labeled PD-L1-Fc recombinant fusion protein, and fluorescence-labeled PD-L1-Fc recombinant fusion protein. The lower limit of quantitation was 0.2 μg/mL.

6.1.1.2 Assay of anti-avelumab antibody

Anti-avelumab antibody in human serum samples was detected by electrochemiluminescence (ECL) using immobilized streptavidin, biotin-labeled avelumab, and ruthenium-labeled avelumab. The sensitivity of this assay method was 15.5 ng/mL. The upper limit of avelumab concentration in samples that does not affect the assay of anti-avelumab antibody was 31.3 μg/mL.

In the foreign phase I study (Study 001), the Japanese phase I study (Study 002), and the global phase II study (Study 003) which used the above assay methods, the maximum avelumab concentration in serum at the time point when anti-avelumab antibody measurement was performed was 129, 426, and 363 μg/mL, respectively. Based on the above findings, the applicant explained that avelumab in test samples may have affected the measurement of anti-avelumab antibody.

6.1.2 Changes in the manufacturing process of the drug substance and the drug product during the development stage

The manufacturing processes of the drug substance and the drug product were changed during the development [see Sections "2.1.4 Manufacturing process development" and "2.2.3 Manufacturing process development"]. The drug product manufactured by the initial manufacturing process was used in studies submitted in the present application, i.e., the foreign phase I study (Study 001), the dose titration part and the extension part of the Japanese phase I study (Study 002), and Part A of the global

phase II study (Study 003). The drug product manufactured by the proposed manufacturing processes was used in the foreign phase I study (Study 001), in the extension part of the Japanese phase I study (Study 002), and in Part B of the global phase II study (Study 003).

The applicant explained that the changes in the manufacturing processes of the drug substance and the drug product would not affect the PK of avelumab, for the following reasons:

- Comparability assessment of quality attributes was performed on the drug substance and the drug product before and after the change of the manufacturing process, which confirmed the comparability of the drug substance and the drug product, respectively [see Sections "2.1.4 Manufacturing process development" and "2.2.3 Manufacturing process development"].
- Data of serum avelumab concentration following avelumab (10 mg/kg) administration in the foreign phase I study (Study 001), the Japanese phase I study (Study 002), and the global phase II study (Study 003) were pooled separately for each of the total number of dose and compared between those obtained from the drug product manufactured by the initial manufacturing process and those manufactured by the proposed manufacturing process. Results did not show any clear difference in serum avelumab concentration (Table 9).
- In population pharmacokinetics (PPK) analysis, the drug product was not selected as a significant covariate for PK of avelumab [see Section "6.2.4 PPK analysis"].

Table 9. Serum avelumab concentration following avelumab (10 mg/kg) administration

Number of times of dose	Manufacturing process	n	C_{eoi}	n	C_{trough}
1	Initial	134	240 ± 109	641	21.8 ± 19.2
	Proposed	425	228 ± 63.2	454	19.5 ± 10.6
3	Initial	44	264 ± 75.2	440	26.8 ± 21.6
	Proposed	0	-	331	25.9 ± 17.6
4	Initial	80	264 ± 75.1	329	26.3 ± 17.6
	Proposed	249	251 ± 82.2	260	25.1 ± 17.5

Arithmetic mean ± SD; -, Not calculated

6.2 Clinical pharmacology

PK of avelumab in cancer patients was investigated after a single-dose administration of avelumab.

6.2.1 Japanese clinical study

6.2.1.1 Japanese phase I study (CTD 5.3.5.2.2, Study 002 [September 2013 – ongoing (data cut-off, November 20, 2015)])

An open-label, uncontrolled study to investigate PK, etc., of avelumab was conducted in 17 patients with advanced solid cancer (17 patients included in PK analysis) in the dose titration part and in 34 patients with unresectable advanced/relapsed gastric cancer (34 patients included in PK analysis) in the extension part. In the dose titration part, avelumab (3, 10, 20 mg/kg) was to be administered intravenously quaque 2 weeks (Q2W) and, in the extension part, avelumab (10 mg/kg) was to be administered intravenously Q2W, and serum avelumab concentration was investigated.

Table 10 shows PK parameters of avelumab following the first dose in the dose titration part. C_{max}, AUC_{336h}, and AUC_{inf} of avelumab increased roughly in proportion to the dose within the dose range investigated. In the 10 mg/kg group of the dose titration part, serum concentration at the end of the

infusion (C_{eoi}) of avelumab (geometric mean [geometric coefficient of variation (CV) (%)]) was 170 (20.8) and 202 (26.0) μg/mL, respectively, following the first and the second dose, and remained at a roughly constant level after the second dose.

Anti-avelumab antibody was detected in 3 of 51 patients (5.9%) who were measured for anti-avelumab antibody after avelumab administration.

Table 10. PK parameters of avelumab following the first dose

Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max}[*1] (h)	AUC_{336h} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_z (mL/kg)
3	5	64.0 (22.2)	1.68 (0.97, 2.07)	5632[*2] (28.7)	6055[*2] (32.0)	94.0 (31.7)	0.496[*2] (32.0)	61.0[*2] (25.3)
10	6	179 (19.6)	1.53 (1.00, 3.08)	18,729[*2] (36.5)	21,510[*2] (45.4)	122 (33.1)	0.471[*2] (44.1)	73.8[*2] (17.2)
20	6	459 (13.6)	1.68 (1.00, 4.92)	46,966 (22.8)	53,717 (24.3)	112 (11.6)	0.373 (24.2)	60.6 (21.7)

Geometric mean (geometric CV [%]), *1 Median (range); *2 n = 4

6.2.2 Foreign clinical studies

6.2.2.1 Foreign phase I study (CTD 5.3.5.2.1, Study 001 [January 2013 – ongoing (data cut-off, June 9, 2016)])

An open-label, uncontrolled study in 1490 patients with advanced solid cancer (86 patients included in PK analysis) was conducted to investigate the PK, etc., of avelumab. In the dose titration part, avelumab (1, 3, 10, 20 mg/kg) was to be administered intravenously Q2W and, in the extension part, avelumab (10 mg/kg) was to be administered intravenously Q2W, and serum avelumab concentration was investigated (Table 11).

C_{max}, AUC_{336h}, and AUC_{inf} of avelumab increased more than proportionally to dose within the dose range from 1 to 3 mg/kg and roughly in proportion to dose within the dose range from 3 to 20 mg/kg. The applicant explained that the non-linear response of PK parameters of avelumab may have been due to the saturation of the PD-L1 binding-mediated elimination pathway with the increase in avelumab dose.

Anti-avelumab antibody was detected in 48 of 1336 patients (3.6%) who were measured for anti-avelumab antibody after avelumab administration.

Table 11. PK parameters of avelumab following the first dose

Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max}[*2] (h)	AUC_{336h} (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	Vz (mL/kg)
1	4	18.4 (21.8)	1.50 (1.02, 13.0)	833, 1669	828, 1747	46.1, 76.8	1.21, 0.563	80.3, 62.4
3	13	78.9 (29.5)	1.50 (1.00, 13.0)	6078[*3] (32.1)	6521[*3] (34.8)	81.2[*3] (30.3)	0.461[*3] (34.2)	54.1[*3] (27.8)
10[*1]	48	294 (32.5)	1.50 (1.00, 25.0)	25,154[*4] (25.3)	27,654[*4] (27.0)	94.6[*4] (22.0)	0.362[*4] (27.3)	49.4[*4] (25.5)
20	21	470 (29.9)	1.72 (0.95, 13.0)	38,298[*5] (42.0)	42,710[*5] (47.6)	99.1[*5] (29.9)	0.469[*5] (47.3)	67.1[*5] (30.0)

Geometric mean (geometric CV [%]) (individual values for n = 2); *1 Pooled results of the dose titration part and the extension part; *2 Median (range); *3 n = 12; *4 n = 39; *5 n = 15

6.2.3 Study of relationship between exposure and changes in QT/QTc interval

In the foreign phase I study (Study 001), the Japanese phase I study (Study 002), and the global phase II study (Study 003), the relationship between serum avelumab concentration relative to ΔQTcF (change in QT interval corrected using Fredericia equation from baseline) and ΔQTcP (change in QT interval corrected for heart rate by the secondary correction factor specific to the study population from baseline) was investigated in 689 patients in whom serum avelumab concentration could be measured at the time point of electrocardiographic measurement, using a linear mixed-effects model. Results showed no clear relationship between serum avelumab concentration and ΔQTcF or ΔQTcP.

Based on the above, the applicant explained that avelumab is unlikely to cause QT/QTc prolongation when administered by the proposed dosage regimen.

6.2.4 PPK analysis

PPK analysis was performed using a non-linear mixed-effects model (software used, NONMEM version 7.3.0), based on PK data of avelumab (10,220 measuring time points in 1629 patients) obtained from the foreign phase I study (Study 001), the Japanese phase I study (Study 002), and the global phase II study (Study 003). PK of avelumab was described by a 2-compartment model.

The following parameters were evaluated as possible covariates for CL, intercompartmental clearance (Q), central volume of distribution (V1), and peripheral volume of distribution (V2) of avelumab: Age, body weight, sex, race, estimated glomerular filtration rate (eGFR), serum albumin, serum bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), Ig, PD-L1 expression level (cut-off level, 1%), total protein, prothrombin time-international normalized ratio, whole body tumor volume, number of times of treatment with antineoplastic agents, dose of avelumab, Eastern Cooperative Oncology Group Performance Status (ECOG PS), cancer type, immunogenicity, drug product, concomitant drugs (acetaminophen, opioid, systemic corticoid, ibuprofen, biological products, or aspirin), past history of treatment with biological products, and premedication (acetaminophen or diphenhydramine). As a result, the following parameters were selected as significant covariates: (a) Body weight, sex, serum albumin, whole body tumor volume, dose of avelumab, and cancer type for CL; (b) cancer type and premedication with acetaminophen for Q; (c) body weight and sex for V1; and (d) eGFR, cancer type, immunogenicity, and premedication with acetaminophen for V2. The applicant explained the above results as follows:

- The effect of body weight, sex, eGFR, serum albumin, whole body tumor volume, immunogenicity, and premedication with acetaminophen on the exposure to avelumab (area under the serum concentration-time curve at steady state [AUC_{ss}]) was mostly within the range of the inter-individual variability (25.2%) of CL, suggesting that the effect of these covariates on PK of avelumab is limited.
- CL of avelumab following 10 mg/kg administration decreased by 26% compared to that following 3 mg/kg administration. This result is considered to be due to the saturation of the PD-L1 binding-mediated elimination pathway at 10 mg/kg administration.
- In patients with MCC, AUC_{ss} of avelumab showed higher levels exceeding the range of the inter-individual variability compared to the level observed in patients with other types of cancer. However, the result is unlikely to be a significant variation, taking account of the fact that AUC_{ss} was estimated

from PK data with only a small number of measuring time points and with large variations obtained from the global phase II study (Study 003).

6.2.5 Relationship of exposure to avelumab with efficacy and safety

6.2.5.1 Relationship between exposure and efficacy

Based on the data obtained from the global phase II study (Study 003), the relationship between the exposure to avelumab (estimated values[10)] of C_{trough}, $C_{trough,ss}$ [serum concentration at the end of the dosing interval at steady state], AUC_{ss}, and mean serum avelumab concentration following the first dose, and observed value of $C_{trough,ss}$[11)]) and the best overall response was investigated using a logistic regression model. Results showed a correlation between estimated $C_{trough,ss}$ and the best overall response, suggesting that the response rate increases with the increase in $C_{trough,ss}$.

Based on the data obtained from the global phase II study (Study 003), the relationship between the exposure to avelumab (estimated values[10)] of C_{max}, C_{trough}, AUC, $C_{max,ss}$ [maximum serum concentration observed postdose at steady state], $C_{trough,ss}$, and AUC_{ss}, following the first dose) and progression-free survival (PFS) or overall survival (OS) was investigated using a Cox proportional hazard model. Results showed that both PFS and OS are correlated with $C_{trough,ss}$ and AUC_{ss}, suggesting that PFS and OS increased with the increase in $C_{trough,ss}$ and AUC_{ss}.

6.2.5.2 Relationship between exposure and safety

Based on the data obtained from the foreign phase I study (Study 001), the Japanese phase I study (Study 002), and the global phase II study (Study 003), the following relationships were investigated using a logistic regression model: (a) Relationship between the exposure to avelumab (estimated values[10)] of C_{trough}, $C_{trough,ss}$, and AUC_{ss} following the first dose) and the incidences of adverse events (Grade ≥1, Grade ≥2, and Grade ≥3) and immune-related adverse events (Grade ≥1) observed after avelumab administration, and (b) relationship between the exposure to avelumab (estimated values[10)] of C_{max}, C_{trough}, and AUC after the first dose) and the incidence of infusion reaction. Results showed a correlation between $C_{trough,ss}$ and immune-related adverse events (Grade ≥1), suggesting that the incidence of immune-related adverse events (Grade ≥1) increased with the increase in $C_{trough,ss}$.

6.2.6 Effect of decreased renal and hepatic function on PK of avelumab

No clinical study investigating the PK of avelumab was conducted on patients with renal or hepatic impairment. However, the applicant explained that decreased renal or hepatic function is unlikely to affect the PK of avelumab, taking account of the following:

- Avelumab is considered to be eliminated by the target antigen binding-mediated pathway and by the protein degradation pathway, which suggests that decreased hepatic function is unlikely to affect the exposure to avelumab.
- Since avelumab is a high molecular weight compound (molecular weight, approximately 147,000), it is unlikely to be excreted from the kidney.

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10) Estimated by PPK analysis [see "6.2.4 PPK analysis"].

11) The median values of C_{trough} (observed value) in each patient (a) on Day 43 after the start of administration, (b) at >300 hours and <360 hours after the last dose, and (c) at 336 hours after administration were used.

- PPK analysis showed that the effect of serum albumin, serum bilirubin, AST, ALT, and eGFR on the PK of avelumab was limited [see Section "6.2.4 PPK analysis"].

6.2.7 Difference in PK of avelumab between Japanese and non-Japanese patients

The applicant explained that, taking account of the observation that no clear difference was observed between Japanese patients and non-Japanese patients in PK parameters following the administration of avelumab (3, 10, 20 mg/kg) in the Japanese phase I study (Study 002) and the foreign phase I study (Study 001) [see Sections "6.2.1.1 Japanese phase I study" and "6.2.2.1 Foreign phase I study"], there is no clear difference in PK of avelumab between Japanese and non-Japanese patients.

6.R Outline of the review conducted by PMDA

6.R.1 Effect of anti-avelumab antibody on PK of avelumab

Incidences of anti-avelumab antibody were investigated in the foreign phase I study (Study 001), the Japanese phase I study (Study 002), and the global phase II study (Study 003). As a result, anti-avelumab antibody was observed in 61 of 1577 patients (3.9%) from whom samples were collected after the first dose of avelumab.

The applicant's explanation on the effect of anti-avelumab antibody on the PK of avelumab:
In the foreign phase I study (Study 001), the Japanese phase I study (Study 002), and the global phase II study (Study 003), C_{trough} following intravenous administration of avelumab (10 mg/kg) Q2W was lower in anti-avelumab antibody-positive patients than in negative patients at all measuring time points (Table 12). However, given that there were only a limited number of anti-avelumab antibody-positive patients and that avelumab present in the samples may be affected the results of the anti-avelumab antibody measurement performed by the method used in the above clinical studies [see Section "6.1.1.2 Assay of anti-avelumab antibody"], it is difficult to draw any clear conclusion regarding the effect of anti-avelumab antibody on the PK of avelumab.

Table 12. Avelumab concentration following avelumab (10 mg/kg) administration (μg/mL)

Day of measurement	Anti-avelumab antibody-positive patients		Anti-avelumab antibody-negative patients	
	n	C_{trough}	n	C_{trough}
15	15	16.4 ± 13.2	1279	21.3 ± 16.4
29	13	13.5 ± 15.2	1181	24.7 ± 16.4
43	6	19.5 ± 25.9	951	27.1 ± 19.5
57	2	Below the lower limit of quantitation, 25.6	480	26.4 ± 18.5
71	3	0.103 ± 0.179	416	28.6 ± 25.6
85	7	5.28 ± 6.87	533	31.1 ± 19.8
127	6	18.2 ± 19.3	208	38.0 ± 32.8
169	4	21.2 ± 22.2	201	36.8 ± 21.8

Arithmetic mean ± SD (individual values for n = 2)

PMDA's view:
PMDA accepted the explanation of the applicant. However, information on the effect of anti-avelumab antibody on the PK of avelumab should be continuously collected, and when new findings become available, the information should be provided to healthcare professionals in an appropriate manner.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of results data from a total of 3 clinical studies, 1 Japanese phase I study, 1 global phase II study, and 1 foreign phase I study, as listed in Table 13.

Table 13. List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Subjects	Number of enrollments	Dosage regimen (intravenous administration in all studies)	Main endpoints
Evaluation	Japan	002	I	(i) Patients with advanced solid cancer (ii) Patients with unresectable advanced/relapsed gastric cancer	51 (a) 17 (b) 34	(a) Avelumab (3, 10, 20 mg/kg) Q2W (b) Avelumab (10 mg/kg) Q2W	Safety PK
	Global	003	II	Among patients with metastatic, unresectable MCC, Part A: Patients with a history of chemotherapy Part B: Patients without a history of chemotherapy	Part A 88 Part B 29	Avelumab (10 mg/kg) Q2W	Efficacy Safety PK
	Foreign	001	I	Patients with advanced solid cancer	1688 (a) 53 (b) 1635	(a) Avelumab (1, 3, 10, 20 mg/kg) Q2W (b) Avelumab (10 mg/kg) Q2W	Safety PK

The outline of each clinical study was described below.

Main adverse events observed in each clinical study, except death, are described in Section "7.2 Adverse events, etc. observed in clinical studies," and PK-related data are described in Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese study

7.1.1.1 Japanese phase I study (CTD 5.3.5.2.2, Study 002 [September 2013 – ongoing (data cut-off, November 20, 2015)])

An open-label, uncontrolled study was conducted in patients with advanced solid cancer (target sample size, 18 subjects) in the dose titration part and patients with unresectable advanced/relapsed gastric cancer in the extension part (target sample size, 40 subjects) in order to investigate the safety, etc., of avelumab in 12 study centers in Japan.

In the dose titration part, avelumab (3, 10, 20 mg/kg) was to be administered intravenously Q2W and, in the extension part, avelumab (10 mg/kg) was to be administered intravenously Q2W. The treatment was to be continued until the patient showed disease progression or met the criteria for treatment discontinuation.

All of 51 patients enrolled in the study (17 in dose titration part, 34 in extension part) received avelumab and were included in the safety analysis population.

In the dose titration part, tolerability of avelumab was evaluated during the dose limiting toxicity (DLT) assessment period which was defined as 3 weeks after the start of avelumab administration. DLT was

not observed in 17 patients receiving avelumab (5 in the 3 mg/kg group, 6 in the 10 mg/kg group, 6 in the 20 mg/kg group).

As for safety, death occurred during the avelumab administration period or within 30 days after the end of administration in 2 of 34 patients (5.9%) in the extension part. The causes of death were myocardial infarction and acute kidney injury/tumor lysis syndrome (TLS)[12] in 1 patient each. A causal relationship to avelumab could not be ruled out for acute kidney injury/TLS (1 patient).

7.1.2 Global study

7.1.2.1 Global phase II study (CTD 5.3.5.1.1, Study 003 [July 2014 – ongoing (Part A) (efficacy data cut-off, March 3, 2016; safety data cut-off, June 9, 2016), March 2016 – ongoing (Part B) (data cut-off, December 30, 2016)])

An open-label, uncontrolled study in patients with metastatic, unresectable MCC was conducted to investigate the efficacy and safety of avelumab in 38 study centers in 8 countries including Japan. Part A of the study was conducted on patients with a history of chemotherapy[13] (target sample size, 84 subjects) and Part B on patients without a history of chemotherapy (target sample size, 112 subjects).

Avelumab (10 mg/kg) was to be administered intravenously Q2W until the patient showed disease progression or met the criteria for treatment discontinuation.

Of 166 patients enrolled in the study (125 in Part A, 41 in Part B), 117 patients (88 in Part A, 29 in Part B) excluding 49 patients who did not receive avelumab were included in the efficacy analysis population, and this population was subjected to safety analysis as well.

The primary endpoint in Part A was the response rate[14] by Independent Endpoint Review Committee (IERC) assessment based on Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.1, and 2 interim analyses were planned. The first interim analysis was to be conducted to evaluate the futility at the time point when 20 subjects received avelumab and were followed up for at least 3 months. The second interim analysis was to be conducted to evaluate the efficacy warranting early study discontinuation at the time point when 56 subjects received avelumab and were followed up for at least 6 months. The final analysis was planned to be conducted at the time point when all patients receiving avelumab were followed up for at least 6 months. Avelumab was to be considered effective if response was observed in ≥20 of 56 patients in the second interim analysis, and in ≥26 of 88 patients in the final analysis. The overall probability of type I error was controlled at 0.025.[15]

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12) After the data cut-off, the diagnosis of acute renal failure/TLS was changed to multi-organ failure (not causally related to avelumab) by the investigator based on the autopsy report.

13) Patients with a history of ≥1 regimen of chemotherapy using any of the following antineoplastic agents (none of them approved for MCC in Japan) were eligible for enrollment:
Cyclophosphamide hydrate, nogitecan hydrochloride, doxorubicin hydrochloride, epirubicin hydrochloride, vincristine sulfate, carboplatin, cisplatin, and etoposide.

14) Since there was no published report that served as a useful reference for threshold response rate at the start of the study, the rate was 20%, the level considered to be clinically significant.

15) From the Group Sequential Methods with Applications to Clinical Trials (Chapman & Hall/CRC 2000, Boca Raton, USA), section 12.1.2, the nominal significance level in the second interim analysis and in the final analysis was calculated to be 0.0045 and 0.0211 (one-sided), respectively, and the overall probability of type I error to be 0.0223. As for the CI of the response rate in the final analysis, 95.9% CI was to be calculated using the one-sided significance level of 0.0205, the value obtained by subtracting 0.0045 (the nominal significance level at the second interim analysis) from 0.025 (one-sided type-I error).

As for the efficacy, IERC recommended study continuation as a result of the first interim analysis (data cut-off, [redacted], 20[redacted]). Results of the second interim analysis (data cut-off, [redacted], 20[redacted]) showed that the response rate [99.1% confidence interval (CI)] by IERC assessment based on RECIST ver. 1.1 was 30.4% [15.7, 48.5] (17 of 56 patients), with the lower limit of the 99.1% CI of the response rate failing to meet the pre-defined threshold response rate (20%). IERC therefore recommended to continue the study until the final analysis.

Table 14 shows the response rate by IERC assessment based on RECIST ver. 1.1 at the time point of the final analysis (data cut-off, March 3, 2016). A total of 28 patients in the entire population responded to the treatment, with the lower limit of the 95.9% CI of the response rate exceeding the pre-defined threshold response rate (20%).

Table 14. Best overall response and response rate in the final analysis (RECIST ver. 1.1, efficacy analysis population, IERC assessment, data cut-off, March 3, 2016)

Best overall response	Number of patients (%)	
	Entire population N = 88	Japanese population N = 3
Complete response (CR)	8 (9.1)	1 (33.3)
Partial response (PR)	20 (22.7)	0
Stable disease (SD)	9 (10.2)	1 (33.3)
Progressive disease (PD)	32 (36.4)	1 (33.3)
Not evaluable (NE)	19 (21.6)	0
Response (CR + PR) (response rate [95.9% CI*] (%))	28 (31.8 [21.9, 43.1])	1 (33.3 [0.8, 90.6])

* Clopper-Pearson method

In Part B, the durable response rate[16] by IERC assessment based on RECIST ver. 1.1 was selected as the primary endpoint, and the response rate by IERC assessment based on RECIST ver. 1.1 was selected as the secondary endpoint. In the application in the US and in EU, an interim analysis on the second endpoint (data cut-off, December 30, 2016) was conducted at the request of Food and Drug Administration (FDA) and European Medicines Agency (EMA), although not planned at the start of the study. Table 15 shows the results with 16 efficacy-evaluable patients who were followed up for ≥13 weeks after the start of avelumab administration (no Japanese patients have been enrolled at this moment).

Table 15. Best overall response and response rate in the interim analysis (RECIST ver. 1.1, efficacy analysis population, IERC assessment, data cut-off, December 30, 2016)

Best overall response	Number of patients (%)
	N = 16
CR	3 (18.8)
PR	7 (43.8)
SD	2 (12.5)
PD	3 (18.8)
NE	1 (6.3)
Response (CR + PR) (response rate [95% CI*] (%))	10 (62.5 [35.4, 84.8])

* Clopper-Pearson method

As for safety, death occurred during the avelumab administration period or within 30 days after the end of administration in 8 of 88 patients (9.1%) in Part A and in 1 of 29 patients (3.4%) in Part B. The causes

16) The rate of response (CR + PR) by RECIST ver. 1.1-based IERC assessment persisting for ≥6 months.

of death other than disease progression (5 patients in Part A) were ileus, pneumonia, and hepatic failure in 1 patient each in Part A and large intestine perforation/sepsis/respiratory failure/encephalopathy in 1 patient in Part B. A causal relationship to avelumab was ruled out in all patients.

7.1.3 Foreign study

7.1.3.1 Foreign phase I study (CTD 5.3.5.2.1, Study 001 [January 2013 – ongoing (data cut-off, June 9, 2016)])

An open-label, uncontrolled study in patients with advanced solid cancer (target sample size, 18-60 subjects in dose titration part, 1610 subjects in extension part) was conducted to investigate the safety, etc., of avelumab in 134 study centers in 11 foreign countries or regions.

Avelumab was to be administered intravenously Q2W at a dose of 1, 3, 10, or 20 mg/kg in the dose titration part and at a dose of 10 mg/kg in the extension part until the patients showed disease progression or met the criteria for treatment discontinuation.

A total of 1688 patients enrolled in the study (53 in dose titration part, 1635 in extension part) received avelumab and were included in the safety analysis population.

In the dose titration part, tolerability of avelumab was evaluated during the DLT assessment period which was defined as 3 weeks after the start of avelumab administration. DLT (Grade 3 blood creatine phosphokinase [CPK] increased and autoimmune disorder) occurred only in 1 patient in the 20 mg/kg group out of 53 patients receiving avelumab (4 in the 1 mg/kg group, 13 in the 3 mg/kg group, 15 in the 10 mg/kg group, 21 in the 20 mg/kg group), with the administered dose not reaching maximum tolerated dose (MTD).

As for safety, death during the avelumab administration period or within 30 days after the end of administration was observed in 9 of 53 patients (17.0%) in the dose titration part (2 of 4 patients in the 1 mg/kg group, 4 of 13 patients in the 3 mg/kg group, 2 of 15 patients in the 10 mg/kg group, 1 of 21 patients in the 20 mg/kg group) and in 218 of 1635 patients (13.3%) in the extension part. The causes of death other than disease progression (6 in dose titration part, 144 in extension part) were duodenal obstruction/ascites (1 mg/kg group), hypoxaemia (1 mg/kg group), and respiratory failure (20 mg/kg group) in 1 patient each in the dose titration part; and respiratory failure in 9 patients, pneumonia in 5 patients, sepsis and general physical health deterioration in 4 patients each, gastrointestinal haemorrhage, death, and cardiac arrest in 3 patients each, hepatic failure, lung infection, intestinal perforation, intestinal obstruction, abdominal pain, dysphagia, hepatitis E, urosepsis, septic shock, acute hepatic failure, arterial rupture, peripheral arterial occlusive disease, dyspnoea at rest, acute respiratory failure, respiratory distress, aspiration, laryngeal haemorrhage, pulmonary hypertension, pulmonary embolism, pneumonitis, cardiac tamponade, cardio-respiratory arrest, cardiac failure, subarachnoid haemorrhage, haemorrhage intracranial, cerebrovascular accident, brain injury, acute kidney injury, suicide attempt, completed suicide, failure to thrive, malignant pleural effusion, gastric cancer, metastatic gastric cancer, tumour haemorrhage, tumour thrombosis, metastases to central nervous system, mesothelioma, metastases to peritoneum, tonsil cancer, lung infection/hypoxia/embolism, sepsis/respiratory distress, and hepatic failure/autoimmune hepatitis in 1 patient each in the extension part. A causal relationship to

avelumab could not be ruled out for hepatic failure/autoimmune hepatitis, acute hepatic failure, respiratory distress, and pneumonitis (1 patient each) in the extension part.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

PMDA concluded that, among the evaluation data submitted, the most important study for evaluating the efficacy and safety of avelumab was the global phase II study (Study 003) conducted to investigate the efficacy and safety of avelumab in patients with metastatic MCC, and decided to evaluate the submitted data focused on this study.

7.R.2 Efficacy

Based on the following review, PMDA has concluded that a certain level of efficacy of avelumab is demonstrated in patients with metastatic, unresectable MCC.

7.R.2.1 Primary endpoint and efficacy evaluation

The applicant's explanation on the reason for selecting the response rate as the primary endpoint in Part A of Study 003 in patients with metastatic, unresectable MCC with a history of chemotherapy:
Given the poor prognosis of the disease and unavailability of the standard treatment leading to OS prolongation, it is clinically significant if patients respond to the treatment with avelumab.

The applicant's explanation on the efficacy of avelumab in patients with metastatic, unresectable MCC:
The final analysis of data obtained from patients with a history of chemotherapy among patients with metastatic, unresectable MCC in Part A of Study 003 showed that the lower limit of 95.9% CI of the response rate, the primary endpoint, significantly exceeded 20%, the threshold response rate pre-defined as a clinically significant response rate [see Section "7.1.2.1 Global phase II study"]. In addition, a response was observed also in the Japanese population enrolled in Part A of Study 003. Since there was no published report that served as a useful reference for the threshold response rate at the start of the study, the threshold response rate was selected based on the estimation of the clinically significant level. A retrospective study based on a published report which became available after the start of the study (*Cancer Med*. 2016;5:2294-301[17)]), etc., suggests that the above selecting the threshold response rate was appropriate.

As for the response rate defined as the secondary endpoint in Part B of Study 003, response was also observed in a certain number of patients without a history of chemotherapy [see Section "7.1.2.1 Global phase II study"].

Taking account of the above results, together with the unavailability of the OS-prolonging standard therapy in patients with metastatic, unresectable MCC, regardless of the presence or absence of history of chemotherapy, avelumab is considered to be effective in these patients.

PMDA accepted the explanation of the applicant.

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17) A retrospective study evaluating the effectiveness of chemotherapy given to patients with MCC in routine clinical settings. It is reported that the response rate [95% CI] of patients with MCC (n = 30) to chemotherapy routinely received as the secondary treatment was 23.3% [9.9, 42.3].

7.R.3 Safety [for adverse events, see Section "7.2 Adverse events, etc., observed in clinical studies"]

Based on the following review, PMDA has concluded that adverse events requiring particular attention in administering avelumab to patients with MCC are hepatic dysfunction, interstitial lung disease (ILD), renal disorder, infusion reaction, gastro-intestinal disorder (colitis/severe diarrhoea in particular), thyroid dysfunction, dysfunction adrenal, type 1 diabetes mellitus, nerve disorder (Guillain-Barre syndrome, encephalitis/meningitis in particular), cardiac disorder (myocarditis in particular), and myositis/rhabdomyolysis, and that caution should be exercised against possible occurrence of these adverse events in using avelumab.

PMDA also concluded that although attention should be paid to the occurrence of the above adverse events in using avelumab, it is tolerable provided that appropriate measures, such as monitoring and controlling of adverse events (including adverse drug reactions caused by excessive immune response) and suspension or discontinuation of avelumab administration, are taken by physicians with adequate knowledge and experience of cancer chemotherapy.

7.R.3.1 Safety profile of avelumab

The applicant explained the safety profile of avelumab as follows, based on the safety information obtained from Study 003:

Table 16 shows the outline of safety in Study 003.

Table 16. Outline of safety (Study 003)

	Number of patients (%)	
	Part A N = 88	Part B N = 29
All adverse events	86 (97.7)	28 (96.6)
Grade ≥3 adverse events	55 (62.5)	12 (41.4)
Adverse events leading to death	8 (9.1)	1 (3.4)
Serious adverse events	37 (42.0)	8 (27.6)
Adverse events leading to treatment discontinuation	5 (5.7)	6 (20.7)
Adverse events leading to treatment suspension*	21 (23.9)	8 (27.6)

* Excluding suspension or interruption of administration due to infusion reaction.

In Part A of Study 003, all-grade adverse events with an incidence of ≥10% were fatigue in 33 patients (37.5%), diarrhoea in 20 patients (22.7%), nausea in 19 patients (21.6%), decreased appetite in 18 patients (20.5%), oedema peripheral in 17 patients (19.3%), cough in 16 patients (18.2%), constipation in 15 patients (17.0%), arthralgia and pain in extremity in 14 patients (15.9%) each, anaemia, infusion reaction, and weight decreased in 13 patients (14.8%) each, dizziness and rash in 12 patients (13.6%) each, hypertension, abdominal pain, vomiting, and asthenia in 11 patients (12.5%) each, and back pain, headache, and pruritus in 9 patients (10.2%) each. Grade ≥3 adverse events with an incidence of ≥5% were anaemia in 9 patients (10.2%), lymphopenia in 6 patients (6.8%), and hypertension in 5 patients (5.7%). Serious adverse events with an incidence of ≥2% were disease progression and acute kidney injury in 4 patients (4.5%) each, anaemia in 3 patients (3.4%), ileus, abdominal pain, general physical health deterioration, asthenia, and cellulitis in 2 patients (2.3%) each. There were no adverse events leading to treatment discontinuation with an incidence of ≥2%.

In Part B of Study 003, all-grade adverse events with an incidence of ≥10% were fatigue in 9 patients (31.0%), constipation in 8 patients (27.6%), lipase increased and weight decreased in 5 patients (17.2%) each, anaemia, abdominal pain, infusion reaction, and hyponatraemia in 4 patients (13.8%) each, nausea, diarrhoea, bronchitis, hypertension, cough, dyspnoea, hyperkalaemia, hyperglycaemia, dry skin, amylase increased, and ALT increased in 3 patients (10.3%) each. Grade ≥3 adverse events with an incidence of ≥5% were hypertension in 3 patients (10.3%), pulmonary embolism and AST increased in 2 patients (6.9%) each. There were no serious adverse events with an incidence of ≥5%. The adverse event leading to treatment discontinuation with an incidence of ≥5% was infusion reaction in 2 patients (6.9%).

PMDA's view:
Adverse events with a high incidence, serious adverse events, and Grade ≥3 adverse events observed in Study 003 are highly likely to occur after avelumab administration. Patients receiving avelumab should be monitored for these adverse events with consideration given to the relationship to avelumab. Because of the extremely limited safety information on avelumab, relevant information should be continuously collected after the market launch, and when new information becomes available, the information should be provided to healthcare professionals without delay.

7.R.3.2 Difference in safety profile between Japanese and non-Japanese patients

The applicant's explanation on the difference in the safety profile of avelumab between Japanese patients and non-Japanese patients:
Because of the extremely limited number of patients with MCC subjected to evaluation of safety of avelumab, safety was investigated using the pooled data of the Japanese and foreign clinical studies (Studies 003, 001, and 002) which were conducted using the same dosage regimen as in Study 003 (10 mg/kg, Q2W). Table 17 shows the outline of the safety profile in Japanese and non-Japanese patients.

Table 17. Outline of safety (Studies 003, 001, 002)

	Number of patients (%)	
	Japanese patients N = 43	Non-Japanese patients N = 1764
All adverse events	41 (95.3)	1722 (97.6)
Grade ≥3 adverse events	20 (46.5)	1018 (57.7)
Adverse events leading to death	2 (4.7)	229 (13.0)
Serious adverse events	10 (23.3)	783 (44.4)
Adverse events leading to treatment discontinuation	7 (16.3)	249 (14.1)
Adverse events leading to suspension*	10 (23.3)	369 (20.9)

* Excluding suspension or interruption of administration due to infusion reaction.

The all-grade adverse event with a ≥10% higher incidence in Japanese patients than in non-Japanese patients was dry skin (6 Japanese [14.0%], 69 non-Japanese [3.9%]). Grade ≥3 adverse events with a ≥5% higher incidence in Japanese patients than in non-Japanese patients were anaemia (8 Japanese [18.6%], 105 non-Japanese [6.0%]) and ileus (3 Japanese [7.0%], 4 non-Japanese [0.2%]). The serious adverse event with a ≥3% higher incidence in Japanese patients than in non-Japanese patients was ileus (3 Japanese [7.0%], 5 non-Japanese [0.3%]). There were no adverse events leading to treatment discontinuation with a ≥3% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's view:

Because of the limited number of Japanese who received avelumab, there are limitations to the comparison of the safety of avelumab between Japanese and non-Japanese patients. However, avelumab is tolerable in Japanese patients as well, taking account of the following:

- Adverse events with a higher incidence in Japanese patients than in non-Japanese patients were (a) dry skin, (b) anaemia, and (c) ileus. However, (a) dry skin was Grade ≤2 in all affected patients, (b) no serious anaemia was observed in Japanese patients, and (c) a causal relationship of observed serious ileus to avelumab was ruled out in all affected patients.
- There was no clear difference between Japanese and non-Japanese patients in incidences of adverse events leading to treatment discontinuation.

In the following sections, PMDA reviewed the safety based mainly on the safety results in Study 003, focusing on serious adverse events for which a causal relationship to avelumab could not be ruled out as well as adverse events, etc., for which cautions are required in treatment with nivolumab and pembrolizumab, drugs that inhibit the binding of PD-L1 and PD-1 as does avelumab.

7.R.3.3 Hepatic dysfunction

The applicant's explanation on avelumab-induced hepatic dysfunction:

As hepatic dysfunction, events corresponding to "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow standardised MedDRA queries [SMQ])," "Hepatitis, non-infectious (narrow SMQ)," "Liver neoplasms, benign (incl cysts and polyps) (narrow SMQ)," "Liver related investigations, signs and symptoms (narrow SMQ)," "Cholestasis and jaundice of hepatic origin (narrow SMQ)," or "Liver-related coagulation and bleeding disturbances (narrow SMQ)" in Medical Dictionary for Regulatory Activities (MedDRA) were tabulated.

Table 18 shows incidences of hepatic dysfunction in Study 003.

Table 18. Incidences of hepatic dysfunction (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction	20 (22.7)	10 (11.4)	4 (13.8)	2 (6.9)
ALT increased	6 (6.8)	3 (3.4)	3 (10.3)	1 (3.4)
AST increased	6 (6.8)	1 (1.1)	2 (6.9)	2 (6.9)
GGT increased	5 (5.7)	4 (4.5)	0	0
International normalised ratio increased	2 (2.3)	1 (1.1)	0	0
Ascites	1 (1.1)	1 (1.1)	0	0
Hepatic failure	1 (1.1)	1 (1.1)	0	0
Liver injury	1 (1.1)	1 (1.1)	0	0
Transaminases increased	1 (1.1)	1 (1.1)	0	0
Hyperbilirubinaemia	1 (1.1)	0	0	0
Cholestasis	1 (1.1)	0	0	0
Hepatic function abnormal	1 (1.1)	0	0	0
Blood bilirubin increased	0	0	1 (3.4)	0

In Part A of Study 003, fatal hepatic dysfunction (hepatic failure) was observed in 1 patient, but its causal relationship to avelumab was ruled out. Serious hepatic dysfunction was observed in 3 patients (transaminases increased, hepatic failure, and liver injury in 1 patient each), and a causal relationship to

avelumab could not be ruled out for transaminases increased (1 patient). Hepatic dysfunction leading to treatment discontinuation was observed in 2 patients (ALT increased, gamma-glutamyl transferase [GGT] increased, and transaminase increased in 1 patient each [including duplicate counting]).

In Part B of Study 003, no fatal or serious hepatic dysfunction was observed. Hepatic dysfunction leading to treatment discontinuation was observed in 1 patient (AST increased and ALT increased).

In the avelumab (10 mg/kg, Q2W) group of Study 001, hepatic dysfunction was observed in 255 of 1650 patients (15.5%). In Study 001, fatal hepatic dysfunction was observed in 7 patients (hepatic failure in 3 patients, acute hepatic failure, hepatic encephalopathy, autoimmune hepatitis/hepatic failure, and ascites in 1 patient each). A causal relationship to avelumab could not be ruled out for acute hepatic failure and autoimmune hepatitis/hepatic failure (1 patient each). In Study 001, serious hepatic dysfunction was observed in 54 patients (events observed in multiple patients; ascites in 20 patients, blood bilirubin increased and transaminases increased in 5 patients each, AST increased and hepatic failure in 4 patients each, ALT increased and autoimmune hepatitis in 3 patients each, hyperbilirubinaemia, hepatic encephalopathy, hepatocellular injury, and cholestasis in 2 patients each [including duplicate counting]). Of these, a causal relationship to avelumab could not be ruled out for autoimmune hepatitis (3 patients), AST increased and transaminase increased (2 patients each), ALT increased, acute hepatic failure, blood bilirubin increased, GGT increased, hepatocellular injury, hepatic enzyme increased, and hepatic failure (1 patient each).

In the avelumab (10 mg/kg, Q2W) group of Study 002, hepatic dysfunction was observed in 4 of 40 patients (10.0%). In Study 002, no fatal or serious hepatic dysfunction was observed.

In the Japanese and foreign clinical studies (Part A and Part B of Study 003, Study 001, and Study 002), hepatic dysfunction occurred in 283 of 1807 patients (15.7%) after avelumab (10 mg/kg, Q2W) administration. In these patients, time from the start of avelumab until the first occurrence of hepatic dysfunction (median and range) was 40 (1-489) days. Hepatic dysfunction occurred within 3 months after the start of avelumab administration in 235 of 283 patients (83.0%), with the dysfunction commonly occurring at around 40 days after the start of avelumab administration. The outcome was recovery in 97 of 283 patients (34.3%), not-recovery in 181 of 283 patients (64.0%), and death in 5 of 283 patients (1.8%). Hepatic dysfunction led to discontinuation of avelumab in 31 of 283 patients (11.0%). The time from treatment discontinuation to resolution of hepatic dysfunction (median and range) was 57 (1-529) days.

In clinical studies using avelumab, including those not described above,[18)] there was no hepatic dysfunction that met Hy's law criteria (defined based on Guidance for industry. Drug-Induced Liver Injury: premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009).

PMDA's view:
In the Japanese and foreign clinical studies, avelumab caused hepatic dysfunction, and there were patients who died of autoimmune hepatitis or hepatic failure, warranting caution against hepatic dysfunction in administering avelumab. Although a majority of hepatic dysfunction occurred within 3

18) In clinical studies other than Studies 003, 001, and 002, the data cut-off date was [redacted], 20[redacted].

months after the start of administration, the occurrences continued even after 3 months. Patients should be monitored by periodical test for hepatic function before and during treatment with avelumab. The information on the measures to be taken in case of hepatic dysfunction recommended in Study 003, such as criteria for suspension or discontinuation of treatment with avelumab, should be appropriately provided to healthcare professionals using the package insert, etc.

7.R.3.4 ILD

The applicant's explanation on avelumab-induced ILD:
As ILD, events corresponding to "Interstitial lung disease (narrow SMQ)," "Acute respiratory distress syndrome (PT)," or "Acute respiratory failure (PT)" in MedDRA were tabulated.

In Part A of Study 003, ILD was observed in 2 of 88 patients (2.3%; pneumonitis and radiation pneumonitis in 1 patient each). There were no ILD cases that were fatal, serious, Grade ≥3, or led to treatment discontinuation.

In Part B of Study 003, no ILD occurred.

In the avelumab (10 mg/kg, Q2W) group of Study 001, ILD was observed in 57 of 1650 patients (3.5%). In Study 001, fatal ILD was observed in 3 patients (acute respiratory failure in 2 patients, pneumonitis in 1 patient). A causal relationship to avelumab could not be ruled out for acute respiratory failure and pneumonitis (1 patient each). In Study 001, serious ILD was observed in 25 patients (pneumonitis in 12 patients, acute respiratory failure in 11 patients, lung infiltration, radiation pneumonitis, and acute respiratory distress syndrome (ARDS) in 1 patient each [including duplicate counting]). A causal relationship to avelumab could not be ruled out for pneumonitis (11 patients), acute respiratory failure, radiation pneumonitis, and ARDS (1 patient each).

In the avelumab (10 mg/kg, Q2W) group of Study 002, no ILD was observed. In Study 002, no fatal or serious ILD was observed.

In 59 of 1807 patients (3.3%) who experienced ILD after avelumab (10 mg/kg, Q2W) administration in the Japanese and foreign clinical studies (Part A and Part B of Study 003, Study 001, and Study 002), the time (median and range) from the start of avelumab administration to the first occurrence of ILD was 52 (1-500) days, with ILD occurring within 3 months after the start of avelumab administration in 44 of 59 patients (74.6%). The outcome was recovery in 34 of 59 patients (57.6%), not-recovery in 23 of 59 patients (39.0%), and death in 2 of 59 patients (3.4%). ILD led to discontinuation of avelumab in 7 of 59 patients (11.9%). The time from treatment discontinuation to resolution of ILD (median, range) was 32 (1-391) days.

Table 19 shows the details of patients who experienced serious ILD in clinical studies.[19)]

[19)] Includes clinical studies other than Studies 003, 002, and 001 (Study B9991001 in patients with urothelial carcinoma [avelumab monotherapy], Study B9991002 [combination therapy of avelumab and axitinib] and Study B9991003 [combination therapy of avelumab and axitinib] both in patients with renal cell carcinoma, Study B9991004 in patients with advanced solid cancer [combination therapy of avelumab with other drug (utomilumab, PF-04518600, or PD0360324: none approved in Japan)], Study B9991009 in patients with ovarian cancer [combination therapy of avelumab and liposome formulation of doxorubicin hydrochloride], Study B9991005 [combination therapy of avelumab with crizotinib or PF 06463922 (not approved in Japan)], Study EMR100070-004 [avelumab monotherapy], and Study EMR100070-005 [avelumab monotherapy] all in 3 in patients with non-small cell lung cancer (NSCLC), Study EMR100070-007 [avelumab monotherapy] in patients with gastric cancer, and Study EMR100070-008 in patients with gastric cancer or oesophageal cancer [avelumab monotherapy]).

Table 19. Patients who experienced serious ILD

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Timing of occurrence (Day)	Causal relationship to avelumab	Outcome
Study 001								
88	Female	10 mg/kg	NSCLC	Acute respiratory failure	4	1	No	Recovered
69	Male	10 mg/kg	NSCLC	ARDS	4	1	Yes	Not recovered
65	Male	10 mg/kg	Urothelial carcinoma	Pneumonitis	3	3	Yes	Not recovered
69	Female	10 mg/kg	NSCLC	Acute respiratory failure	5	7	No	Death
65	Female	10 mg/kg	Urothelial carcinoma	Acute respiratory failure	4	10	No	Unknown
71	Female	10 mg/kg	NSCLC	Radiation pneumonitis	4	11	Yes	Not recovered
66	Male	10 mg/kg	Mesothelioma	Pneumonitis	2	15	Yes	Recovered
74	Male	10 mg/kg	Mesothelioma	Acute respiratory failure	3	16	No	Recovered
32	Female	10 mg/kg	Breast cancer	Pneumonitis	3	20	Yes	Recovered
54	Male	10 mg/kg	Urothelial carcinoma	Pneumonitis	5	20	Yes	Death
51	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Pneumonitis	2	22	Yes	Recovered
37	Female	10 mg/kg	Breast cancer	Pneumonitis	1	31	Yes	Recovered
74	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Pneumonitis	3	39	Yes	Not recovered
63	Female	10 mg/kg	Ovarian cancer	Lung infiltration	3	41	No	Recovered
76	Female	10 mg/kg	NSCLC	Acute respiratory failure	5	46	Yes	Death
51	Female	10 mg/kg	Ovarian cancer	Acute respiratory failure	3	47	No	Recovered
64	Male	10 mg/kg	NSCLC	Pneumonitis	4	51	Yes	Not recovered
49	Male	10 mg/kg	Head and neck cancer	Acute respiratory failure	4	56	No	Recovered
47	Female	10 mg/kg	NSCLC	Acute respiratory failure	3	56	No	Recovered
74	Male	10 mg/kg	NSCLC	Pneumonitis	2	75	Yes	Recovered
63	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Pneumonitis	2	80	No	Not recovered
56	Female	10 mg/kg	Adrenocortical carcinoma	Pneumonitis	3	156	Yes	Recovered
52	Female	10 mg/kg	NSCLC	Acute respiratory failure	4	157	No	Recovered
80	Female	10 mg/kg	NSCLC	Pneumonitis	3	183	Yes	Recovered
				Acute respiratory failure	3	200	Yes	Recovered
49	Female	10 mg/kg	NSCLC	Acute respiratory failure	3	191	No	Recovered
Study B9991004								
50	Male	10 mg/kg	NSCLC	Pneumonitis	Unknown	21	Yes	Recovered
Study B999105								
56	Male	10 mg/kg	NSCLC	Pneumonitis	Unknown	21	Yes	Recovered
77	Male	10 mg/kg	NSCLC	Pneumonitis	Unknown	32	Yes	Recovered
Study B9991009								
56*	Female	10 mg/kg	Ovarian cancer	Pneumonitis	Unknown	35	Yes	Not recovered
Study EMR100070-004								
63*	Male	10 mg/kg	NSCLC	ILD	Unknown	Unknown	Yes	Not recovered
71	Male	10 mg/kg	NSCLC	Acute respiratory failure	Unknown	22	No	Death
53	Female	10 mg/kg	NSCLC	Pneumonitis	Unknown	27	Yes	Recovered
64	Male	10 mg/kg	NSCLC	Pneumonitis	Unknown	28	Yes	Recovered
66	Male	10 mg/kg	NSCLC	ARDS	Unknown	28	No	Not recovered
63	Male	10 mg/kg	NSCLC	Acute respiratory failure	Unknown	35	No	Recovered
59	Male	10 mg/kg	NSCLC	Pneumonitis	Unknown	35	Unknown	Unknown
62*	Male	10 mg/kg	NSCLC	ILD	Unknown	78	Yes	Death
68	Male	10 mg/kg	NSCLC	ILD	Unknown	183	Yes	Recovered
51*	Male	10 mg/kg	NSCLC	ILD	Unknown	255	Yes	Death
Study EMR100070-005								
86	Male	10 mg/kg	NSCLC	Pneumonitis	Unknown	41	Yes	Not recovered
81	Male	10 mg/kg	NSCLC	Pneumonitis	Unknown	53	Yes	Recovered
76	Male	10 mg/kg	NSCLC	Pneumonitis	Unknown	99	Yes	Recovered
Study EMR100070-007								
50	Male	10 mg/kg	Gastric cancer	Pneumonitis	Unknown	30	No	Recovered

* Japanese patient

PMDA's view:

In the Japanese and foreign clinical studies, avelumab-induced ILD occurred, resulting in death in some of the affected patients, warranting caution against ILD in treatment with avelumab. Before treatment with avelumab, patients should be carefully selected by checking for past or current ILD. During the treatment with avelumab, patients should be monitored for occurrence of ILD and, in case of clinical symptoms suggestive of ILD, appropriate measures should be taken. Healthcare professionals should be appropriately cautioned about above using the package insert, etc. Information regarding the measures to be taken in case of ILD recommended in Study 003, such as criteria for suspension or discontinuation of avelumab administration, should be appropriately provided to healthcare professionals using the package insert, etc.

7.R.3.5 Renal disorder

The applicant's explanation on avelumab-induced renal disorder:

As renal disorder, events corresponding to "Acute renal failure (broad SMQ)," "Autoimmune nephritis (PT)," "Lupus nephritis (PT)," "Nephritis haemorrhagic (PT)," "Perinephritis (PT)," or "Tubulointerstitial nephritis and uveitis syndrome (PT)" in MedDRA were tabulated.

Table 20 shows incidences of renal disorder in Study 003.

Table 20. Incidences of renal disorder (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal disorder	9 (10.2)	2 (2.3)	5 (17.2)	1 (3.4)
Blood creatinine increased	5 (5.7)	0	2 (6.9)	0
Acute kidney injury	4 (4.5)	1 (1.1)	2 (6.9)	0
Anuria	1 (1.1)	1 (1.1)	0	0
Renal failure	1 (1.1)	0	0	0
Tubulointerstitial nephritis	1 (1.1)	0	0	0
Autoimmune nephritis	0	0	1 (3.4)	1 (3.4)

In Part A of Study 003, there was no fatal renal disorder. Serious renal disorder was observed in 5 patients (acute kidney injury in 4 patients, tubulointerstitial nephritis in 1 patient). A causal relationship to avelumab could not be ruled out for tubulointerstitial nephritis (1 patient). There was no renal disorder leading to treatment discontinuation.

In Part B of Study 003, there was no renal disorder that was fatal, serious, or led to treatment discontinuation.

In the avelumab (10 mg/kg, Q2W) group of Study 001, renal disorder was observed in 146 of 1650 patients (8.8%). In Study 001, fatal renal disorder was observed in 1 patient (acute kidney injury), but its causal relationship to avelumab was ruled out. In Study 001, serious renal disorder was observed in 28 patients (acute kidney injury in 23 patients, renal failure in 4 patients, prerenal failure in 1 patient). A causal relationship to avelumab could not be ruled out for acute kidney injury (1 patient).

In the avelumab (10 mg/kg, Q2W) group of Study 002, renal disorder was observed in 3 of 40 patients (7.5%). In Study 002, fatal renal disorder was observed in 1 patient (acute kidney injury), and its causal relationship to avelumab could not be ruled out.

PMDA's view:

In the Japanese and foreign clinical studies, avelumab caused serious renal disorders such as acute kidney injury, resulting in death in some of the affected patients, warranting caution against renal disorder in administering avelumab. Therefore, the occurrences of renal disorder in clinical studies, etc. should be confirmed, patients should be monitored for renal function during treatment with avelumab and, if any abnormalities are observed, appropriate measures such as suspension of avelumab administration should be taken. These caution statements should be appropriately provided to healthcare professionals using the package insert, etc.

7.R.3.6 Infusion reaction

The applicant explained avelumab-induced infusion reaction regarding (a) incidence and timing of infusion reaction in clinical studies, (b) control of infusion speed, and (c) premedication, as follows:

As infusion reaction, events corresponding to diagnosis-related infusion reaction[20] or symptom-related infusion reaction[21] were tabulated.

(a) Incidence and timing of infusion reaction in clinical studies

Tables 21 and 22 show the summary of infusion reactions and adverse events observed in Study 003.

Table 21. Summary of infusion reactions (Study 003)

	Number of patients (%)	
	Part A N = 88	Part B N = 29
All adverse events	19 (21.6)	6 (20.7)
Grade ≥3 adverse events	0	0
Adverse events leading to death	0	0
Serious adverse events	1 (1.1)	0
Adverse events leading to treatment discontinuation	0	0
Adverse events leading to treatment suspension*	10 (11.4)	2 (6.9)
Adverse events leading to treatment interruption	10 (11.4)	2 (6.9)
Adverse events leading to reduction of infusion speed	9 (10.2)	1 (3.4)

* Including treatment interruption due to infusion reaction.

Table 22. Incidences of infusion reaction (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion reaction	19 (21.6)	0	6 (20.7)	0
Infusion related reaction	13 (14.8)	0	3 (10.3)	0
Pyrexia	2 (2.3)	0	2 (2.3)	0
Chills	2 (2.3)	0	1 (3.4)	0
Back pain	1 (1.1)	0	0	0
Drug hypersensitivity	1 (1.1)	0	0	0
Hypersensitivity	1 (1.1)	0	0	0
Hypotension	1 (1.1)	0	0	0
Dyspnoea	0	0	1 (3.4)	0
Flushing	0	0	1 (3.4)	0

[20] Among adverse events that correspond to "Infusion related reaction," "Drug hypersensitivity," "Anaphylactic reaction," "Hypersensitivity," or "Type I hypersensitivity" in MedDRA PT, those that occurred during the period from the start of avelumab administration until the next day.

[21] Among adverse events that correspond to "Pyrexia," "Chills," "Flushing," "Hypotension," "Dyspnoea," "Wheezing," "Abdominal pain," or "Urticaria" in MedDRA PT, those that occurred on the day of the start of avelumab administration and resolved within 2 days.

In Part A of Study 003, serious infusion reaction was observed in 1 of 88 patients (1.1%; infusion related reaction, Grade 2), and its causal relationship to avelumab could not be ruled out. The patient recovered from the reaction after interruption of avelumab administration.

In the avelumab (10 mg/kg, Q2W) group of Study 001, infusion reaction was observed in 420 of 1650 patients (25.5%). In Study 001, there was no fatal infusion reaction. In Study 001, serious infusion reaction was observed in 19 patients (infusion related reaction in 14 patients, pyrexia in 3 patients, chills, anaphylactic reaction, type I hypersensitivity, and dyspnoea in 1 patient each [including duplicate counting]), and a causal relationship to avelumab could not be ruled out in any of the affected patients. All patients recovered from the reaction after treatment discontinuation, interruption, or reduction of infusion speed.

In the avelumab (10 mg/kg, Q2W) group of Study 002, infusion reaction was observed in 12 of 40 patients (30.0%). In Study 002, there was no fatal or serious infusion reaction.

Tables 23 and 24 show the incidence of the first-time infusion reaction and the frequency of infusion reaction, classified by the number of doses of avelumab administration, in 157 patients receiving avelumab (10 mg/kg, Q2W) in Studies 003 and 002,[22] both of which were conducted with the identical rules for pre-medication.

Table 23. Incidence of first-time infusion reaction, classified by the number of doses of avelumab administration (Study 003 and Study 002)

Number of doses of avelumab administration	Number of cases	Number of patients (%)
		Patients with the first-time occurrence (all Grades)
1	157	31 (19.7)
2	115	5 (4.3)
3	103	1 (1.0)
≥4	90	0

Table 24. Frequency of infusion reaction (Study 003 and Study 002)

Frequency of infusion reaction	Number of patients (%)
	N = 157
1	32 (20.4)
2	4 (2.5)
3	0
4	0
5	1 (0.6)
≥6	0

(b) Control of infusion speed

In Studies 003, 001, and 002, the protocol was to administer avelumab over ≥60 minutes for the initial dose and, if infusion reaction occurred during avelumab administration, to take the following measures:

- If Grade 1, avelumab administration may be continued at half the normal infusion speed.
- If Grade 2, the avelumab administration should be interrupted. When patient conditions are stabilized (to Grade ≤1), administration should be resumed at half the infusion speed before treatment

[22] Studies 003 and 002 required administration of an antihistamine (diphenhydramine 20-50 mg), an antipyretic analgesic (acetaminophen 650 mg), etc., as a pre-mediation at 30 to 60 minutes before avelumab administration. In Study 001, there was no requirement for pre-medication at the start of the study but, in the seventh amendment of the clinical study protocol ([redacted], 20[redacted]), the same requirement for premedication as that for Study 003 and Study 002 was added.

interruption. If Grade 2 infusion reaction occurs after the resumption of administration, administration should be discontinued, and administration should not be resumed.

- If Grade ≥3, avelumab administration should be discontinued, and administration should not be resumed.

In the Japanese and foreign clinical studies (Part A and Part B of Study 003, Study 001, Study 002), infusion reaction was observed in 457 of 1807 patients (25.3%) receiving avelumab (10 mg/kg, Q2W). In these studies, data were not sufficiently collected after the change in avelumab infusion speed following the occurrence of infusion reaction, but were available from some of the patients and subjected to investigation for the control of avelumab infusion speed.

(i) Grade 1 infusion reaction occurred in 175 of 1807 patients (9.7%), and the avelumab infusion speed was reduced by half in at least 24 of them. (ii) Grade 2 infusion reaction occurred in 270 of 1807 patients (14.9%), and avelumab injection was interrupted in at least 137 of them and the infusion speed was reduced by half in at least 100 of them. As a result, it was unclear whether infusion reaction recurred in any of patients with interrupted administration or reduced infusion speed. However, it was confirmed that the infusion reaction resolved eventually.

(c) Premedication

The protocol of Study 003 required administration of an antihistamine (diphenhydramine 20-50 mg), antipyretic analgesic (acetaminophen 650 mg), etc., at 30 to 60 minutes before avelumab administration.[23)]

The infusion reaction-preventing effect of the pre-medication was as follows. Among 1738 patients receiving avelumab (10 mg/kg) in Study 001 or 003, infusion reaction occurred after the first dose of avelumab in 325 of 1615 patients (20.1%) with pre-medication and in 24 of 123 patients (19.5%) without pre-medication, showing no clear difference. Grade ≥3 infusion reaction was observed in 5 of 1615 patients (0.3%) with pre-medication and in 2 of 123 patients (1.6%) without pre-medication, showing a tendency of a lower incidence in patients with pre-medication.

PMDA's view:

In Study 003 and other clinical studies, serious infusion reaction was induced by avelumab even in patients who had received pre-medication such as antihistamine and antipyretic analgesic, warranting caution against infusion reaction in treatment with avelumab. Also, there were patients who experienced infusion reaction only after multiple cycles of avelumab and patients who had infusion reaction multiple times. Information on infusion reaction in clinical studies, including the above incidences, should be provided appropriately to healthcare professionals using the package insert, etc.

Information regarding the speed of avelumab administration and the type of the pre-medication used in Study 003 should be provided appropriately in the Precautions for Dosage and Administration section to raise caution.

[23)] The protocol permitted changing the actual method for the pre-medication according to the standard administration method or the guideline established at each study center. Administration of corticosteroid as a pre-medication was prohibited.

7.R.3.7 Gastro-intestinal disorder

The applicant's explanation avelumab-induced gastro-intestinal disorder:

As gastro-intestinal disorder, events corresponding to "Gastrointestinal conditions not elsewhere classified (NEC) (high level group term [HLGT])," "Gastrointestinal haemorrhages NEC (HLGT)," "Gastrointestinal infections (HLGT)," "Gastrointestinal inflammatory conditions (HLGT)," "Gastrointestinal motility and defaecation conditions (HLGT)," "Gastrointestinal signs and symptoms (HLGT)," "Gastrointestinal stenosis and obstruction (HLGT)," "Gastrointestinal ulceration and perforation (HLGT)," or "Gastrointestinal vascular conditions (HLGT)" in MedDRA were tabulated.

Table 25 shows the incidences of gastro-intestinal disorder in Study 003.

Table 25. Gastro-intestinal disorder reported by ≥2 patients in either part (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Gastro-intestinal disorder	49 (55.7)	7 (8.0)	15 (51.7)	2 (6.9)
Diarrhoea	20 (22.7)	0	3 (10.3)	0
Nausea	19 (21.6)	0	3 (10.3)	0
Constipation	15 (17.0)	1 (1.1)	8 (27.6)	0
Abdominal pain	11 (12.5)	2 (2.3)	4 (13.8)	0
Vomiting	11 (12.5)	0	2 (6.9)	1 (3.4)
Abdominal discomfort	4 (4.5)	0	0	0
Abdominal pain upper	3 (3.4)	0	0	0
Ileus	2 (2.3)	2 (2.3)	0	0
Gastric haemorrhage	2 (2.3)	1 (1.1)	0	0
Gastrooesophageal reflux disease	2 (2.3)	0	0	0
Flatulence	2 (2.3)	0	0	0

In Part A of study 003, fatal gastro-intestinal disorder occurred in 1 patient (ileus), but its causal relationship to avelumab was ruled out. Serious gastro-intestinal disorder was observed in 6 patients (ileus and abdominal pain in 2 patients each, gastrointestinal haemorrhage, gastric haemorrhage, enterocolitis, faecaloma, and oesophageal spasm in 1 patient each [including duplicate counting]). A causal relationship to avelumab could not be ruled out for ileus/enterocolitis (1 patient). Gastro-intestinal disorder leading to treatment discontinuation was observed in 1 patient (ileus).

In Part B of Study 003, fatal gastro-intestinal disorder occurred in 1 patient (large intestine perforation), but its causal relationship to avelumab was ruled out. Serious gastro-intestinal disorder was observed in 2 patients (large intestine perforation, abdominal pain, and vomiting in 1 patient each [including duplicate counting]), but their causal relationship to avelumab was ruled out. There was no gastro-intestinal disorder leading to treatment discontinuation.

In the avelumab (10 mg/kg, Q2W) group of Study 001, gastro-intestinal disorder was observed in 1001 of 1650 patients (60.7%). In Study 001, fatal gastro-intestinal disorder was observed in 7 patients (gastrointestinal haemorrhage in 3 patients, abdominal pain, dysphagia, intestinal obstruction, and intestinal perforation in 1 patient each), but a causal relationship to avelumab was ruled out in all affected patients. In Study 001, serious gastro-intestinal disorder was observed in 154 patients (events observed in multiple patients; abdominal pain in 39 patients, vomiting in 27 patients, nausea in 22 patients, small intestinal obstruction in 20 patients, dysphagia in 14 patients, constipation and diarrhoea in 12 patients each, gastrointestinal haemorrhage in 10 patients, intestinal obstruction and obstruction gastric in 7 patients each, ileus and colitis in 4 patients each, abdominal distension, abdominal pain lower, gastritis,

and haematemesis in 3 patients each, large intestine perforation, abdominal pain upper, duodenal obstruction, large intestinal obstruction, oesophagitis, and subileus in 2 patients each [including duplicate counting]). Of these, a causal relationship to avelumab could not be ruled out for vomiting (5 patients), colitis (3 patients), nausea, abdominal pain, and diarrhoea (2 patients each), abdominal distension, gastric haemorrhage, and oesophageal achalasia (1 patient each) (including duplicate counting).

In the avelumab (10 mg/kg, Q2W) group of Study 002, gastro-intestinal disorder was observed in 21 of 40 patients (52.5%). In Study 002, there was no fatal gastro-intestinal disorder. In Study 002, serious gastro-intestinal disorder was observed in 5 patients (ileus in 2 patients, intestinal obstruction, gastric haemorrhage, and upper gastrointestinal haemorrhage in 1 patient each). A causal relationship to avelumab was ruled out in all of the affected patients.

PMDA's view:
In the Japanese and foreign clinical studies, serious gastro-intestinal disorders such as ileus for which a causal relationship to avelumab could not be ruled out were observed, warranting caution against gastro-intestinal disorder in treatment with avelumab. As for colitis and diarrhoea, serious cases were observed also with nivolumab and pembrolizumab, drugs that inhibit the binding of PD-L1 and PD-1 as does avelumab. In addition, the protocols of the clinical studies of avelumab stipulated special criteria for dose adjustment and measures to address colitis and diarrhoea, thereby strictly controlling the safety. Thus, particular caution is required in treatment with avelumab. Information on the measures to be taken, such as criteria for suspension or discontinuation of avelumab administration, in case of colitis or diarrhoea recommended in Study 003 should be appropriately provided to healthcare professionals using the package insert, etc.

7.R.3.8 Endocrine dysfunction

The applicant explained each of avelumab-induced endocrine dysfunctions ([a] thyroid dysfunction, [b] pituitary dysfunction, [c] adrenal dysfunction, and [d] type 1 diabetes mellitus) as follows:
As endocrine dysfunction, events corresponding to "Endocrine disorders (system organ class [SOC]) (except Diabetic complications [HLGT] and Neoplastic and ectopic endocrinopathies [HLGT])," "Type 1 diabetes mellitus (PT)," "Latent autoimmune diabetes in adults (PT)," "Diabetic ketoacidosis (PT)," "Diabetes mellitus (PT)," or "Hyperglycaemia (PT)" in MedDRA were tabulated.

(a) Thyroid dysfunction:
Table 26 shows the incidences of thyroid dysfunction in Study 003.

Table 26. Incidences of thyroid dysfunction (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hypothyroidism	5 (5.7)	1 (1.1)	1 (3.4)	0
Hyperthyroidism	2 (2.3)	0	0	0

In Part A of Study 003, there was no fatal thyroid dysfunction. Serious thyroid dysfunction was observed in 1 patient (hypothyroidism), and its causal relationship to avelumab could not be ruled out. There was no thyroid dysfunction leading to treatment discontinuation.

In Part B of Study 003, there was no thyroid dysfunction that was fatal, serious, or led to treatment discontinuation.

Table 27 shows the details of patients who had serious thyroid dysfunction in clinical studies.[19)]

Table 27. Patients who had serious thyroid dysfunction

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 003								
74	Male	10 mg/kg	MCC	Hypothyroidism	Unknown	247	Yes	Recovered
Study 001								
67	Male	10 mg/kg	Urothelial carcinoma	Hyperthyroidism	2	43	Yes	Recovered
65	Male	10 mg/kg	Urothelial carcinoma	Thyroiditis acute	1	43	Yes	Recovered
33	Female	10 mg/kg	Adrenocortical carcinoma	Thyroiditis	1	58	Yes	Recovered
53	Female	10 mg/kg	Gastric cancer or oesophageal carcinoma	Hypothyroidism	3	87	Yes	Not recovered
75	Female	10 mg/kg	Urothelial carcinoma	Hypothyroidism	2	98	Yes	Recovered
73	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Hypothyroidism	1	230	Yes	Recovered
Study B9991003								
65	Female	10 mg/kg	Renal cell carcinoma	Hyperthyroidism	Unknown	83	No	Recovered
Study B9991009								
41	Female	10 mg/kg	Ovarian cancer	Basedow's disease	Unknown	32	Yes	Recovered

(b) Pituitary dysfunction

Table 28 shows the details of patients who had pituitary dysfunction in clinical studies.[19)]

Table 28. Patients who had pituitary dysfunction

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Seriousness	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 001									
67	Female	10 mg/kg	Ovarian cancer	Hypopituitarism	2	Non-serious	492	Yes	Not recovered

(c) Adrenal dysfunction

Table 29 shows the details of patients who had adrenal dysfunction in clinical studies.[19)]

Table 29. Patients who had adrenal dysfunction

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Seriousness	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 001									
59	Female	10 mg/kg	Adrenocortical carcinoma	Adrenocortical insufficiency acute	2	Serious	1	No	Recovered
				Adrenal insufficiency	2	Non-serious	2	Yes	Not recovered
49	Female	10 mg/kg	Adrenocortical carcinoma	Adrenal insufficiency	3	Serious	20	No	Recovered
68	Male	10 mg/kg	Urothelial carcinoma	Adrenal insufficiency	3	Serious	29	No	Recovered
54	Female	10 mg/kg	Adrenocortical carcinoma	Adrenal insufficiency	3	Serious	40	Yes	Recovered
60	Female	10 mg/kg	NSCLC	Adrenal insufficiency	2	Non-serious	46	Yes	Not recovered
59	Male	10 mg/kg	NSCLC	Adrenal insufficiency	2	Non-serious	56	No	Not recovered
52	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Adrenal insufficiency	2	Non-serious	57	Yes	Not recovered
33	Female	10 mg/kg	Adrenocortical carcinoma	Adrenal insufficiency	2	Non-serious	60	No	Not recovered
49	Male	10 mg/kg	Adrenocortical carcinoma	Adrenal insufficiency	2	Serious	85	Yes	Recovered
69	Female	10 mg/kg	NSCLC	Adrenal insufficiency	2	Non-serious	99	No	Not recovered
75	Male	10 mg/kg	NSCLC	Adrenal insufficiency	1	Non-serious	168	Yes	Not recovered
59	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Adrenal mass	1	Non-serious	169	No	Not recovered
49	Female	10 mg/kg	NSCLC	Adrenal insufficiency	3	Serious	191	Yes	Recovered
68	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Adrenal insufficiency	3	Serious	211	Yes	Not recovered
60	Female	10 mg/kg	Adrenocortical carcinoma	Adrenal insufficiency	2	Non-serious	220	Yes	Recovered
73	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Adrenal insufficiency	2	Serious	230	Yes	Recovered
47	Male	10 mg/kg	Urothelial carcinoma	Adrenal insufficiency	3	Serious	379	Yes	Not recovered
Study B9991002									
70	Female	10 mg/kg	Renal cell carcinoma	Adrenal insufficiency	Unknown	Serious	189	Yes	Unknown
Study B9991003									
63	Female	10 mg/kg	Renal cell carcinoma	Adrenal insufficiency	Unknown	Serious	53	No	Not recovered
65*	Female	10 mg/kg	Renal cell carcinoma	Primary adrenal insufficiency	Unknown	Serious	83	Yes	Recovered
Study EMR100070-004									
67	Male	10 mg/kg	NSCLC	Adrenal insufficiency	Unknown	Serious	20	Yes	Recovered

* Japanese patient

(d) Type 1 diabetes mellitus

Table 30 shows the details of patients[24)] who experienced type 1 diabetes mellitus in clinical studies.[19)]

[24)] Including patient who, although not reported as type 1 diabetes mellitus, was diagnosed with newly developed type 1 diabetes based on medical evaluation (presence/absence of ketoacidosis, presence/absence of low insulin symptoms, necessity of insulin therapy).

Table 30. Patients who had type 1 diabetes mellitus

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Seriousness	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 003									
74[*1]	Male	10 mg/kg	MCC	Type 1 diabetes mellitus	1	Non-serious	259	Yes	Not recovered
Study 001									
69[*2]	Female	10 mg/kg	Ovarian cancer	Diabetes mellitus	3	Serious	99	Yes	Not recovered
60[*3]	Female	10 mg/kg	Mesothelioma	Hyperglycaemia	3	Serious	568	Yes	Recovered
Study B9991004									
50[*4]	Male	10 mg/kg	Head and neck cancer	Diabetes mellitus	Unknown	Serious	27	Yes	Not recovered
				Diabetic ketoacidosis	Unknown	Serious	30	Yes	Recovered

[*1] Japanese patient; [*2] Had ketoacidosis and required long-term insulin therapy; [*3] Had low insulin level, requiring long-term insulin therapy; [*4] Had ketoacidosis and required long-term insulin therapy.

PMDA's view:

In the Japanese and foreign clinical studies, avelumab caused serious thyroid dysfunction, adrenal dysfunction, and type 1 diabetes mellitus, warranting caution against these adverse events in treatment with avelumab. Therefore, healthcare professionals should be informed of the incidences of these adverse events in clinical studies using the package insert, etc., and cautioned to appropriately monitor patients during treatment with avelumab and, if any abnormalities are observed, take appropriate measures such as suspension or discontinuation of avelumab administration. Also, healthcare professionals should be appropriately informed of the recommended measures to be taken in case of these adverse events, using materials.

Pituitary dysfunction does not require any particular caution currently because of the scarcity of occurrences in the Japanese and foreign clinical studies. However, information should be collected continuously after the market launch, and when new information becomes available, the information should be appropriately provided to healthcare professionals.

7.R.3.9 Nerve disorder

The applicant's explanation on avelumab-induced nerve disorder:

As nerve disorder, events corresponding to "Guillain-Barre syndrome (narrow SMQ)," "Peripheral neuropathy (narrow SMQ)," "Nervous system disorders (SOC)," "Encephalopathy (PT)," "Myasthenia gravis and related conditions (high level term [HLT])," "Noninfectious encephalitis (narrow SMQ)," or "Noninfectious meningitis (narrow SMQ)" in MedDRA were tabulated.

Table 31 shows the incidences of nerve disorder in Study 003.

Table 31. Nerve disorder reported by ≥2 patients in either part (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Nerve disorder	33 (37.5)	1 (1.1)	5 (17.2)	1 (3.4)
Dizziness	12 (13.6)	0	2 (6.9)	0
Headache	9 (10.2)	0	0	0
Hypoaesthesia	4 (4.5)	0	0	0
Dysgeusia	3 (3.4)	0	0	0
Neuropathy peripheral	3 (3.4)	0	0	0
Paraesthesia	2 (2.3)	0	0	0
Somnolence	2 (2.3)	0	0	0

In Part A of Study 003, there was no fatal nerve disorder. Serious nerve disorder was observed in 1 patient (encephalopathy), but its causal relationship to avelumab was ruled out. There was no nerve disorder leading to treatment discontinuation.

In Part B of Study 003, fatal nerve disorder was observed in 1 patient (encephalopathy, serious), but its causal relationship to avelumab was ruled out. There was no nerve disorder leading to treatment discontinuation.

In the avelumab (10 mg/kg, Q2W) group of Study 001, nerve disorder was observed in 534 of 1650 patients (29.6%). In Study 001, fatal nerve disorder was observed in 4 patients (brain injury, cerebrovascular accident, haemorrhage intracranial, and subarachnoid haemorrhage in 1 patient each), but a causal relationship to avelumab was ruled out in all of these patients. Serious nerve disorder was observed in 54 patients. (events observed in multiple patients; cerebrovascular accident in 5 patients, seizure in 4 patients, haemorrhage intracranial, headache, spinal cord compression, syncope, and transient ischaemic attack in 3 patients each, dizziness, hemiparesis, hypoaesthesia, subarachnoid haemorrhage, and vocal cord paralysis in 2 patients each). Of these, a causal relationship to avelumab could not be ruled out for posterior reversible encephalopathy syndrome, hypoaesthesia, neuropathy peripheral, embolic stroke, monoplegia, syncope, seizure, dizziness, and Guillain-Barre syndrome (1 patient each).

In the avelumab (10 mg/kg, Q2W) group of Study 002, nerve disorder was observed in 8 of 40 patients (20.0%). In Study 002, no fatal or serious nerve disorder was observed.

Table 32 shows the details of patients who had Guillain-Barre syndrome in clinical studies.[19)]

Table 32. Patients who had Guillain-Barre syndrome

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	CTCAE Grade	Seriousness	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 001									
80	Male	10 mg/kg	Urothelial carcinoma	Guillain-Barre syndrome	3	Serious	70	Yes	Not recovered

Table 33 shows the details of patients who had serious encephalitis/meningitis in clinical studies.[19).]

Table 33. Patients who had serious encephalitis/meningitis

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	CTCAE Grade	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study B99911009								
68	Female	10 mg/kg	Ovarian cancer	Meningitis	Unknown	48	No	Death
Study EMR100070-004								
57	Female	10 mg/kg	NSCLC	Encephalitis	Unknown	247	Yes	Recovered

In clinical studies,[19)] there was no patient who had myasthenia gravis.

PMDA's view:

In the Japanese and foreign clinical studies, serious nerve disorders such as Guillain-Barre syndrome and encephalitis/meningitis for which a causal relationship to avelumab could not be ruled out were observed. Serious nerve disorder was observed also with nivolumab and pembrolizumab, drugs that inhibit the binding of PD-L1 and PD-1 as does avelumab, warranting caution against nerve disorder in treatment with avelumab. Information on the incidences of these adverse events in clinical studies should be provided to healthcare professionals using the package insert, etc., for raising caution.

7.R.3.10 Cardiac disorder

The applicant's explanation on avelumab-induced cardiac disorder:

As cardiac disorder, events corresponding to "Cardiomyopathy (narrow SMQ)," "Cardiac failure (narrow SMQ)," "Cardiac arrhythmias (HLGT)," "Myocarditis (PT)," or "Autoimmune myocarditis (PT)" in MedDRA were tabulated.

Table 34 shows the incidences of cardiac disorder in Study 003.

Table 34. Cardiac disorder reported by ≥2 patients in either part (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorder	15 (17.0)	2 (2.3)	2 (6.9)	0
Tachycardia	3 (3.4)	0	1 (3.4)	0
Sinus bradycardia	3 (3.4)	0	0	0
Atrial flutter	2 (2.3)	1 (1.1)	0	0
Atrial fibrillation	2 (2.3)	0	0	0
Sinus tachycardia	1 (1.1)	1 (1.1)	1 (3.4)	0
Bradycardia	1 (1.1)	0	0	0
Cardiac failure	1 (1.1)	0	0	0
Supraventricular extrasystoles	1 (1.1)	0	0	0
Tachyarrhythmia	1 (1.1)	0	0	0

In Part A of Study 003, no fatal cardiac disorder was observed. Serious cardiac disorder was observed in 2 patients (tachycardia and atrial flutter in 1 patient each), but a causal relationship to avelumab was ruled out in both patients. There was no cardiac disorder leading to treatment discontinuation.

In Part B of study 003, there was no cardiac disorder that was fatal, serious, or led to treatment discontinuation.

In the avelumab (10 mg/kg, Q2W) group of Study 001, cardiac disorder was observed in 140 of 1650 patients (8.5%). In Study 001, fatal cardiac disorder was observed in 5 patients (cardiac arrest in 3

patients, cardiac failure and cardio-respiratory arrest in 1 patient each), but a causal relationship to avelumab was ruled out in all of these patients. In Study 001, serious cardiac disorder was observed in 27 patients (events observed in multiple patients; atrial fibrillation in 10 patients, cardiac arrest in 4 patients, tachycardia in 3 patients, cardiac failure congestive, and myocarditis in 2 patients each [including duplicate counting]). Of these, a causal relationship to avelumab could not be ruled out for cardiac arrest, tachycardia, and myocarditis (1 patient each).

In the avelumab (10 mg/kg, Q2W) group of Study 002, cardiac disorder was observed in 1 of 40 patients (2.5%). In Study 002, there was no fatal or serious cardiac disorder.

Table 35 shows the details of patients who had myocarditis in clinical studies.[19)]

Table 35. Patients who had myocarditis

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Seriousness	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 001									
46	Female	20 mg/kg	Thymoma	Myocarditis	3	Serious	18	Yes	Recovered
63	Male	10 mg/kg	Head and neck cancer	Myocarditis	2	Serious	207	No	Recovered
Study EMR100070-004									
55	Male	10 mg/kg	NSCLC	Autoimmune myocarditis	Unknown	Serious	15	Yes	Death
Study B9991002									
69	Male	10 mg/kg	Renal cell carcinoma	Myocarditis	Unknown	Serious	20	Yes	Death
Study B9991003									
55	Male	10 mg/kg	Renal cell carcinoma	Myocarditis	Unknown	Serious	29	Yes	Recovered

PMDA's view:

There were fatal or serious cardiac disorders for which a causal relationship to avelumab could not be ruled out in the Japanese and foreign clinical studies, warranting caution against cardiac disorder in treatment with avelumab. Serious myocarditis was observed also with nivolumab and pembrolizumab, drugs that inhibit the binding of PD-L1 and PD-1 as does avelumab, and the adverse event caused death in multiple patients in the clinical studies on avelumab, requiring particular caution in treatment with avelumab. Information on the recommended measures to be taken in case of myocarditis should be appropriately provided to healthcare professionals using the package insert, etc.

7.R.3.11 Myositis/rhabdomyolysis

The applicant's explanation on avelumab-induced myositis/rhabdomyolysis:

As myositis/rhabdomyolysis, events corresponding to "Rhabdomyolysis/myopathy (narrow SMQ)," "Myositis (PT)," or "Blood creatine phosphokinase increased (PT)" in MedDRA were tabulated.

Table 36 shows the incidences of myositis/rhabdomyolysis in Study 003.

Table 36. Incidences of myositis/rhabdomyolysis (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myositis/rhabdomyolysis	7 (8.0)	2 (2.3)	1 (3.4)	0
Blood CPK increased	6 (6.8)	2 (2.3)	1 (3.4)	0
Rhabdomyolysis	1 (1.1)	0	0	0

In Part A of Study 003, there was no fatal or serious myositis/rhabdomyolysis. Myositis/rhabdomyolysis leading to treatment discontinuation was observed in 1 patient (blood CPK increased).

In Part B of Study 003, there was no myositis/rhabdomyolysis that was fatal, serious, or led to treatment discontinuation.

In the avelumab (10 mg/kg, Q2W) group of Study 001, myositis/rhabdomyolysis was observed in 24 of 1650 patients (1.5%). In Study 001, there was no fatal myositis/rhabdomyolysis. In Study 001, serious myositis/rhabdomyolysis was observed in 4 patients (blood CPK increased and myositis in 2 patients each), and a causal relationship to avelumab was not ruled out in any of these patients.

In the avelumab (10 mg/kg, Q2W) group of Study 002, myositis/rhabdomyolysis was observed in 2 of 40 patients (0.5%). In Study 002, there was no fatal or serious myositis/rhabdomyolysis.

Table 37 shows the details of patients who had rhabdomyolysis in clinical studies.[19)]

Table 37. Patients who had rhabdomyolysis

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Seriousness	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 003									
76	Male	10 mg/kg	MCC	Rhabdomyolysis	2	Non-serious	52	No	Not recovered

PMDA's view:
In the Japanese and foreign clinical studies, serious myositis for which a causal relationship to avelumab could not be ruled out was observed. In addition, serious myositis/rhabdomyolysis was observed also with nivolumab and pembrolizumab, drugs that inhibit the binding of PD-L1 and PD-1 as does avelumab. Therefore, caution should be exercised against myositis/rhabdomyolysis in treatment with avelumab. Information on the incidences of myositis/rhabdomyolysis in clinical studies should be appropriately provided to healthcare professionals using the package insert, etc.

7.R.3.12 Other

Based on the mechanism of action of avelumab and on the incidences of adverse events observed with nivolumab and pembrolizumab, drugs that inhibit the binding of PD-L1 and PD-1 as does avelumab, the applicant explained (a) eye disorder, (b) skin disorder, (c) venous thromboembolism, and (d) pancreatitis, which are adverse events supposedly induced by avelumab, as follows:

(a) Eye disorder

As eye disorder, events corresponding to "Eye disorders (SOC)" in MedDRA were tabulated.

Table 38 shows the incidences of eye disorder in Study 003.

Table 38. Incidences of eye disorder (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorder	12 (13.6)	2 (2.3)	2 (6.9)	0
Vision blurred	4 (4.5)	0	1 (3.4)	0
Eye pruritus	2 (2.3)	0	0	0
Glaucoma	1 (1.1)	1 (1.1)	0	0
Eye inflammation	1 (1.1)	1 (1.1)	0	0
Eyelid function disorder	1 (1.1)	1 (1.1)	0	0
Retinal artery occlusion	1 (1.1)	1 (1.1)	0	0
Lacrimation increased	1 (1.1)	0	1 (3.4)	0
Dry eye	1 (1.1)	0	0	0
Diplopia	1 (1.1)	0	0	0
Eye pain	1 (1.1)	0	0	0
Eye irritation	1 (1.1)	0	0	0
Keratitis	1 (1.1)	0	0	0
Photophobia	1 (1.1)	0	0	0
Eye allergy	1 (1.1)	0	0	0
Ocular hyperaemia	1 (1.1)	0	0	0
Ulcerative keratitis	1 (1.1)	0	0	0
Vitreous haemorrhage	0	0	1 (3.4)	0

In Part A of Study 003, no fatal eye disorder was observed. Serious eye disorder was observed in 2 patients (eyelid function disorder, glaucoma, retinal artery occlusion, and ulcerative keratitis in 1 patient each [including duplicate counting]), but a causal relationship to avelumab was ruled out in all patients. There was no eye disorder leading to treatment discontinuation.

In Part B of Study 003, there was no eye disorder that was fatal, serious, or led to treatment discontinuation.

In the avelumab (10 mg/kg, Q2W) group of Study 001, eye disorder was observed in 100 of 1650 patients (6.1%). In Study 001, there was no fatal eye disorder. Serious eye disorder was observed in 5 patients (eye pain, ocular retrobulbar haemorrhage, retinopathy hypertensive, vision blurred, and visual impairment in 1 patient each). A causal relationship to avelumab could not be ruled out for vision blurred (1 patient).

In the avelumab (10 mg/kg, Q2W) group of Study 002, eye disorder was observed in 1 of 40 patients (2.5%). In Study 002, there was no fatal or serious eye disorder.

Table 39 shows the details of patients who had uveitis in clinical studies.

Table 39. Patients who had uveitis

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Seriousness	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 001									
84	Male	10 mg/kg	Urothelial carcinoma	Uveitis	2	Non-serious	26	Yes	Not recovered
70	Female	10 mg/kg	NSCLC	Iritis	2	Non-serious	26	Yes	Recovered

(b) Skin disorder

As skin disorder, events corresponding to "Severe cutaneous adverse reactions (narrow SMQ)," "Epidermal and dermal conditions (HLGT)," "Pigmentation disorders (HLGT)," "Psoriasis (PT)," or "Palmar-plantar erythrodysaesthesia syndrome (PT)" in MedDRA were tabulated.

Table 40 shows the incidences of skin disorder in Study 003.

Table 40. Incidences of skin disorder (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorder	28 (31.8)	0	7 (24.1)	0
Rash	12 (13.6)	0	1 (3.4)	0
Pruritus	9 (10.2)	0	2 (6.9)	0
Dry skin	5 (5.7)	0	3 (10.3)	0
Rash maculo-papular	5 (5.7)	0	1 (3.4)	0
Pruritus generalised	1 (1.1)	0	1 (3.4)	0
Eczema	1 (1.1)	0	0	0
Dermatitis	1 (1.1)	0	0	0
Dermatitis contact	1 (1.1)	0	0	0
Seborrhoeic dermatitis	1 (1.1)	0	0	0
Dermatitis bullous	1 (1.1)	0	0	0
Skin disorder	1 (1.1)	0	0	0
Skin plaque	1 (1.1)	0	0	0
Skin lesion	0	0	1 (3.4)	0

In Parts A and B of Study 003, there was no skin disorder that was fatal, serious, or led to treatment discontinuation.

In the avelumab (10 mg/kg, Q2W) group of Study 001, skin disorder was observed in 370 of 1650 patients (22.4%). In Study 001, there was no fatal skin disorder. In Study 001, serious skin disorder was observed in 3 patients (psoriasis, rash generalised, and rash maculo-papular in 1 patient each). A causal relationship to avelumab could not be ruled out for psoriasis and rash generalised (1 patient each).
In the avelumab (10 mg/kg, Q2W) group of Study 002, skin disorder was observed in 16 of 40 patients (40.0%). In Study 002, there was no fatal or serious skin disorder.

In clinical studies other than those mentioned above, there was no fatal skin disorder, while serious skin disorder for which a causal relationship to avelumab could not be ruled out was observed in 3 patients (rash in 2 patients, dermatitis exfoliative in 1 patient).

(c) Venous thromboembolism

As venous thromboembolism, events corresponding to "Embolic and thrombotic events, venous (narrow SMQ)" in MedDRA were tabulated.

Table 41 shows the incidences of venous thromboembolism in Study 003.

Table 41. Incidences of venous thromboembolism (Study 003)

PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Venous thromboembolism	5 (5.7)	2 (2.3)	3 (10.3)	2 (6.9)
Deep vein thrombosis	2 (2.3)	1 (1.1)	1 (3.4)	0
Superior vena caval thrombosis	1 (1.1)	1 (1.1)	3 (10.3)	0
Jugular vein thrombosis	1 (1.1)	0	2 (6.9)	0
Thrombophlebitis superficial	1 (1.1)	0	1 (3.4)	0
Pulmonary embolism	0	0	2 (6.9)	2 (6.9)
Venous thrombosis	0	0	1 (3.4)	0

In Part A of Study 003, there was no fatal venous thromboembolism. Serious venous thromboembolism was observed in 2 patients (deep vein thrombosis and superior vena cava syndrome in 1 patient each), but a causal relationship to avelumab was ruled out in all of the patients. There was no venous thromboembolism leading to treatment discontinuation.

In Part B of Study 003, there was no fatal venous thromboembolism. Serious venous thromboembolism was observed in 1 patient (pulmonary embolism), but its causal relationship to avelumab was ruled out. There was no venous thromboembolism leading to treatment discontinuation.

In the avelumab (10 mg/kg, Q2W) group of Study 001, venous thromboembolism was observed in 62 of 1650 patients (3.8%). In Study 001, fatal venous thromboembolism was observed in 1 patient (pulmonary embolism), but its causal relationship to avelumab was ruled out. Serious venous thromboembolism was observed in 18 patients (pulmonary embolism in 10 patients, deep vein thrombosis in 7 patients, jugular vein thrombosis in 2 patients, subclavian vein thrombosis in 1 patient [including duplicate counting]), but a causal relationship to avelumab was ruled out in all of the patients.

In Study 002, no venous thromboembolism was observed.

In clinical studies other than those mentioned above, fatal venous thromboembolism was observed in 2 patients (pulmonary embolism and superior vena cava syndrome in 1 patient each), but a causal relationship to avelumab was ruled out in all of the patients. Serious venous thromboembolism for which a causal relationship to avelumab could not be ruled out was observed in 1 patient (venous thrombosis limb).

(d) Pancreatitis

As pancreatitis, events corresponding to “Acute pancreatitis (narrow SMQ)” or “Autoimmune pancreatitis (PT)” in MedDRA were tabulated.

Table 42 shows the details of patients who had pancreatitis in clinical studies.[19)]

Table 42. Patients who had pancreatitis

Age	Sex	Avelumab dose per administration	Primary disease	Adverse event (MedDRA PT)	Grade	Seriousness	Timing of occurrence (day)	Causal relationship to avelumab	Outcome
Study 001									
60	Male	10 mg/kg	Gastric cancer or oesophageal carcinoma	Pancreatitis	2	Non-serious	51	No	Not recovered
66	Male	10 mg/kg	Urothelial carcinoma	Pancreatitis acute	3	Non-serious	148	No	Recovered
Study B9991003									
68	Male	10 mg/kg	Renal cell carcinoma	Autoimmune pancreatitis	Unknown	Serious	117	Yes	Recovered

PMDA's view:

In the Japanese and foreign clinical studies, there were cases of eye disorder, skin disorder, venous thromboembolism, and pancreatitis for which a causal relationship to avelumab could not be ruled out. However, because of the limited number of patients who had these adverse events, it is practically impossible currently to draw a conclusion on a causal relationship of these adverse events to avelumab. Although it is not necessary to pay any specific attention to these events at this moment, information should be collected continuously after the market launch, and when new information becomes available, the information should be appropriately provided to healthcare professionals.

7.R.4 Clinical positioning and indications

The proposed indication for avelumab was "unresectable Merkel cell carcinoma," and the Precautions for Indications section contained the following requirements:

- Eligible patients should be selected based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including the efficacy and safety of avelumab.

As a result of the review of Sections "7.R.2 Efficacy" and "7.R.3 Safety" and of the review described below, PMDA concluded that the package insert should include, in the "Clinical Studies" section, the detailed information on patients enrolled in Study 003, and that avelumab should be indicated for "unresectable Merkel cell carcinoma," as proposed by the applicant. PMDA also concluded that it is unnecessary to include the above proposed precaution in the Precautions for Indications section.

7.R.4.1 Target patients for treatment with avelumab

In Japanese and foreign clinical practice guidelines and representative clinical oncology textbooks, descriptions on avelumab in the treatment of MCC are as shown below.

- National Cancer Institute-Physician Data Query (NCI-PDQ) (published September 13, 2016): Patients with metastatic MCC are recommended to participate in clinical studies on avelumab, etc.

The applicant's explanation on the clinical positioning and the indication of avelumab:

Since results of Study 003 suggest clinical usefulness of avelumab in patients with metastatic MCC regardless of history of chemotherapy, avelumab is positioned as a treatment option for the patient group enrolled in Study 003, and also treatment with avelumab is acceptable to patients with nonmetastatic MCC, the patient group not investigated in Study 003, taking account of the following:

- Avelumab binds to the extracellular domain of PD-L1, thereby inhibiting the binding of PD-L1 with PD-1, which is considered to enhance immune activity of cancer antigen-specific T cells against tumors, leading to suppression of tumor growth [see Section "3.R.1 Mechanism of action of avelumab and its efficacy against MCC"]. Avelumab is thus expected to be effective regardless of the presence or absence of metastasis.
- In clinical practice, chemotherapy is often given to patients with nonmetastatic MCC in a similar manner as to patients with metastatic MCC (National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Merkel cell carcinoma [NCCN Guideline] [v. 1.2017]).

Based on the above, the proposed indication for avelumab was specified "Unresectable Merkel cell carcinoma." In order to provide accurate information on patients enrolled in Study 003, the caution statement is included in the Precautions for Indications section, requiring eligible patients to be selected based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including the efficacy and safety of avelumab.

PMDA's view:
PMDA generally accepted the above explanation of the applicant and concluded that avelumab should be indicated for "Unresectable Merkel cell carcinoma," as proposed by the applicant. Also, the following caution statement proposed in the Precautions for Indications section at the application is unnecessary because it does not state any specific cautions.

- Eligible patients should be selected based on a good understanding of the study results in the "Clinical Studies" section of the package insert, including the efficacy and safety of avelumab.

7.R.4.2 Efficacy and safety of avelumab in patients with or without expression of PD-L1, etc.

Since avelumab is an antibody against human PD-L1, PMDA asked the applicant to explain the efficacy and safety of avelumab in patients with or without expression of PD-L1 and patients treatable with avelumab.

The applicant's response:
In Study 003, information on PD-L1 expression in tumor tissue samples was collected using clone 7310 (Agilent Technologies), and subjected to investigations described in (a) and (b) below.

(a) Efficacy
Efficacy of avelumab was investigated in subgroups classified by PD-L1 expression level in tumor tissue samples (cut-off level, 1% or 5%) among patients in whom PD-L1 expression level could be confirmed in Part A of Study 003. Table 43 shows the efficacy of avelumab in subgroups classified by PD-L1 expression level. The response rate tended to be higher in patients with positive PD-L1 expression compared with patients with negative PD-L1 expression, regardless of the cut-off level of PD-L1 expression, but a certain level of the response rate was achieved even in patients with negative PD-L1 expression, suggesting that avelumab is effective regardless of the expression level of PD-L1.

Table 43. Response rate classified by PD-L1 expression level
(RECIST ver. 1.1, efficacy analysis population, IERC assessment, data cut-off, March 3, 2016)

Cut-off level of PD-L1 expression	PD-L1 expression	Number of patients	Response rate [95% CI] (%)	Odds ratio [95% CI]
1%	Positive	58	34.5 [22.5, 48.1]	2.28 [0.53, 13.78]
	Negative	16	18.8 [4.0, 45.6]	
5%	Positive	19	52.6 [28.9, 75.6]	3.59 [1.04, 12.31]
	Negative	55	23.6 [13.2, 37.0]	

(b) Safety

Among the patient populations with PD-L1 expression level of <1% and ≥1% in Part A of Study 003, the incidence was 100% and 96.6%, respectively, for adverse events, 87.5% and 56.9%, respectively, for Grade ≥3 adverse events, and 43.8% and 41.4%, respectively, for serious adverse events. Among the population with PD-L1 expression level of <5% and ≥5%, the incidence was 96.4% and 100%, respectively, for adverse events, 65.5% and 57.9%, respectively, for Grade ≥3 adverse events, and 43.6% and 36.8%, respectively, for serious adverse events. Although there are limitations to the evaluation because of the limited number of patients, no clear difference was observed in the safety of avelumab between the PD-L1-positive and negative populations classified according to each cut-off level of PD-L1 expression in tumor tissue samples.

Based on the results of (a) and (b) above, the applicant considers that avelumab is effective and tolerable regardless of the expression level of PD-L1.

PMDA's view:

The above explanation of the applicant is acceptable. However, information on PD-L1 level and other response predictors of avelumab should be collected continuously, and when new information becomes available, the information should be appropriately provided to healthcare professionals.

7.R.5 Dosage and administration

The proposed dosage and administration for avelumab was "The usual adult dosage is 10 mg/kg (body weight) of avelumab (genetical recombination) intravenously infused once every 2 weeks," and the Precautions for Dosage and Administration section contained the following statements:

- Avelumab should be administered by intravenous infusion over at least 1 hour.
- In order to alleviate infusion reaction that may occur in treatment with avelumab, an antihistamine, antipyretic analgesics, etc., should be administered before treatment with avelumab up to the fourth dose. The premedication should be based on the prior experience of infusion reaction or on the severity and clinical judgment.
- A guide for suspension/discontinuation of avelumab administration in case of adverse drug reaction

As a result of the review of Sections "7.R.2 Efficacy" and "7.R.3 Safety" and of the review described below, PMDA concluded that the following cautions should be provided in the Precautions for Dosage and Administration section of the package insert, and the dosage and administration of avelumab should be "The usual adult dosage is 10 mg/kg (body weight) of avelumab (genetical recombination) intravenously infused over 1 hour or more once every 2 weeks."

- The efficacy and safety of avelumab in combination with other antineoplastic drugs have not been established.

- In order to alleviate infusion reaction that may occur in treatment with avelumab, an antihistamine, antipyretic analgesics, etc., should be administered before treatment with avelumab.
- A guide for suspension/discontinuation of avelumab administration in case of adverse drug reaction

7.R.5.1 Dosage and administration of avelumab

The applicant's explanation on the justification for the proposed dosage and administration of avelumab for patients with MCC:

Study 003 was conducted using the dosage and administration based on the results of the following studies and, as a result, clinical efficacy of avelumab in patients with MCC was demonstrated. Therefore, the proposed dosage and administration of avelumab was based on these studies. The duration of infusion was based on that used in Study 003 and described in the Precautions for Dosage and Administration section.

- In the dose titration part of the foreign phase I study (Study 001), Q2W administration of avelumab at 1, 3, 10, or 20 mg/kg did not reach MTD, and DLT was not observed at ≤10 mg/kg but observed in 1 patient in the 20 mg/kg group, suggesting that avelumab is better tolerated at 10 mg/kg than at higher doses. Also, in the extension part of Study 001, there was no particular safety concern in patients receiving avelumab 10 mg/kg Q2W.
- In the dose titration part of the Japanese phase I study (Study 002), Q2W administration of avelumab at 3, 10, or 20 mg/kg did not cause DLT, suggesting that avelumab 10 mg/kg is well tolerated in Japanese patients as well.

PMDA's view:

PMDA generally accepted the explanation of the applicant. As for the duration of avelumab infusion, since it is more appropriate that the administration method specified in Study 003 be clearly described in the Dosage and Administration section, the Dosage and Administration section should be "The usual adult dosage is 10 mg/kg (body weight) of avelumab (genetical recombination) intravenously infused over 1 hour or more once every 2 weeks."

7.R.5.2 Premedication

The applicant's explanation on the method for premedication:

In Study 003 and other clinical studies, premedication was to be used regardless of the number of doses of avelumab administration. However, given the results described below, it is more appropriate to use premedication to alleviate infusion reaction up to the fourth dose and, after the fourth dose, to decide whether to use premedication or not based on presence or absence of the past history of avelumab-induced infusion reaction. Therefore, this administration method is included in the Precautions for Dosage and Administration section.

- In Study 003 and other clinical studies, the first-case of infusion reaction occurred more frequently in the first to third dose of avelumab, and in only a small number of patients after the fourth dose [see Section "7.R.3.6 Infusion reaction"].
- In Study 003 and other clinical studies, even if infusion reaction recurred in the fourth or later dose in patients who had experienced infusion reaction in a previous avelumab administration, the severity of the relapsed infusion reaction was seldom Grade 3 or more.

PMDA's view:
PMDA accepted the applicant's explanation regarding the caution statement for alleviating the infusion reaction. As for the number of doses of premedications, however, because of the limited information available on the safety in patients not receiving premedications in the fourth and later dose of avelumab, the same precaution in Study 003, etc., should be included in the Precautions for Dosage and Administration section.

7.R.5.3 Avelumab dose adjustment

The applicant's explanation on avelumab dose adjustment:
In Study 003, criteria were specified for dose adjustment, such as suspension or discontinuation of avelumab administration and reduction in the infusion speed, and the clinical usefulness of avelumab was demonstrated by complying with these criteria. Therefore, the guide for dose adjustment will be included in the Precautions for Dosage and Administration section based on the criteria used in Study 003, with the following modifications:

- Dose adjustment criteria for rash: Although the criteria were specified in Study 003, there were few patients who had Grade ≥3 or serious rash in clinical studies. Therefore, the criteria are excluded.
- Dose adjustment criteria for colitis/diarrhoea: In Study 003, avelumab administration was to be discontinued in case of Grade 3 colitis/diarrhoea. However, in accordance with the dose adjustment criteria in the Japanese and foreign package inserts of nivolumab and pembrolizumab, avelumab administration should be suspended until the severity of the adverse event decreases to Grade ≤1.
- Dose adjustment criteria for myositis: Study 003 did not stipulate any dose adjustment criteria specific to myositis. However, since avelumab-induced myositis was observed in Study 001, the dose adjustment criteria include the requirement to suspend avelumab administration in case of Grade 2 or 3 myositis until the severity decreases to Grade ≤1.
- Dose adjustment criteria for myocarditis: Study 003, at the beginning of the study, did not stipulate any dose adjustment criteria specific to myocarditis. However, since avelumab-induced myocarditis was observed in the dose titration part (20 mg/kg group) of Study 001 and in Study B9991002,[19] and the following criteria were included in the 10th amendment of the protocol ([redacted], 20[redacted]) of Study 003, these criteria are specified.
  (i) If myocarditis is suspected from newly observed cardiac sign, laboratory test, or electrocardiogram, avelumab administration should be suspended until the cardiac symptom improves or the suspected immune-related myocarditis is ruled out.
  (ii) If diagnosis of immune-related myocarditis is made, avelumab administration should be discontinued and should never be resumed.
- Dose adjustment criteria for Grade 2 adverse drug reaction[25]: The protocol of Study 003 stipulated that avelumab administration should be suspended until the adverse drug reaction improves to Grade ≤1 and that avelumab administration should be discontinued if the same adverse drug reaction recurs at Grade 2 after the resumption of the administration. However, the above criteria are excluded in

[25] Except endocrine disorder controllable by hormone replacement therapy

line with the dose adjustment criteria for nivolumab and pembrolizumab in the Japanese and foreign package inserts.

- Although the protocol for Study 003 stipulated that avelumab administration should be discontinued in case of Grade 3 adverse drug reactions,[26] avelumab administration should be suspended until the adverse drug reaction improves to Grade ≤1 in line with the dose adjustment criteria for nivolumab and pembrolizumab in the Japanese and foreign package inserts.

PMDA's view:
PMDA generally accepted the explanation of the applicant. As for the criteria stipulated in the Precautions for Dosage and Administration section proposed as the guides for avelumab dose adjustment that are different from those in Study 003, except the dose adjustment criteria for rash, should be modified as shown below.

- Regarding the dose adjustment criteria for colitis/diarrhoea, myositis, Grade 2 adverse drug reactions, and Grade ≥3 adverse drug reactions proposed by the applicant, the efficacy and safety of avelumab are unknown when the proposed criteria are complied with. Therefore, the same dose adjustment criteria as those of proven clinical usefulness used in Study 003 should be selected.
- Regarding the dose adjustment criteria for myocarditis, since it is difficult to differentiate immune-related myocarditis from other myocarditis, avelumab administration should be suspended or discontinued if myocarditis is suspected from newly observed cardiac sign, laboratory test, or electrocardiogram.

Based on the above, PMDA concluded that the following description should be included in the Precautions for Dosage and Administration section:

- If adverse drug reactions occur in patients treated with avelumab, suspension, etc., of avelumab administration should be considered by referring to the criteria listed in the following table.

[26] Except (a) to (e) below: (a) Transient (≤6 hours) Grade 3 influenza-like symptom or pyrexia that is controlled by medical management, (b) among transient (≤24 hours) Grade 3 fatigue, local reaction, headache, nausea, and vomiting, those that improved to Grade ≤1, (c) among laboratory values (except Grade ≥3 liver function test increased) that exceeded the normal range, those that were considered unlikely related to avelumab by the investigator, were not clinically related, and recovered to Grade ≤1 within 7 days under sufficient medical management, (d) tumor flare defined as regional pain, irritation, or rash at tumor site or at suspected tumor site, (e) among patients with ECOG PS ≥3, patients who did not recover to ECOG PS ≤2 within 14 days (if ECOG PS ≥3 on the day of study drug administration, administration in the next cycle should not be given).

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity*	Measures
ILD	Grade 2	Suspend treatment with avelumab until ILD improves to Grade ≤1.
	Grade 3 or 4	Discontinue treatment with avelumab.
Hepatic dysfunction	AST or ALT increased to 3 - 5 times the upper limit of normal, or total bilirubin increased to 1.5 - 3 times the upper limit of normal	Suspend treatment with avelumab until the dysfunction improves to Grade ≤1.
	AST or ALT increased to >5 times the upper limit of normal, or total bilirubin increased to >3 times the upper limit of normal	Discontinue treatment with avelumab.
Colitis/diarrhoea	Grade 2	Suspend treatment with avelumab until the symptom improves to Grade ≤1.
	Grade 3 or 4	Discontinue treatment with avelumab.
Endocrine disorder (except type 1 diabetes mellitus)	Symptomatic endocrine disorder	Suspend treatment with avelumab until the symptom improves to Grade ≤1.
	Suspected adrenal crisis	Suspend or discontinue treatment with avelumab.
Myocarditis	Myocarditis suspected from newly observed cardiac sign, laboratory test, or ECG	Suspend or discontinue treatment with avelumab.
Infusion reaction	Grade 1	Decrease the infusion speed by half.
	Grade 2	Interrupt treatment with avelumab. If patient conditions have stabilized (Grade ≤1), resume treatment at half the original infusion speed.
	Grade 3 or 4	Discontinue treatment with avelumab.
Other adverse drug reactions (including type 1 diabetes mellitus)	Grade 2	Suspend treatment with avelumab until the symptom recovers to Grade ≤1. If the same adverse drug reaction of Grade 2 occurs after the resumption of administration, discontinue treatment with avelumab.
	Grade 3 or 4	Discontinue treatment with avelumab.

* Grade is assessed according to NCI-CTCAE (Common Terminology Criteria for Adverse Events) v 4.0.

7.R.5.4 Concomitant use with other antineoplastic drugs

PMDA asked the applicant to explain the efficacy and safety of avelumab in combination with other antineoplastic drugs.

The applicant's explanation:

Currently, there are no data of efficacy or safety of avelumab in combination with other antineoplastic drugs in clinical studies.

PMDA's view:

Since the only available clinical study data on avelumab are those of avelumab monotherapy, the efficacy and safety of avelumab in combination with other antineoplastic drugs are unknown. It is therefore not recommended to concomitantly administer avelumab with other antineoplastic drugs. The following caution should be provided in the Precautions for Dosage and Administration section:

- The efficacy and safety of avelumab in combination with other antineoplastic drugs have not been established.

7.R.6 Post-marketing investigations

The applicant's explanation:

Because of the very small number of patients with MCC and the extremely limited number of Japanese patients enrolled in Study 003, a post-marketing surveillance will be conducted covering all patients

receiving avelumab after the market launch. Also, the applicant explained the following surveillance plan.

The surveillance will mainly investigate the incidences of events defined as safety specifications, except those that may occur in patient groups with only an extremely limited proportion of them receiving avelumab (such as embryo-fetal toxicity observed in pregnant patients). Thus, the surveillance will focus on the incidences of ILD, hepatic dysfunction, colitis/severe diarrhoea, endocrine disorder (thyroid disorder, adrenal insufficiency, type 1 diabetes mellitus, and hypopituitarism), myocarditis, nerve disorder (including Guillain-Barre syndrome), uveitis, renal disorder, myositis/rhabdomyolysis, severe infusion reaction, encephalitis/meningitis, myasthenia gravis, pancreatitis, etc.).

Target sample size is 48 based on the incidences of adverse drug reactions in Studies 001, 002, and 003, with feasibility taken into account because of the extremely rare occurrences of MCC.

The follow-up period is 1 year from the observations in Studies 001, 002, and 003 that most of the events defined as safety specifications were observed within 1 year after the start of avelumab administration and that there were no adverse events that tended to increase in the incidence more than 1 year after the start of avelumab administration.

PMDA's view:
Since safety information of avelumab in Japanese patients with MCC is extremely limited, relevant information should be collected promptly and in an unbiased manner after the market launch, and safety information thus obtained should be provided to healthcare professionals without delay. Therefore, the post-marketing surveillance should cover all patients receiving avelumab, as proposed by the applicant, for a certain period after the market launch.

Because of the extremely limited amount of information available on avelumab, the following should be included in the safety specifications for avelumab taking account of the reviews in Sections "5.5.2 Effect on embryo-fetal development and administration in pregnant women" and "7.R.3 Safety": ILD, hepatic dysfunction, colitis/severe diarrhoea, thyroid dysfunction, dysfunction adrenal, type 1 diabetes mellitus, myocarditis, nerve disorder (including Guillain-Barre syndrome), renal disorder, myositis/rhabdomyolysis, infusion reaction, encephalitis/meningitis, and embryo-fetal toxicity. Information on these safety specifications should be actively collected in the surveillance.

The target sample size and the follow-up period planned by the applicant are appropriate.

7.2 Adverse events, etc. observed in clinical studies

Among clinical data submitted for safety evaluation, data on death are described in Section "7.1 Evaluation data." Main adverse events other than death were as shown below.

7.2.1 Japanese phase I study (Study 002)

7.2.1.1 Dose titration part

Adverse events were observed in 5 of 5 patients (100%) in the 3 mg/kg group, 6 of 6 patients (100%) in the 10 mg/kg group, and 5 of 6 patients (83.3%) in the 20 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 5 patients (60.0%) in

the 3 mg/kg group, 5 of 6 patients (83.3%) in the 10 mg/kg group, and 3 of 6 patients (50.0%) in the 20 mg/kg group. Table 44 shows adverse events reported by ≥2 patients in any group.

Table 44. Adverse events reported by ≥2 patients in any group

SOC PT (MedDRA/J ver. 19.0)	Number of patients (%)					
	3 mg/kg (n = 5)		10 mg/kg (n = 6)		20 mg/kg (n = 6)	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	5 (100)	0	6 (100)	1 (16.7)	5 (83.3)	2 (33.3)
Gastrointestinal disorders						
Vomiting	2 (40.0)	0	1 (16.7)	0	2 (33.3)	0
Nausea	3 (60.0)	0	0	0	0	0
General disorders and administration site conditions						
Pyrexia	1 (20.0)	0	2 (33.3)	0	1 (16.7)	0
Injury, poisoning and procedural complications						
Infusion reaction	1 (20.0)	0	2 (33.3)	0	2 (33.3)	0
Skin and subcutaneous tissue disorders						
Rash maculo-papular	2 (40.0)	0	1 (16.7)	0	1 (16.7)	0
Rash	1 (20.0)	0	2 (66.7)	0	2 (40.0)	0
Investigations						
White blood cell count decreased	1 (20.0)	0	2 (33.3)	0	0	0

Serious adverse events were observed in 1 of 5 patients (20.0%) in the 3 mg/kg group and in 1 of 6 patients (16.7%) in the 20 mg/kg group. The serious adverse events observed were altered state of consciousness and headache in 1 patient (20.0%) each in the 3 mg/kg group and tonic convulsion in 1 patient (16.7%) in the 20 mg/kg group. A causal relationship to the study drug was ruled out for all these events.

There were no adverse events leading to discontinuation of the study drug.

7.2.1.2 Extension part

Adverse events were observed in 32 of 34 patients (94.1%) and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 27 of 34 patients (79.4%). Table 45 shows adverse events with an incidence of ≥10%.

Table 45. Adverse events with an incidence of ≥10%

SOC PT (MedDRA/J ver. 19.0)	Number of patients (%) (n = 34)	
	All Grades	Grade ≥3
All adverse events	34 (100)	17 (50.0)
Gastrointestinal disorders		
Nausea	7 (20.6)	0
Abdominal pain	5 (14.7)	1 (2.9)
Vomiting	5 (14.7)	0
General disorders and administration site conditions		
Pyrexia	5 (14.7)	0
Fatigue	4 (11.8)	0
Blood and lymphatic system disorders		
Anaemia	9 (26.5)	8 (23.5)
Injury, poisoning and procedural complications		
Infusion reaction	5 (14.7)	0
Metabolism and nutrition disorders		
Decreased appetite	7 (20.6)	1 (2.9)
Skin and subcutaneous tissue disorders		
Pruritus	6 (17.6)	0
Rash	4 (11.8)	0
Dry skin	5 (14.7)	0

Serious adverse events were observed in 8 of 34 patients (23.5%). The serious adverse events observed were ileus in 2 patients (5.9%), gastric haemorrhage, upper gastrointestinal haemorrhage, intestinal obstruction, biliary tract infection, myocardial infarction, acute kidney injury, and TLS in 1 patient (2.9%) each. Of these, a causal relationship to the study drug could not be ruled out for acute kidney injury and TLS (1 patient each).

Adverse events leading to discontinuation of the study drug were observed in 6 of 34 patients (17.6%). They were nausea, gastric haemorrhage, upper gastrointestinal haemorrhage, colitis, ascites, vomiting, fatigue, oedema peripheral, anaemia, acute kidney injury, hyperuricaemia, TLS, dehydration, AST increased, and ALT increased in 1 patient (2.9%) each. Of these, a causal relationship to the study drug could not be ruled out for colitis, oedema peripheral, anaemia, acute kidney injury, hyperuricaemia, TLS, dehydration, AST increased, and ALT increased (1 patient each).

7.2.2 Global phase II study (Study 003)

Adverse events were observed in 86 of 88 patients (97.7%) in Part A and in 28 of 29 patients (96.6%) in Part B. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 62 of 88 patients (70.5%) in Part A and in 23 of 29 patients (79.3%) in Part B. Table 46 shows adverse events with an incidence of ≥10% in either part.

Table 46. Adverse events with an incidence of ≥10% in either part

SOC PT	Number of patients (%)			
	Part A (MedDRA/J ver. 19.0) N = 88		Part B (MedDRA/J ver. 19.1) N = 29	
	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	86 (97.7)	55 (62.5)	28 (96.6)	12 (41.4)
Gastrointestinal disorders				
Nausea	19 (21.6)	0	3 (10.3)	0
Diarrhoea	20 (22.7)	0	3 (10.3)	0
Abdominal pain	11 (12.5)	2 (2.3)	4 (13.8)	0
Constipation	15 (17.0)	0	8 (27.6)	0
Vomiting	11 (12.5)	1 (1.1)	2 (6.9)	1 (3.4)
General disorders and administration site conditions				
Fatigue	33 (37.5)	2 (2.3)	9 (31.0)	0
Oedema peripheral	17 (19.3)	0	2 (6.9)	0
Asthenia	11 (12.5)	0	0	0
Infections and infestations				
Bronchitis	0	0	3 (10.3)	0
Musculoskeletal and connective tissue disorders				
Arthralgia	14 (15.9)	1 (1.1)	2 (6.9)	0
Pain in extremity	14 (15.9)	1 (1.1)	2 (6.9)	0
Blood and lymphatic system disorders				
Anaemia	13 (14.8)	9 (10.2)	4 (13.8)	1 (3.4)
Vascular disorders				
Hypertension	11 (12.5)	5 (5.7)	3 (10.3)	3 (10.3)
Respiratory, thoracic and mediastinal disorders				
Cough	16 (18.2)	0	3 (10.3)	0
Dyspnoea	8 (9.1)	0	3 (10.3)	1 (3.4)
Injury, poisoning and procedural complications				
Infusion reaction	13 (14.8)	0	4 (13.8)	1 (3.4)
Nervous system disorders				
Headache	9 (10.2)	0	0	0
Dizziness	12 (13.6)	0	2 (6.9)	0
Metabolism and nutrition disorders				
Hyperkalaemia	0	0	3 (10.3)	0
Hyperglycaemia	0	0	3 (10.3)	0
Hyponatraemia	5 (5.7)	1 (1.1)	4 (13.8)	0
Decreased appetite	18 (20.5)	2 (2.3)	0	0
Skin and subcutaneous tissue disorders				
Pruritus	9 (10.2)	0	2 (6.9)	0
Rash	12 (13.6)	0	0	0
Dry skin	5 (5.7)	0	3 (10.3)	0
Investigations				
Amylase increased	0	0	3 (10.3)	1 (3.4)
ALT increased	6 (6.8)	3 (3.4)	3 (10.3)	1 (3.4)
Lipase increased	0	0	5 (17.2)	1 (3.4)
Weight decreased	13 (14.8)	0	5 (17.2)	0

Serious adverse events were observed in 37 of 88 patients (42.0%) in Part A and in 8 of 29 patients (27.6%) in Part B. They were disease progression and acute kidney injury in 4 patients (4.5%) each, anaemia in 3 patients (3.4%), ileus, abdominal pain, general physical health deterioration, asthenia, and cellulitis in 2 patients (2.3%) each, gastric haemorrhage, gastrointestinal haemorrhage, oesophageal spasm, enterocolitis, faecaloma, chest pain, fatigue, non-cardiac chest pain, pain, Klebsiella sepsis, Streptococcal sepsis, herpes zoster, erysipelas, diabetic foot infection, urinary tract infection, pneumonia, lung infection, liver injury, hepatic failure, eyelid function disorder, ulcerative keratitis, retinal artery occlusion, glaucoma, synovitis, musculoskeletal pain, bone pain, flank pain, chondrocalcinosis, microcytic anaemia, normochromic normocytic anaemia, leukocytosis, superior vena cava syndrome, deep vein thrombosis, pleural effusion, dyspnoea, dyspnoea exertional, infusion reaction, pericardial effusion, atrial flutter, tachycardia, encephalopathy, tubulointerstitial nephritis, confusional state, anxiety, delirium, hyponatraemia, diabetes mellitus, hypothyroidism, pericardial effusion malignant, malignant

neoplasm progression, neoplasm progression, metastases to meninges, squamous cell carcinoma of skin, squamous cell carcinoma, and transaminases increased in 1 patient (1.1%) each in Part A; and large intestine perforation, abdominal pain, vomiting, disease progression, general physical health deterioration, gait disturbance, sepsis, anaemia, lymphoedema, hypotension, dyspnoea, respiratory failure, pulmonary embolism, dyspnoea exertional, infusion reaction, encephalopathy, hydronephrosis, and paraneoplastic syndrome in 1 patient (3.4%) each in Part B. Of these, a causal relationship to the study drug could not be ruled out for ileus, enterocolitis, synovitis, chondrocalcinosis, infusion reaction, tubulointerstitial nephritis, hypothyroidism, and transaminases increased (1 patient each) in Part A and for gait disturbance, infusion reaction, and paraneoplastic syndrome (1 patient each) in Part B.

Adverse events leading to discontinuation of the study drug were observed in 5 of 88 patients (5.7%) in Part A and in 6 of 29 patients (20.7%) in Part B. They were ileus, pericardial effusion, ALT increased, transaminases increased, GGT increased, and blood CPK increased in 1 patient (1.1%) each in Part A, and infusion reaction in 2 patients (6.9%) and disease progression, gait disturbance, cholangitis, paraneoplastic syndrome, AST increased, ALT increased, and electrocardiogram abnormal in 1 patient (3.4%) each in Part B. Of these, a causal relationship to the study drug could not be ruled out for ileus, ALT increased, transaminases increased, GGT increased, and blood CPK increased (1 patient each) in Part A, and for infusion reaction (2 patients) and gait disturbance, cholangitis, paraneoplastic syndrome, AST increased, and ALT increased (1 patient each) in Part B.

7.2.3 Foreign phase I study (Study 001)

7.2.3.1 Dose titration part

Adverse events were observed in 4 of 4 patients (100%) in the 1 mg/kg group, 13 of 13 patients (100%) in the 3 mg/kg group, 15 of 15 patients (100%) in the 10 mg/kg group, and 53 of 53 patients (100%) in the 20 mg/kg group. Adverse events for which a causal relationship to the study drug could not be ruled out were observed in 3 of 4 patients (75.0%) in the 1 mg/kg group, 9 of 13 patients (69.2%) in the 3 mg/kg group, 14 of 15 patients (93.3%) in the 10 mg/kg group, and 17 of 53 patients (81.0%) in the 20 mg/kg group. Table 47 shows adverse events reported by ≥30% of patients in any group.

Table 47. Adverse events with reported by ≥30% of patients in any group

SOC PT (MedDRA/J ver. 19.0)	Number of patients (%)							
	1 mg/kg N = 4		3 mg/kg N = 13		10 mg/kg N = 15		20 mg/kg N = 21	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
All adverse events	4 (100)	4 (100)	13 (100)	8 (61.5)	15 (100)	10 (66.7)	21 (100)	13 (61.9)
Gastrointestinal disorders								
Nausea	1 (25.0)	0	2 (15.4)	0	6 (40.0)	0	2 (9.5)	0
Vomiting	2 (50.0)	0	1 (7.7)	0	2 (13.3)	0	1 (4.8)	0
General disorders and administration site conditions								
Fatigue	2 (50.0)	0	7 (53.8)	1 (7.7)	13 (86.7)	1 (6.7)	6 (28.6)	0
Pyrexia	4 (100)	0	2 (15.4)	0	4 (26.7)	0	4 (19.0)	0
Influenza like illness	1 (25.0)	0	1 (7.7)	0	4 (26.7)	0	7 (33.3)	0
Disease progression	0	0	4 (30.8)	4 (30.8)	2 (13.3)	2 (13.3)	0	0
Blood and lymphatic system disorders								
Anaemia	2 (50.0)	2 (50.0)	4 (30.8)	2 (15.4)	6 (40.0)	1 (6.7)	3 (14.3)	2 (9.5)
Lymphopenia	2 (50.0)	1 (25.0)	3 (23.1)	0	2 (13.3)	0	0	0
Metabolism and nutrition disorders								
Hypoalbuminaemia	2 (50.0)	1 (25.0)	2 (15.4)	1 (7.7)	1 (6.7)	0	1 (4.8)	0
Hyponatraemia	2 (50.0)	1 (25.0)	2 (15.4)	2 (15.4)	0	0	0	0
Investigations								
AST increased	2 (50.0)	1 (25.0)	2 (15.4)	0	1 (6.7)	1 (6.7)	5 (23.8)	0
Weight decreased	1 (25.0)	0	1 (7.7)	0	5 (33.3)	0	1 (4.8)	0
Blood creatinine increased	2 (50.0)	0	0	0	0	0	2 (9.5)	0

Serious adverse events were observed in 3 of 4 patients (75.0%) in the 1 mg/kg group, 6 of 13 patients (46.2%) in the 3 mg/kg group, 6 of 15 patients (40.0%) in the 10 mg/kg group, and 8 of 21 patients (38.1%) in the 20 mg/kg group. They were duodenal obstruction, ascites, pneumonia, peritonitis bacterial, hypoxia, blood alkaline phosphatase increased, AST increased, and ALT increased in 1 patient (25.0%) each in the 1 mg/kg group; disease progression in 4 patients (30.8%), large intestinal obstruction, lung infection, embolism, dyspnea, and hyponatraemia in 1 patient (7.7%) each in the 3 mg/kg group; disease progression and autoimmune disorder in 2 patients (13.3%) each, abdominal pain lower, abdominal pain, constipation, influenza like illness, fatigue, pelvic pain, decreased appetite, and hypokalaemia in 1 patient (6.7%) each in the 10 mg/kg group; and pneumonia, kidney infection, urinary tract infection, myositis, haematoma, hypotension, dyspnoea, pleural effusion, respiratory failure, dysphonia, autoimmune disorder, blood alkaline phosphatase increased, and amylase increased in 1 patient (4.8%) each in the 20 mg/kg group. Of these, a causal relationship to the study drug could not be ruled out for blood alkaline phosphatase increased, AST increased, and ALT increased (1 patient each) in the 1 mg/kg group; autoimmune disorder (2 patients), abdominal pain lower, influenza like illness, and fatigue (1 patient each) in the 10 mg/kg group; and myositis, dysphonia, autoimmune disorder, and amylase increased (1 patient each) in the 20 mg/kg group.

Adverse events leading to discontinuation of the study drug were observed in 1 of 4 patients (25.0%) in the 1 mg/kg group, 1 of 13 patients (7.7%) in the 3 mg/kg group, 4 of 15 patients (26.7%) in the 10 mg/kg group, and 6 of 21 patients (28.6%) in the 20 mg/kg group. They were AST increased in 1 patient (25.0%) in the 1 mg/kg group; embolism and dyspnoea in 1 patient (7.7%) each in the 3 mg/kg group; disease progression in 2 patients (13.3%), diarrhoea, decreased appetite, and autoimmune disorder in 1 patient (6.7%) each in the 10 mg/kg group; and blood CPK increased in 2 patients (9.5%), myositis, pain in extremity, pleural effusion, respiratory failure, dysphonia, infusion reaction, autoimmune disorder,

and amylase increased in 1 patient (4.8%) each in the 20 mg/kg group. Of these, a causal relationship to the study drug could not be ruled out for AST increased (1 patient) in the 1 mg/kg group; autoimmune disorder (1 patient) in the 10 mg/kg group; and blood CPK increased (2 patients), and myositis, pain in extremity, dysphonia, infusion reaction, autoimmune disorder, and amylase increased (1 patient each) in the 20 mg/kg group.

7.2.3.2 Extension part

Adverse events were observed in 1596 of 1635 patients (97.6%), and adverse events for which a causal relationship to the study drug could not be ruled out were observed in 1088 of 1635 patients (66.5%). Table 48 shows adverse events with an incidence of ≥10%.

Table 48. Adverse events with an incidence of ≥10%

SOC PT (MedDRA/J ver. 19.0)	Number of patients (%) N = 1635	
	All Grades	Grade ≥3
All adverse events	1596 (97.6)	943 (57.7)
Gastrointestinal disorders		
Nausea	412 (25.2)	27 (1.7)
Diarrhoea	306 (18.7)	21 (1.3)
Abdominal pain	236 (14.4)	50 (3.1)
Constipation	302 (18.5)	15 (0.9)
Vomiting	268 (16.4)	31 (1.9)
General disorders and administration site conditions		
Disease progression	173 (10.6)	166 (10.2)
Pyrexia	227 (13.9)	5 (0.3)
Fatigue	517 (31.6)	48 (2.9)
Oedema peripheral	189 (11.6)	8 (0.5)
Infections and infestations		
Urinary tract infection	163 (10.0)	18 (1.1)
Musculoskeletal and connective tissue disorders		
Arthralgia	164 (10.0)	17 (1.0)
Back pain	193 (11.8)	24 (1.5)
Blood and lymphatic system disorders		
Anaemia	240 (14.7)	94 (5.7)
Respiratory, thoracic and mediastinal disorders		
Cough	221 (13.5)	2 (0.1)
Dyspnoea	220 (13.5)	68 (4.2)
Injury, poisoning and procedural complications		
Infusion reaction	283 (17.3)	10 (0.6)
Metabolism and nutrition disorders		
Decreased appetite	300 (18.3)	16 (1.0)
Investigations		
Weight decreased	270 (16.5)	12 (0.7)

Serious adverse events were observed in 734 of 1635 patients (44.9%). Serious adverse events reported by ≥8 patients were observed in 734 of 1635 patients (44.9%). They were disease progression in 169 patients (10.3%), dyspnoea in 47 patients (2.9%), pneumonia in 41 patients (2.5%), pleural effusion in 40 patients (2.4%), abdominal pain in 38 patients (2.3%), vomiting in 27 patients (1.7%), sepsis in 25 patients (1.5%), acute kidney injury in 23 patients (1.4%), pyrexia, respiratory failure, and nausea in 22 patients (1.3%) each, anaemia in 21 patients (1.3%), small intestinal obstruction in 20 patients (1.2%), ascites in 19 patients (1.2%), dehydration in 17 patients (1.0%), asthenia in 16 patients (1.0%), chronic obstructive pulmonary disease in 15 patients (0.9%), dysphagia, infusion reaction, and back pain in 14 patients (0.9%) each, urinary tract infection in 13 patients (0.8%), diarrhoea, hyponatraemia, hypotension, and non-cardiac chest pain in 12 patients (0.7%) each, pneumonitis, haemoptysis, and

constipation in 11 patients (0.7%) each, gastrointestinal haemorrhage, lung infection, pulmonary embolism, and atrial fibrillation in 10 patients (0.6%) each, cellulitis, urosepsis, pneumonia aspiration, dyspnoea exertional, hypoxia, and hypercalcaemia in 9 patients (0.6%) each, and fatigue, acute respiratory failure, and adrenal insufficiency in 8 patients (0.5%) each. Of these, a causal relationship to the study drug could not be ruled out for infusion reaction (14 patients), pneumonitis (11 patients), pyrexia (6 patients), adrenal insufficiency (5 patients), diarrhoea and vomiting (4 patients each), colitis, autoimmune hepatitis, dyspnoea, and hypothyroidism (3 patients each), abdominal pain, localised oedema, non-cardiac chest pain, asthenia, autoimmune disorder, transaminases increased, lipase increased, and blood CPK increased (2 patients each), and nausea, gastric haemorrhage, chills, hyperthermia, disease progression, general physical health deterioration, systemic inflammatory response syndrome, fatigue, oedema peripheral, hepatocellular injury, hepatic failure, acute hepatic failure, cholecystitis acute, vision blurred, myositis, musculoskeletal chest pain, back pain, thrombocytopenia, autoimmune neutropenia, anaemia, flushing, pneumothorax, acute respiratory distress syndrome, pleural effusion, respiratory distress, respiratory failure, hypoxia, pulmonary arterial hypertension, chronic obstructive pulmonary disease, radiation pneumonitis, cardiac arrest, tachycardia, Guillain-Barre syndrome, posterior reversible encephalopathy syndrome, hypoaesthesia, embolic stroke, syncope, monoplegia, dizziness, seizure, nephrotic syndrome, acute kidney injury, mental disorder, hypovolaemia, hyperkalaemia, hyperglycaemia, decreased appetite, dehydration, hyponatraemia, hypophosphataemia, diabetes mellitus, thyroiditis acute, thyroiditis, hyperthyroidism, endocrine disorder, psoriasis, rash generalised, type I hypersensitivity, anaphylactic reaction, sarcoidosis, AST increased, amylase increased, GGT increased, hepatic enzyme increased, blood bilirubin increased, neutrophil count decreased, and weight decreased (1 patient each).

Adverse events leading to discontinuation of the study drug were observed in 235 of 1635 patients (14.4%). Adverse events leading to discontinuation of the study drug reported by ≥8 patients were disease progression in 36 patients (2.2%), infusion reaction in 32 patients (2.0%), fatigue in 9 patients (0.6%), and GGT increased in 8 patients (0.5%). Of these, a causal relationship to the study drug could not be ruled out for infusion reaction (32 patients), GGT increased (6 patients), fatigue (4 patients), diarrhoea, arthralgia, pneumonitis, ALT increased, lipase increased, and blood CPK increased (3 patients each), colitis, autoimmune hepatitis, myositis, acute kidney injury, adrenal insufficiency, autoimmune disorder, and AST increased (2 patients each), and nausea, stomatitis, enterocolitis, vomiting, localised oedema, general physical health deterioration, oedema peripheral, hepatocellular injury, hyperbilirubinaemia, rheumatoid arthritis, arthritis, autoimmune neutropenia, respiratory distress, dyspnoea, radiation pneumonitis, Guillain-Barre syndrome, posterior reversible encephalopathy syndrome, syncope, peripheral motor neuropathy, seizure, nephrotic syndrome, hyperkalaemia, hyperglycaemia, diabetes mellitus, hypothyroidism, hyperthyroidism, rash, rash maculo-papular, pemphigoid, type I hypersensitivity, anaphylactic reaction, sarcoidosis, transaminases increased, haemoglobin decreased, hepatic enzyme increased, blood alkaline phosphatase increased, and neutrophil count decreased (1 patient each).

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The assessment is currently ongoing. Results and PMDA's conclusion will be reported in Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that the product has a certain level of efficacy in the treatment of unresectable MCC, and that the product has acceptable safety in view of its benefits (see Attachment). Avelumab is a drug with a new active ingredient which is considered to suppress tumor growth by binding to the extracellular domain of PD-L1, thereby causing, among others, inhibition of the binding of PD-L1 and PD-1, leading to enhancement of cytotoxic activity of antigen-specific T cells. Avelumab is thus clinically meaningful as a treatment option for unresectable MCC. Safety, indication, dosage and administration, post-marketing investigations, etc., will be further discussed at the Expert Discussion.

PMDA has concluded that avelumab may be approved if avelumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 29, 2017

Product Submitted for Approval

Brand Name	Bavencio Injection 200 mg
Non-proprietary Name	Avelumab (Genetical Recombination)
Applicant	Merck Serono Co., Ltd.
Date of Application	March 7, 2017

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of its review described in Section "7.R.2 Efficacy" in the Review Report (1), PMDA concluded that avelumab (genetical recombination) (hereinafter referred to as avelumab) has a certain level of efficacy in patients with metastatic, unresectable Merkel cell carcinoma (MCC), based on the results of Part A and Part B of the global phase II study (Study EMR100070-003 [Study 003]) in these patients, as shown below.

- In Part A of the study in patients with a history of chemotherapy, the results of the final analysis of the response rate (%) [95.9% confidence interval (CI)], the primary endpoint, were 31.8% [21.9, 43.1], with the lower limit of the interval significantly exceeding the threshold response rate (20%).
- In Part B of the study in patients without a history of chemotherapy, the results of the interim analysis of the response rate (%) [95% CI], the secondary endpoint, were 62.5% [35.4, 84.8], showing a certain level of response (10 of 16 patients).

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.2 Safety

As a result of its review described in Section "7.R.3 Safety" in the Review Report (1), PMDA has concluded that adverse events requiring particular attention in treatment with avelumab to patients with unresectable MCC are hepatic dysfunction, interstitial lung disease (ILD), renal disorder, infusion reaction, gastro-intestinal disorder (in particular, colitis, severe diarrhoea), thyroid dysfunction, dysfunction adrenal, type 1 diabetes mellitus, nerve disorder (in particular, Guillain-Barre syndrome, encephalitis/meningitis), cardiac disorder (in particular, myocarditis), and myositis/rhabdomyolysis.

Particular caution should be exercised against possible occurrence of these adverse events in using avelumab.

PMDA also concluded that although attention should be paid to the occurrence of the above adverse events in using avelumab, it is tolerable provided that appropriate measures, such as monitoring and controlling of adverse events (including adverse drug reactions caused by excessive immune response) and suspension/discontinuation of avelumab administration, are taken by physicians with adequate knowledge and experience in cancer chemotherapy.

In the foreign labelings of nivolumab (genetical recombination) (nivolumab) and pembrolizumab (genetical recombination) (pembrolizumab), the drugs that inhibit the binding of programmed cell death ligand-1 (PD-L1) with programmed cell death-1 (PD-1) as does avelumab, a caution is provided that organ transplant rejection occurred when anti-PD-1 antibody was administered to patients with a history of solid organ transplantation. Therefore, PMDA asked the applicant to explain the safety of avelumab in patients with a history of organ transplantation.

The applicant's explanation:
Avelumab has not so far been used in patients with a history of solid organ transplantation. However, in the foreign phase I study (Study B9991007) in patients with progressive classical Hodgkin lymphoma (cHL), graft-versus-host disease (GVHD) for which a causal relationship to avelumab could not be ruled out was observed in 2 patients with a history of allogeneic haematopoietic stem cell transplant.[27)] Also, organ transplant rejection was reported after anti-PD-1 antibody administration in a patient with a history of renal transplantation (*N Engl J Med*. 2016;374:896-8). There are no cases of organ transplant rejection after avelumab administration, and GVHD occurred in only a limited number of patients. However, given the reports on nivolumab and pembrolizumab, organ transplant rejection and GVHD may occur when avelumab is administered to patients with a history of organ transplantation.

PMDA's view:
Taking account of the facts that there are no cases of organ transplant rejection after avelumab administration and there are only limited cases of GVHD, and that there is no sufficient information to determine that GVHD was definitely caused by avelumab in these affected patients, it is difficult to draw any clear conclusion on the relationship between avelumab and organ transplant rejection or GVHD. It is therefore unnecessary to raise caution currently. However, given the reports on nivolumab and pembrolizumab, avelumab also may cause organ transplant rejection or GVHD when administered to

27) The details of the 2 patients are as follows: One patient was a 32-year-old woman. She had received allogeneic haematopoietic stem cell transplant 5 years before avelumab administration and, 2 years before avelumab administration, experienced GVHD of the liver and received donor lymphocyte transfusion. Subsequently, cHL relapsed and administration of avelumab (70 mg/body every 2 weeks) was initiated. On Day 21 after the start of avelumab administration, the patient had pruritus, soft faeces, nausea, and bloating, accompanied by alanine aminotransferase increased (Grade 3), aspartate aminotransferase increased (Grade 3), total bilirubin increased (Grade 3), lipase increased (Grade 4), and amylase increased (Grade 3), from which diagnosis of GVHD (Grade 3, serious) was made and avelumab administration was discontinued. The causal relationship of these adverse events to avelumab could not be ruled out. Another patient was a 30-year-old man. He received allogeneic haematopoietic stem cell transplant 2 years before avelumab administration. Subsequently, cHL relapsed and administration of avelumab (500 mg/body every 2 weeks) was initiated. On Day 20 after the start of avelumab administration, the patient experienced hepatic dysfunction accompanied by biliary sepsis and was diagnosed with GVHD (Grade 3, serious), upon which avelumab administration was discontinued. The causal relationship of the adverse events to avelumab could not be ruled out. Several months after the discontinuation of avelumab, thickening of the skin of the abdominal wall and the elbow/knee joints was observed and diagnosis of scleroderma-like skin GVHD (Grade 3, serious) was made. The causal relationship of the adverse event to avelumab could not be ruled out.

patients with a history of organ transplantation. Therefore, relevant information should be collected continuously after the market launch, and when new information becomes available, the information should be appropriately provided to healthcare professionals.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

1.3 Clinical positioning and indications

As a result of its review described in Section "7.R.4 Clinical positioning and indications" in the Review Report (1), PMDA concluded that avelumab should be indicated for "unresectable Merkel cell carcinoma," as proposed by the applicant. As for the caution statement "Eligible patients should be selected based on a good understanding of the study results in the 'Clinical Studies' section of the package insert, including the efficacy and safety of avelumab" proposed in the Precautions for Indications section at the application, PMDA concluded that such a statement is unnecessary because it does not state any specific cautions.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to set the indication as above, to which the applicant agreed.

1.4 Dosage and administration

As a result of its review described in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA concluded that the following cautions should be provided in the Precautions for Dosage and Administration section of the package insert, and the dosage and administration of avelumab should be "The usual adult dosage is 10 mg/kg (body weight) of avelumab (genetical recombination) intravenously infused over 1 hour or more once every 2 weeks."

Precautions for Dosage and Administration

- The efficacy and safety of avelumab in combination with other antineoplastic drugs have not been established.
- In order to alleviate infusion reaction that may occur in treatment with avelumab, an antihistamine, antipyretic analgesics, etc., should be administered before treatment with avelumab.
- If adverse drug reactions occur in patients treated with avelumab, suspension, etc., of avelumab administration should be considered by referring to the criteria listed in the following table.

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity*	Measures
ILD	Grade 2	Suspend treatment with avelumab until ILD improves to Grade ≤1.
	Grade 3 or 4	Discontinue treatment with avelumab.
Hepatic dysfunction	AST or ALT increased to 3 - 5 times the upper limit of normal, or total bilirubin increased to 1.5 - 3 times the upper limit of normal	Suspend treatment with avelumab until the dysfunction improves to Grade ≤1.
	AST or ALT increased to >5 times the upper limit of normal, or total bilirubin increased to >3 times the upper limit of normal	Discontinue treatment with avelumab.
Colitis/diarrhoea	Grade 2	Suspend treatment with avelumab until the symptom improves to Grade ≤1.
	Grade 3 or 4	Discontinue treatment with avelumab.
Endocrine disorder (except type 1 diabetes mellitus)	Symptomatic endocrine disorder	Suspend treatment with avelumab until the symptom improves to Grade ≤1.
	Suspected adrenal crisis	Suspend or discontinue treatment with avelumab.
Myocarditis	Myocarditis suspected from newly observed cardiac sign, laboratory test, or ECG	Suspend or discontinue treatment with avelumab.
Infusion reaction	Grade 1	Decrease the infusion speed by half.
	Grade 2	Interrupt treatment with avelumab. If patient conditions have stabilized (Grade ≤1), resume treatment at half the original infusion speed.
	Grade 3 or 4	Discontinue treatment with avelumab.
Other adverse drug reactions (including type 1 diabetes mellitus)	Grade 2	Suspend treatment with avelumab until the symptom recovers to Grade ≤1. If the same adverse drug reaction of Grade 2 occurs after the resumption of administration, discontinue treatment with avelumab.
	Grade 3 or 4	Discontinue treatment with avelumab.

* Grade is assessed according to NCI-CTCAE (National Cancer Institute-Common Terminology Criteria for Adverse Events) v 4.0.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above, PMDA instructed the applicant to set the Dosage and Administration and Precautions for Dosage and Administration sections as above, to which the applicant agreed.

1.5 Risk management plan (draft)

In order to evaluate the safety, etc., of avelumab in routine use after the market launch, the applicant plans to conduct a post-marketing surveillance covering all patients treated with avelumab, with the target sample size of 48 patients and the follow-up period of 1 year.

As a result of its review described in Section "7.R.6 Post-marketing investigations" in the Review Report (1), PMDA concluded that the applicant should conduct a surveillance covering all patients treated with avelumab during a certain period after the market launch, thereby collect safety information promptly and in an unbiased manner, and provide safety information thus obtained to healthcare professionals without delay.

Also, PMDA concluded that the surveillance plan ([i] safety specifications, [ii] target sample size and follow-up period) should be designed as shown below:

(i) The following should be included in safety specifications in the risk management plan, as proposed: ILD, hepatic dysfunction, colitis/severe diarrhoea, thyroid dysfunction, dysfunction adrenal, type

1 diabetes mellitus, myocarditis, nerve disorder (including Guillain-Barre syndrome), renal disorder, myositis/rhabdomyolysis, infusion reaction, encephalitis/meningitis, and embryo-fetal toxicity. Also, use in patients with a history of organ transplantation (including haematopoietic stem cell transplant) should be included in safety specifications, taking account of the results in the review in Section "1.2 Safety."

(ii) Target sample size and follow-up period proposed by the applicant are acceptable.

The above conclusions of PMDA were supported by the expert advisors at the Expert Discussion.

Based on the above discussions, PMDA instructed the applicant to re-examine the surveillance plan.

The applicant's response:
The safety specifications for the surveillance will include ILD, hepatic dysfunction, colitis/severe diarrhoea, thyroid dysfunction, dysfunction adrenal, type 1 diabetes mellitus, myocarditis, nerve disorder (including Guillain-Barre syndrome), renal disorder, myositis/rhabdomyolysis, infusion reaction, encephalitis/meningitis, embryo-fetal toxicity, and use in patients with a history of organ transplantation (including haematopoietic stem cell transplant).

PMDA accepted the applicant's response.

In view of the discussion above and in Section "1.2 Safety," PMDA has concluded that the risk management plan (draft) for avelumab should include the safety and efficacy specifications presented in Table 49, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 50.

Table 49. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• ILD • Hepatic dysfunction • Colitis/severe diarrhoea • Thyroid dysfunction • Dysfunction adrenal • Type 1 diabetes mellitus • Myocarditis • Nerve disorder (including Guillain-Barre syndrome) • Renal disorder • Myositis/rhabdomyolysis • Infusion reaction	• Encephalitis/meningitis • Embryo-fetal toxicity • Use in patients with a history of organ transplantation (including haematopoietic stem cell transplant)	• None
Efficacy specification		
• Efficacy in routine clinical use		

Table 50. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing surveillance (all-case surveillance) • Post-marketing clinical study (extension of Part B in Study 003)	• Provision of information based on data from the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals • Preparation and provision of materials for patients

Table 51. Outline of post-marketing surveillance plan (draft)

Objective	To investigate the safety, etc., of avelumab in routine use after the market launch
Survey method	All-case surveillance by central registration method
Population	All patients receiving avelumab
Follow-up period	1 year
Planned sample size	48 patients
Main survey items	Safety specifications: ILD, hepatic dysfunction, colitis/severe diarrhoea, thyroid dysfunction, dysfunction adrenal, type 1 diabetes mellitus, myocarditis, nerve disorder (including Guillain-Barre syndrome), renal disorder, myositis/rhabdomyolysis, infusion reaction, encephalitis/meningitis, embryo-fetal toxicity, and use in patients with a history of organ transplantation (including haematopoietic stem cell transplant) Other main survey items: Patient characteristics (age, sex, condition of the primary disease, performance status, past illness, complications, prior treatments, etc.), status of avelumab administration, concomitant drugs, concomitant therapies, adverse events, etc.

1.6 Other

1.6.1 Quality

In response to the PMDA's instructions, given during the preparation of the Review Report (1), (a) to control the inhibitory activity against interaction between PD-L1 and PD-1, (b) to control amino acid-substituted analogs, and (c) to include peptide mapping in identification tests, the applicant explained as follows:

(a) The inhibitory activity will be included in critical quality attributes (CQA) and in the drug product specifications.

(b) Amino acid-substituted analogs will be included in in-process control tests.

(c) Peptide mapping will be included in the drug product specifications.

PMDA accepted the explanation of the applicant and, based on the submitted data and on the above review, concluded that the quality of the drug substance and the drug product is controlled appropriately.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1, 5.3.5.2.2) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. As a result, PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the submitted product application documents. The following findings were noted during the investigations carried out by some of the participating medical institutions although they did not significantly affect the overall evaluation of the study. These were notified to the head of the pertinent medical instructions for improvement.

Matters to be improved

Medical instructions

- Protocol deviations (noncompliance with the rules related to reporting of serious adverse events)

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the proposed indication and dosage and administration as shown below, with the following conditions for approval, provided that appropriate cautions will be included in the package insert and information concerning the proper use of avelumab will be supplied appropriately after the market launch, and that the compliance with the proper use of avelumab will be ensured under the supervision of a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution that is able to properly respond to emergencies. Since the product is designated as an orphan drug, the re-examination period is 10 years. The product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Unresectable Merkel cell carcinoma

Dosage and Administration

The usual adult dosage is 10 mg/kg (body weight) of avelumab (genetical recombination) intravenously infused over 1 hour or more once every 2 weeks.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because data from Japanese clinical studies are extremely limited, the applicant is required to conduct a drug use-results survey, covering all Japanese patients treated with the product after the market launch until data from a certain number of patients have been gathered in order to understand the characteristics of patients using the product, and to promptly collect safety and efficacy data so that necessary actions are taken to ensure proper use of the product.

Warning

1. Avelumab should be administered only to patients considered to be eligible for the therapy with avelumab by a physician with sufficient knowledge and experience in cancer chemotherapy at a medical institution that is able to properly respond to emergencies. The benefits and risks of the therapy should be thoroughly explained to the patient or their family member, and informed consent should be obtained prior to treatment.
2. Interstitial lung disease may occur and has been reported to be fatal in some cases. Patients should be closely monitored for initial symptoms (shortness of breath, dyspnoea, cough, etc.) by chest X-ray, etc. If any abnormalities are observed, administration of avelumab should be discontinued and appropriate measures such as administration of corticosteroid should be taken.

Contraindication

Patients with a history of hypersensitivity to any of the ingredients of avelumab

Precautions for Dosage and Administration

(1) The efficacy and safety of avelumab in combination with other antineoplastic drugs have not been established.

(2) In order to alleviate infusion reaction that may occur in treatment with avelumab, an antihistamine, antipyretic analgesics, etc., should be administered before treatment with avelumab.

(3) If adverse drug reactions occur in patients treated with avelumab, suspension, etc., of avelumab administration should be considered by referring to the criteria listed in the following table.

Criteria for dose adjustment in case of adverse drug reactions

Adverse drug reaction	Severity*	Measures
Interstitial lung disease	Grade 2	Suspend treatment with avelumab until ILD improves to Grade ≤1.
	Grade 3 or 4	Discontinue treatment with avelumab.
Hepatic dysfunction	AST or ALT increased to 3 - 5 times the upper limit of normal, or total bilirubin increased to 1.5 - 3 times the upper limit of normal	Suspend treatment with avelumab until the dysfunction improves to Grade ≤1.
	AST or ALT increased to >5 times the upper limit of normal, or total bilirubin increased to >3 times the upper limit of normal	Discontinue treatment with avelumab.
Colitis/diarrhoea	Grade 2	Suspend treatment with avelumab until the symptom improves to Grade ≤1.
	Grade 3 or 4	Discontinue treatment with avelumab.
Endocrine disorder (except type 1 diabetes mellitus)	Symptomatic endocrine disorder	Suspend treatment with avelumab until the symptom improves to Grade ≤1.
	Suspected adrenal crisis	Suspend or discontinue treatment with avelumab.
Myocarditis	Myocarditis suspected from newly observed cardiac sign, laboratory test, or ECG	Suspend or discontinue treatment with avelumab.
Infusion reaction	Grade 1	Decrease the infusion speed by half.
	Grade 2	Interrupt treatment with avelumab. If patient conditions have stabilized (Grade ≤1), resume treatment at half the original infusion speed.
	Grade 3 or 4	Discontinue treatment with avelumab.
Other adverse drug reactions (including type 1 diabetes mellitus)	Grade 2	Suspend treatment with avelumab until the symptom recovers to Grade ≤1. If the same adverse drug reaction of Grade 2 occurs after the resumption of administration, discontinue treatment with avelumab.
	Grade 3 or 4	Discontinue treatment with avelumab.

* Grade is assessed according to NCI-CTCAE (Common Terminology Criteria for Adverse Events) v 4.0.