Report on the Deliberation Results

November 30, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Libtayo I.V. Infusion 350 mg
Non-proprietary Name	Cemiplimab (Genetical Recombination) (JAN*)
Applicant	Sanofi K.K.
Date of Application	March 18, 2022

Results of Deliberation

In its meeting held on November 28, 2022, 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 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

November 15, 2022
Pharmaceuticals and Medical Devices Agency

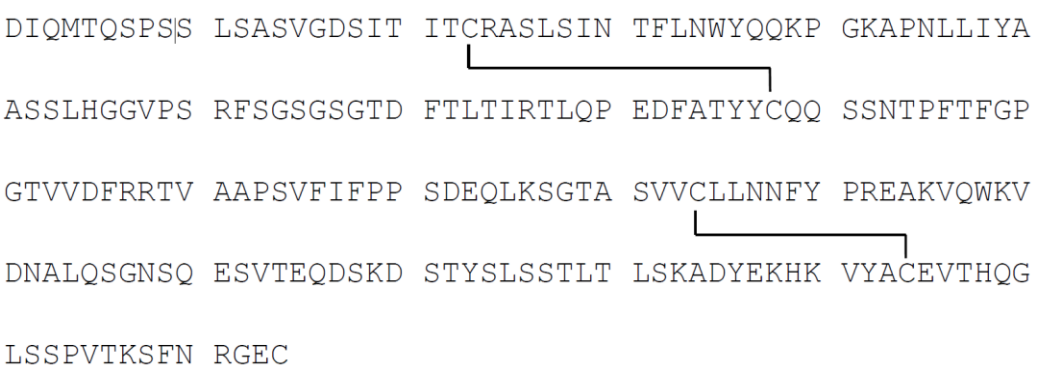
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Libtayo I.V. Infusion 350 mg
Non-proprietary Name	Cemiplimab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	March 18, 2022
Dosage Form/Strength	Injection: Each vial contains 350 mg of Cemiplimab (Genetical Recombination) in 7 mL of solution.
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Cemiplimab is a recombinant anti-human PD-1 monoclonal antibody derived from human IgG4, whose amino acid residue at position 225 is substituted by Pro in the H-chain. Cemiplimab is produced in Chinese hamster ovary cells. Cemiplimab is a glycoprotein (molecular weight: ca. 147,000) composed of 2 H-chains (γ4-chains) consisting of 444 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

Structure

Amino acid sequence:

L-chain



H-chain

EVQLLESGGV LVQPGGSLRL SCAASGFTFS NFGMTWVRQA PGKGLEWVSG

ISGGGRDTYF ADSVKGRFTI SRDNSKNTLY LQMNSLKGED TAVYYCVKWG

NIYFDYWGQG TLVTVSSAST KGPSVFPLAP CSRSTSESTA ALGCLVKDYF

PEPVTVSWNS GALTSGVHTF PAVLQSSGLY SLSSVVTVPS SSLGTKTYTC

NVDHKPSNTK VDKRVESKYG PPCPPCPAPE FLGGPSVFLF PPKPKDTLMI

SRTPEVTCVV VDVSQEDPEV QFNWYVDGVE VHNAKTKPRE EQFNSTYRVV

SVLTVLHQDW LNGKEYKCKV SNKGLPSSIE KTISKAKGQP REPQVYTLPP

SQEEMTKNQV SLTCLVKGFY PSDIAVEWES NGQPENNYKT TPPVLDSDGS

FFLYSRLTVD KSRWQEGNVF SCSVMHEALH NHYTQKSLSL SLGK

Intra-chain disulfide bonds: Solid lines

Inter-chain disulfide bonds:

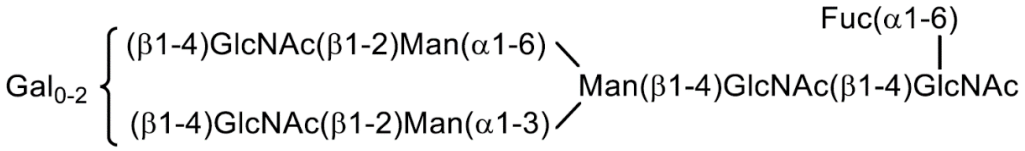
L-chain C214-H-chain C131, H-chain C223-H-chain C223, H-chain C226-H-chain C226

Pyroglutamic acid (partial): H-chain E1

Glycosylation site: H-chain N294

Partial processing: H-chain K444

Main proposed carbohydrate structure



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula: $C_{6392}H_{9832}N_{1692}O_{2002}S_{44}$ (protein moiety, 4 chains)

Molecular weight: ca.147,000

Items Warranting Special Mention

Priority review (PSEHB/PED Notification No. 0418-16 dated April 18, 2022, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

Reviewing Office Office of New Drug V

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of advanced or recurrent cervical cancer that has progressed after chemotherapy, 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 condition. Reports of the following events should be further investigated via post-marketing surveillance: infusion reactions, colitis/severe diarrhea, myositis/rhabdomyolysis/myasthenia gravis, myocarditis/pericarditis, renal dysfunction (tubulointerstitial nephritis, etc.), endocrine dysfunction (thyroid dysfunction/adrenal dysfunction/pituitary dysfunction), type 1 diabetes mellitus, severe skin disorders, neuropathies (Guillain-Barre syndrome, etc.), encephalitis/meningitis, hepatic failure/hepatic dysfunction/hepatitis, interstitial lung disease, use in organ transplant recipients (including hematopoietic stem cell transplant recipients), venous thromboembolism, febrile neutropenia, immune thrombocytopenic purpura, pancreatitis, and uveitis.

Indication

Advanced or recurrent cervical cancer that has progressed after chemotherapy

Dosage and Administration

The usual adult dosage is 350 mg of Cemiplimab (Genetical Recombination) administered as an intravenous infusion over 30 minutes every 3 weeks.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

September 29, 2022

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	Libtayo I.V. Infusion 350 mg
Non-proprietary Name	Cemiplimab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	March 18, 2022
Dosage Form/Strength	Injection: Each vial contains 350 mg of Cemiplimab (Genetical Recombination) in 7 mL of solution.
Proposed Indication	Recurrent or metastatic cervical cancer that has progressed during or after chemotherapy

Proposed Dosage and Administration

The usual adult dosage is 350 mg of Cemiplimab (Genetical Recombination) administered as an intravenous infusion over 30 minutes every 3 weeks.

Table of Contents

List of Abbreviations

See Appendix.

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

1.1 Outline of the proposed product

CD279 (programmed cell death-1 [PD-1]) is a receptor belonging to the CD28 family (a group of molecules that provide co-stimulatory signals which are involved in the regulation of T-cell activation) and is expressed on activated lymphocytes (T cells, B cells, natural killer T cells) etc. PD-1 *in vivo* is thought to bind to PD-1 ligands expressed on antigen-presenting cells (CD274 [programed cell death-ligand 1 (PD-L1)] and CD273 [programed cell death-ligand 2 (PD-L2)]) to negatively regulate immune responses (*Immunol Rev*. 2010; 236: 219-42). PD-L1 and PD-L2 have also been reported to be expressed on a wide range of tumor tissues (*Nat Rev Immunol*. 2008; 8: 467-77) etc., suggesting that the PD-1/PD-1 ligand pathway is one of the mechanisms used by tumor cells to avoid attacks etc. by antigen-specific T cells.

Cemiplimab (Genetical Recombination) (cemiplimab) is a human IgG4 monoclonal antibody that targets human PD-1 discovered by Regeneron (the US). It binds to the extracellular domain of PD-1 (the PD-1 ligand binding site) and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2, resulting in enhancement of tumor antigen-specific T-cell activation and cytotoxic T cell activity against tumor cells and inhibition of tumor growth.

1.2 Development history etc.

Outside Japan, Regeneron (the US) initiated a foreign phase I study in patients with advanced solid malignancies (Study 1423) in February 2015. Then, a global phase III study in patients with advanced or recurrent cervical cancer previously treated with chemotherapy (Study 1676) began in September 2017.

US and EU applications were submitted based mainly on the results from Study 1676 in July 2021 and November 2021, respectively, and the EU application is currently under review. On the other hand, in the US, the application was voluntarily withdrawn in January 2022 after FDA did not align on post-marketing clinical studies. As of July 2022, cemiplimab has been approved for the indication of cervical cancer in 2 countries.

In Japan, Regeneron Pharmaceuticals, Inc. (located in the US) initiated a Japanese phase I study in patients with advanced solid malignancies (Study 1622) in June 2017. Study 1676 initiated patient enrollment in [redacted] 20[redacted].

The applicant has filed a marketing application for cemiplimab, based mainly on the results from Study 1676.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

The cell bank from which a master cell bank (MCB) and a working cell bank (WCB) are derived is registered in a Drug Master File (DMF) (DMF Registration Number, 304MF40010) by Regeneron Pharmaceuticals, Inc. See Supplement for the cell banking procedures.

The MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) were characterized and subjected to purity tests in accordance with the ICH Q5A (R1), Q5B, and Q5D guidelines. Genetic stability of the production cell line was demonstrated, and no viral or non-viral adventitious agents were detected other than endogenous retroviruses and endogenous retrovirus-like particles, which are generally known to be present in rodent cell lines, in any of the tests conducted.

The MCB and WCB are stored at ≤[redacted]℃. There is no plan for generating a new MCB, but a new WCB will be generated as needed.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of [redacted]culture, [redacted]culture, harvest, [redacted]chromatography[redacted], [redacted]chromatography, [redacted] chromatography, virus filtration, [redacted], [redacted],[1)] [redacted], and [redacted]/dispensing/storage/testing.

[redacted]culture, [redacted]chromatography[redacted], [redacted]chromatography, [redacted]chromatography, [redacted], [redacted], and [redacted]/dispensing/storage/testing have been defined as critical steps.

Process validation of the commercial-scale drug substance manufacturing process has been performed.

2.1.3 Safety evaluation of adventitious agents

Except for the host CHO cells, no raw materials of biological origin etc. are used in the drug substance manufacturing process.

The MCB, WCB, and CAL were subjected to purity tests [see Section 2.1.1]. Pre-harvest unprocessed bulk at commercial scale was subjected to tests for bioburden and mycoplasma, *in vitro* test for for adventitious viruses, and test for minute virus of mice. None of the tests revealed contamination with viral or nonviral adventitious agents. These tests are included as in-process controls for pre-harvest unprocessed bulk.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process (Table 1).

[1)] There are 2 types of manufacturing processes: Process B ([redacted]) and Process C ([redacted]) [see Section 2.1.4]. This step is included in Process B only.

Table 1. Results of viral clearance studies

Process step	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Minute virus of mice	Reovirus type 3	Pseudorabies virus
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted] a)
Virus inactivation at low pH	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Virus-retentive filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>17.0	>13.7	>12.3	>17.1

a) Not used for [redacted].

2.1.4 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process A, Process B, Process C). The drug product produced from the drug substance manufactured by Process A was used in phase I and II studies, and the drug product produced from the drug substance manufactured by Process B was used in phase III studies. The proposed commercial processes are Process B and Process C.

- Process A→Process B: change in [redacted], etc.
- Process B→Process C: change in [redacted], etc.

For process changes, comparability of quality attributes between pre-change and post-change drug substances has been demonstrated.

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization was performed as shown in Table 2.

Table 2. Characterization attributes

Primary/high order structure	Amino acid sequence, post-translational modifications ([redacted]), disulfide bonds, free thiol group, secondary structure, tertiary structure, thermostability
Physicochemical properties	Molecular weight, sedimentation rate, size variants, Product-related Substance A
Carbohydrate structure	Monosaccharide compositional analysis, N-linked glycosylation profiles
Biological properties	Binding affinity to PD-1, blockade of PD-1 signaling, CDC activity, ADCC activity

The main biological properties were determined as follows:

- [redacted] demonstrated the binding affinity of cemiplimab to PD-1 [see Section 3.1.1].
- [redacted] cell line expressing human PD-1 was co-cultured with [redacted] cell line expressing [redacted] and [redacted], and a luciferase reporter assay was performed. As determined by luciferase activity mediated by AP-1 signaling, cemiplimab blocked the PD-1/PD-L1 interaction [see Section 3.1.3].
- Using [redacted] cell line, [redacted]-stimulated [redacted] cell line, [redacted] cell line, and [redacted] cell line as the target cells, the ability of cemiplimab to induce antibody dependent cell mediated cytotoxicity (ADCC) [redacted] and complement-dependent cytotoxicity (CDC) (using human complement) was evaluated by measuring the activity of protease released from dead cells. Cemiplimab did not induce ADCC or CDC [see Section 3.1.4].

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization etc. in Section 2.1.5.1, Product-related Substance A and Product-related Substance B were considered product-related substances. High molecular weight species, low molecular weight species, and Impurity C were considered product-related impurities. Impurity A, Impurity B, and Product-related Substance A are controlled by the drug substance and drug product specifications. Impurity C is controlled by the manufacturing process.

2.1.5.3 Process-related impurities

The following were considered process-related impurities: Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, Impurity J, Impurity K, β-Impurity L, host cell protein (HCP), host cell DNA, Impurity O, Impurity P, Impurity Q, Impurity R, Impurity S, and Impurity T. All of the process-related impurities have been demonstrated to be adequately removed by the manufacturing process. Impurity S is controlled by the drug substance and drug product specifications. Impurity M and Impurity T are controlled by the drug substance specification.

2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of content, appearance, identity [redacted], osmolality, pH, [redacted], HCP, purity (size exclusion liquid chromatography [SEC], capillary electrophoresis sodium dodecyl sulfate [CE-SDS] [[redacted]]), charge heterogeneity (capillary isoelectric focusing [cIEF]), endotoxin, microbial limits, potency ([redacted]), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 3.

Table 3. Overview of primary stability studies on drug substance

Study	Process	No. of batches	Storage conditions	Testing period	Storage package
Long-term	B	3	[redacted]°C	[redacted] months	[redacted] container and [redacted] screw cap
	C	3		[redacted] months*1	
Accelerated	B	3	[redacted]°C	[redacted] months	
	C	3		[redacted] months	
Stress	B	1	[redacted]°C/[redacted]%RH	[redacted] months	
	C	2		[redacted] months	
Photostability	B	1	[redacted]°C, an overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		

*1: The stability study is ongoing and continued for [redacted] months.

The long-term testing showed no significant changes in quality attributes throughout the testing period.

The accelerated testing showed an increase in protein content, an increasing trend in Impurity B in [redacted] and in Impurity A in [redacted], and an increase in [redacted] in [redacted].

In the stress testing, the changes observed in the accelerated testing were more prominent.

The photostability testing showed that the drug substance was photosensitive.

Based on the above, a shelf life of [redacted] months has been proposed for the drug substance stored in [redacted] container with [redacted] screw cap, [redacted], at [redacted]℃.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is an aqueous solution for infusion. Each glass vial (10 mL) contains 350 mg of cemiplimab in 7.0 mL of solution and the following excipients: L-histidine, L-histidine monohydrochloride monohydrate, sucrose, L-proline, polysorbate 80, and water for injection.

2.2.2 Manufacturing process

The manufacturing process for the drug product consists of [redacted], inspection, and packaging/labeling/storage/testing.

[redacted] have been defined as critical steps.

Process validation of the commercial-scale drug product manufacturing process has been performed.

2.2.3 Manufacturing process development

The following are major changes made to the drug product manufacturing process during development (Process I, Process II, Process III, Process IV, the proposed commercial process). Phase III studies used the drug products manufactured by Process II and Process III.

- Process I→Process II: change in [redacted], formulation, etc.
- Process II→Process III: change in [redacted]
- Process III→Process IV: change in [redacted] and [redacted]
- Process IV→the proposed commercial process: change in [redacted]

For process changes, comparability of quality attributes between pre-change and post-change drug products has been demonstrated.

2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, appearance, identity [redacted], pH, purity (SEC, CE-SDS [redacted]), charge heterogeneity (cIEF), Impurity S, extractable volume, [redacted], insoluble particulate matter, sterility, potency ([redacted]), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

The primary stability studies on the drug product are shown in Table 4.

Table 4. Overview of primary stability studies on drug product

Study	Formulation	Process	No. of batches	Storage conditions	Testing period	Storage package
Long-term	350 mg	Proposed commercial process[*1]	3	5 ± 3℃	36 months	Glass vial and chlorobutyl rubber stopper
Accelerated	350 mg	Proposed commercial process[*1]	3	[redacted]℃	[redacted] months	
Stress	350 mg	Proposed commercial process[*1]	1	[redacted]℃	[redacted] months	
Photostability	[redacted][*2]	Proposed commercial process[*1]	1	[redacted]℃, an overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		

*1: The drug substance manufactured by Process B was used.
*2: Not included in the present application for marketing in Japan. [redacted]

The long-term testing showed no significant changes in quality attributes throughout the testing period.

The accelerated testing showed an increasing trend in Impurity B in [redacted], an increasing trend in Impurity A in [redacted], and an increase in [redacted] in [redacted].

The stress testing showed a decreasing trend in [redacted] as well as the changes observed in the accelerated testing.

The photostability testing showed that the drug product was photosensitive.

Based on the above, a shelf life of 36 months has been proposed for the drug product packaged in a glass vial with a chlorobutyl rubber stopper (the primary container) and stored at 2℃ to 8℃ in a carton to protect from light.

2.3 Quality control strategy

A cemiplimab quality control strategy was established through the combination of process parameter controls, in-process controls, and the specifications, based on the following studies etc. [for the control of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

- Identification of critical quality attributes (CQAs)
  Concerning product-related impurities, process-related impurities, and general quality attributes, the following CQAs were identified based on information obtained during the development of cemiplimab, relevant findings, etc.
  CQAs: Appearance, color, pH, identity, HCP, [redacted], osmolarity, [redacted], [redacted], purity, [redacted], bioburden, endotoxin, viral safety, insoluble particulate matter, sterility, volume and extractable volume
- Process characterization

After the process steps that impact CQAs were identified, the process control parameters for these steps that have a significant impact on CQAs and process performance were selected, and in-process control items and their acceptable ranges were identified.

2.R Outline of the review conducted by PMDA

Based on the submitted data and the considerations in the following sections, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled. The DMF data for this product were submitted separately by the DMF registrant. See Supplement for the results of the review of DMF by PMDA.

2.R.1 Control of [redacted] particles in the drug product

The applicant explained (a) the reason why the drug product specification includes [redacted] test developed by the applicant, instead of foreign insoluble matter test for injections (Japanese Pharmacopoeia) and (b) [redacted] particle control strategy.

The applicant's explanation:

[redacted] particles were detected in the drug product during development, and therefore an analysis was performed using [redacted]. The particles in the drug product were found to be [redacted] particles. In the drug product, [redacted] particles [redacted], but [redacted] was not observed in [redacted].

[redacted] test is conducted in accordance with [redacted]. If particles are detected, the acceptance criteria are met when [redacted] and [redacted] as compared with [redacted] established for evaluating [redacted].

The control strategy for [redacted] particles in the drug product is shown below.

- [redacted] the drug product, [redacted] is performed, and [redacted].
- As a drug product specification test, [redacted] test is performed.
- Cemiplimab should be administered through an in-line 0.2 to 5 μm filter. [redacted].

There are no reports that [redacted] particles in drug product batches affected the product quality or patient safety in clinical studies. Further, post-marketing information on the control of particles in the manufacturing process will be collected as part of continuous process verification. Therefore, [redacted] particles can be controlled adequately by the above control strategy.

PMDA's conclusion:

Given the above explanation by the applicant, the particle control strategy, including the proposed [redacted] test, is acceptable.

2.R.2 Novel excipients

The drug product contains L-proline, a novel excipient, in an amount higher than the amounts present in existing intravenous formulations.

2.R.2.1 Specification and stability

L-proline conforms to the Japanese Pharmacopoeia, and PMDA concluded that there are no problems with the specification or stability.

2.R.2.2 Safety

Based on the submitted data, PMDA concluded that there are no safety issues with L-proline at the level used in the drug product.

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

3.1 Primary pharmacodynamics

3.1.1 Binding affinity to PD-1 (CTD 4.2.1.1-1)

The binding affinities of cemiplimab to human, cynomolgus monkey, rat, and mouse PD-1 (monomer) were determined by surface plasmon resonance using PD-1 (recombinant proteins). The K_D values of cemiplimab for human and cynomolgus monkey PD-1 (monomer) (n = 1) were 5.61 and 7.61 nmol/L, respectively, and cemiplimab did not bind to rat or mouse PD-1 (monomer).[2)]

The binding affinities of cemiplimab to human and cynomolgus monkey PD-1 (dimer) were determined by surface plasmon resonance using PD-1 fused with mouse IgG2 Fc domain. The K_D values of cemiplimab for human and cynomolgus monkey PD-1 (dimer) (n = 1) were 577 and 499 pmol/L, respectively.

3.1.2 Blockade of binding of PD-1 to PD-L1 and PD-L2 (CTD 4.2.1.1-2)

The ability of cemiplimab to block the binding of human and cynomolgus monkey PD-1 (dimer) to human PD-L1 and PD-L2 was determined by an enzyme-linked immunosorbent assay (ELISA) using PD-1 fused with mouse IgG2 Fc domain and human PD-L1 or human PD-L2 fused with human IgG1 Fc domain. The IC_{50} values of cemiplimab are shown in Table 5.

Table 5. Blockade of binding of PD-1 to PD-1 ligands by cemiplimab

	IC_{50} value (nmol/L)	
	PD-L1	PD-L2
Human PD-1	0.57, 0.63	0.12, 0.13
Cynomolgus monkey PD-1	0.94, 0.99	0.22, 0.23

n = 2 (individual values)

[2)] The amino acid sequences of cynomolgus monkey, mouse, and rat PD-1 extracellular domains (amino acids 21-170) showed 94%, 61%, and 65% homology with human PD-1 extracellular domain.

The ability of cemiplimab to block the binding of human PD-1 to human PD-L1 was determined by an ELISA using human PD-1 fused with human IgG1 Fc domain and human PD-L1 fused with mouse IgG2a Fc domain. The IC_{50} values of cemiplimab (n = 2) were 81 and 89 pmol/L, respectively.

3.1.3 Effects of cemiplimab on immune system (CTD 4.2.1.1-2, 4.2.1.1-4)

The following studies were conducted to determine the effects of cemiplimab on the immune system.

- Jurkat cell line transduced with a human PD-1-CD300a[3)] chimeric receptor[4)] and the AP-1-responsive luciferase gene (Jurkat/PD-1-CD300a/AP-1-Luc) was incubated with human Burkitt's lymphoma Raji cell line transduced with human PD-L1 (Raji/PD-L1). Cemiplimab (0.0017, 0.0051, 0.0152, 0.0457, 0.1372, 0.4115, 1.2346, 3.7037, 11.1111, 33.3333, and 100.0000 nmol/L) was evaluated for its effects on CD3-stimulated[5)] T-cell receptor (TCR) signaling by measuring luciferase activity. The EC_{50} value of cemiplimab (mean ± standard deviation [SD], n = 3) was 1.4 ± 0.12 nmol/L.
- Jurkat cell line transduced with human PD-1 and the AP-1-responsive luciferase gene (Jurkat/PD-1/AP-1-Luc) was incubated with human embryonic kidney 293 (HEK293) cell line transduced with anti-human CD3 mouse IgE antibody and human PD-L1 (HEK293/IgE/PD-L1). Cemiplimab (0.0017, 0.0051, 0.0152, 0.0457, 0.1372, 0.4115, 1.2346, 3.7037, 11.1111, 33.3333, and 100.0000 nmol/L) was evaluated for its effects on TCR signaling by measuring luciferase activity. The EC_{50} value of cemiplimab (mean ± SD, n = 3) was 3.3 ± 0.07 nmol/L.
- Human CD4+ T cells were incubated with HEK293 cell line engineered to express human CD20 and human PD-L1 (HEK293/CD20/PD-L1), and cemiplimab (0.0034, 0.0102, 0.0305, 0.0914, 0.2743, 0.8230, 2.4691, 7.4074, 22.2222, 66.6667, and 200.0000 nmol/L) was evaluated for its effects on CD3-stimulated[6)] T-cell proliferation by measuring ^{3}H-thymidine incorporation. The EC_{50} value of cemiplimab (median [min., max.], n = 8) was 2.5 (0.820, 2.50) nmol/L.
- The potential superagonist activity of cemiplimab immobilized onto the plate was investigated in a human PBMC cytokine release assay. Anti-CD28 and anti-CD3 antibodies were included as positive controls (0.4, 1.1, 3.3, and 10 µg/mL for all). Cytokines were measured by an electrochemiluminescence (ECL) assay using ruthenium-labeled antibodies against various cytokines. Anti-CD28 and anti-CD3 antibodies induced IL-2 and IFN-γ secretion from human PBMCs, but cemiplimab did not. Cemiplimab did not increase IL-12p70, IL-4, IL-10, or IL-13 levels. An increase in TNFα levels was observed in the cemiplimab 10 µg/mL group only, which was similar to those by anti-CD28 and anti-CD3 antibodies.
- Using human CD4+ T cells, the effects of cemiplimab on anti-CD28 antibody (1, 3, and 10 µg/mL)-enhanced T-cell proliferation were determined by measuring ^{3}H-thymidine incorporation. Cemiplimab did not induce T-cell proliferation.
- Human CD8+ T cells were incubated with HEK293 cell line expressing anti-human CD3 mouse IgE antibody(HEK293/IgE) or HEK293 cell line expressing anti-human CD3 mouse IgE antibody and human

[3)] A single-pass transmembrane receptor containing ITIM motifs on its cytoplasmic tail
[4)] A recombinant protein generated by fusing the human PD-1 extracellular domain to the transmembrane and cytoplasmic domains of CD300a
[5)] A recombinant bispecific CD3 × CD20 antibody (30 pmol/L) was added to human CD3-expressing Jurkat cell line and human CD20-expressing Raji cell line.
[6)] A recombinant bispecific CD3 × CD20 antibody (2 nmol/L) was added to human CD4+ T cells expressing human CD3 and human PD-1 and HEK293/CD20/PD-L1 cell line.

FcγR1 (HEK293/IgE/FcγR1), and cemiplimab and the positive control anti-CD28 antibody were evaluated for their effects on T-cell proliferation by measuring ^{3}H-thymidine incorporation. Incubation with anti-CD28 antibody enhanced T-cell proliferation in both of the cell lines tested, but cemiplimab did not.

3.1.4 ADCC and CDC activity (CTD 4.2.1.1-3)

Using human PBMCs as effector cells, the ability of cemiplimab to induce ADCC in Jurkat cell line, Jurkat cell line stimulated with anti-CD3 and anti-CD28 antibodies, HEK293 cell line, and HEK293 cell line expressing human PD-1 (HEK293/PD-1) was evaluated by measuring the activity of protease released from dead cells. Cemiplimab did not induce ADCC against any of these cell lines.

Using Jurkat cell line, Jurkat cell line stimulated with anti-CD3 and anti-CD28 antibodies, HEK293 cell line, and HEK293/PD-1 cell line, the ability of cemiplimab to induce CDC was evaluated by measuring the activity of protease released from dead cells. Cemiplimab did not induce CDC against any of these cell lines.

3.1.5 Anti-tumor activity against malignant tumor cell line (CTD 4.2.1.1-5)

The anti-tumor activity of cemiplimab was investigated in mice[7)] subcutaneously implanted with mouse colorectal carcinoma MC38.Ova cell line[8)] (5/group). The day of implantation was designated as Study Day 0 (Day 0). Cemiplimab 5 or 10 mg/kg was administered intraperitoneally on Days 3, 7, 10, 13, and 17, and tumor volumes were calculated. Statistically significant inhibition of tumor growth was observed with cemiplimab 5 and 10 mg/kg compared to the isotype control antibody on Days 18 and 21 ($P < 0.05$ and $P < 0.01$, respectively, on Day 18; $P < 0.05$ for both on Day 21; Dunnett's multiple comparison test).

The anti-tumor activity of cemiplimab was investigated in mice [7)] subcutaneously implanted with MC38.Ova cell line[8)] (7/group). The day of implantation was designated as Study Day 0 (Day 0). Cemiplimab 2.5 or 5 mg/kg was administered intraperitoneally on Days 3, 7, 10, 14, and 17, and tumor volumes were calculated. Statistically significant inhibition of tumor growth was observed with cemiplimab 2.5 and 5 mg/kg compared to the isotype control antibody on Day 21 ($P < 0.001$, Dunnett's multiple comparison test).

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7) Mice genetically engineered to express a recombinant protein generated by fusing the human PD-1 extracellular domain to the transmembrane and cytoplasmic domains of mouse PD-1

8) MC38 cell line engineered to express chicken ovalbumin

3.2 Safety pharmacology

In 4-week and 26-week repeated dose toxicity studies in cynomolgus monkeys, the effects of cemiplimab (2, 10, or 50 mg/kg) QW IV on the central nervous, cariovascular, and respiratory systems were assessed [see Section 5.2]. There were no drug-related effects.

3.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the non-clinical pharmacology of cemiplimab is acceptable, except for the considerations in the following section.

3.R.1 Mechanism of action and efficacy of cemiplimab

The applicant's explanation about the mechanism of action and efficacy of cemiplimab in the treament of cervical cancer:

Cemiplimab is a human IgG4 monoclonal antibody that targets human PD-1. It binds to the extracellular domain of PD-1 (the PD-1 ligand binding site) and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2 [see Sections 3.1.1 and 3.1.2], resulting in enhancement of tumor antigen-specific T-cell activation and cytotoxic T cell activity against tumor cells and inhibition of tumor growth [see Sections 3.1.3 and 3.1.5].

Although no studies have evaluated the anti-tumor activity of cemiplimab against human cervical cancer cell line, given that PD-L1 expression has been detected in tumor tissues from patients with cervical cancer (*Mod Pathol*. 2016; 29: 753-63) etc., an anti-human PD-1 antibody, cemiplimab, is considered to show efficacy in the treatment of cervical cancer via the above mechanism of action.

The applicant's explanation about differences in pharmacological properties between an anti-PD-1 antibody, cemiplimab, and other anti-PD-1/PD-L1 antibodies approved in Japan:

The pharmacological properties of these drugs are shown in Table 6 (*J Cancer*. 2017; 8: 410-6, etc.). Although there are some differences among the drugs, all drugs show anti-tumor activity mainly by blocking the binding of PD-1 to PD-L1, resulting in enhancement of tumor antigen-specific T-cell activation and cytotoxic T cell activity against tumor cells and inhibition of tumor growth.

Table 6. Pharmacological properties of cemiplimab and other anti-PD-1/PD-L1 antibodies approved in Japan

	Target molecule	Molecules to which the target molecule binds	ADCC activity	CDC activity
Cemiplimab	PD-1	PD-L1, PD-L2	No	No
Nivolumab	PD-1	PD-L1, PD-L2	No	No
Pembrolizumab	PD-1	PD-L1, PD-L2	No	No
Atezolizumab	PD-L1	PD-1, B7.1	No	No
Durvalumab	PD-L1	PD-1, B7.1	No	No
Avelumab	PD-L1	PD-1, B7.1	Yes	No

PMDA's discussion:

The applicant's explanation that the efficacy of cemiplimab is expected in patients with cervical cancer is understandable, from the standpoint of its mechanism of action. However, (1) factors affecting the efficacy of

cemiplimab and (2) differences in pharmacological properties between cemiplimab and nivolumab/pembrolizumab/atezolizumab/avelumab/durvalumab are not fully understood at present. Since such information may be beneficial in terms of selecting eligible patients in the clinical use of cemiplimab, an investigation should be continued, and if a new finding is obtained, the information should be provided appropriately to healthcare professionals in clinical practice.

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

The non-clinical PK of cemiplimab were studied in monkeys.

4.1 Analytical method

4.1.1 Cemiplimab assay

Cemiplimab in monkey serum was quantified by an ELISA using solid phased human PD-1 extracellular domain, biotinylated mouse anti-human IgG4 monoclonal antibody, and horseradish peroxidase (HRP)-conjugated NeutrAvidin.

4.1.2 Anti-cemiplimab antibody assay

Anti-cemiplimab antibodies in monkey serum were detected by an ECL assay using solid phased streptavidin, biotinylated cemiplimab, and ruthenium-labeled cemiplimab.

4.2 Absorption

4.2.1 Single-dose studies

Following a single intravenous (IV) dose of cemiplimab 1, 5, or 15 mg/kg in female monkeys, serum cemiplimab concentrations were determined (Table 7).

Anti-cemiplimab antibodies were detected in all animals.

Table 7. PK parameters of cemiplimab (female monkeys, a single IV dose)

Dose (mg/kg)	n	C_{max} (μg/mL)	t_{max} *1 (h)	AUC_{9day} (μg·day/mL)	$t_{1/2}$ (day)	V_{ss} (mL/kg)
1	5	33.3 ± 1.91	1.5 (0.583, 8.5)	120 ± 10.0	9.84 ± 1.13	36.2, 38.4*2
5	5	121 ± 10.2	1.5 (0.583, 1.5)	518 ± 69.0	10.9 ± 3.82	63.4*3
15	5	355 ± 64.7	0.583 (0.583, 8.5)	1,690 ± 151	12.4 ± 1.67	61.8, 69.4*2

Mean ± SD (Individual values are listed for n = 1 or 2), *1: Median (Min., Max.), *2: n = 2, *3: n = 1

4.2.2 Repeated-dose studies

Cemiplimab 2, 10, or 50 mg/kg QW was administered intravenously for 4 weeks to male and female monkeys, and serum cemiplimab concentrations were determined (Table 8). There were no evident sex differences in cemiplimab exposure or accumulation.

Anti-cemiplimab antibodies were detected in 23 of 30 animals.

Table 8. PK parameters of cemiplimab (male and female monkeys, 4-week repeated IV administration)

Dose (mg/kg)	Day	Sex	n	C_{max} (μg/mL)	t_{max}*1 (h)	AUC_{tau} (μg·day/mL)	$t_{1/2}$*2 (day)
2	1	F	5	52.2 ± 5.90	0.583 (0.583, 0.583)	180 ± 24.5	—
		M	5	54.5 ± 2.62	0.583 (0.583, 0.583)	204 ± 16.9	—
	22	F	3	95.1 ± 25.1	0.583 (0.583, 0.583)	393 ± 128	4.62*3
		M	2	86.5, 118	0.583, 0.583	268, 325	—
10	1	F	5	258 ± 38.1	0.583 (0.583, 0.583)	937 ± 61.1	—
		M	5	254 ± 37.6	0.583 (0.583, 0.583)	960 ± 200	—
	22	F	4	373 ± 160	0.583 (0.583, 24)	1,560 ± 703	10.9, 20.3*4
		M	3	384 ± 75.6	0.583 (0.583, 0.583)	1,380 ± 365	—
50	1	F	5	1,900 ± 289	0.583 (0.583, 0.583)	6,710 ± 1,920	—
		M	5	1,690 ± 498	0.583 (0.583, 0.583)	6,920 ± 1,390	—
	22	F	4	2,180 ± 711	0.583 (0.583, 0.583)	7,740 ± 3,920	20.0, 24.4*4
		M	3	1,790 ± 358	0.583 (0.583, 48)	8,420 ± 3,150	22.7*3

Mean ± SD (Individual values are listed for n = 1 or 2), *1: Median (Min., Max.)
*2: Calculated from the terminal phase in the recovery period.
*3:n = 1, *4: n = 2, —: Not calculated

4.3 Distribution

The applicant's explanation about the tissue distribution of cemiplimab:

Given the volume of distribution of cemiplimab at steady state in monkeys,[9)] monkey plasma volume (44.8 mL/kg) (*Pharm Res.* 1993; 10: 1093-5) etc., cemiplimab is considered to have low tissue distribution and be distributed predominantly into circulation. Thus, a tissue distribution study of cemiplimab was not conducted.

Cemiplimab is a human IgG4 monoclonal antibody, and human IgG crosses the placenta into the fetus. Thus, cemiplimab also has the potential to cross the placenta into the fetus.

4.4 Metabolism and excretion

The applicant's explanation about the metabolism and excretion of cemiplimab:

Since cemiplimab is a monoclonal antibody and hence cleared through catabolism etc., metabolism and excretion studies were not conducted with cemiplimab, based on "Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1 dated March 23, 2012).

Cemiplimab is a human IgG4 monoclonal antibody, and human IgG is excreted in milk. Thus, cemiplimab also can be excreted in milk.

4.R Outline of the review conducted by PMDA

On the basis of the data submitted, PMDA concluded that the applicant's explanation about the non-clinical pharmacokinetics of cemiplimab is acceptable.

9) Estimated to be 59.8 mL/kg by a PPK analysis based on the PK data of cemiplimab from single and repeated IV dose studies in monkeys, etc.

5. Toxicity and Outline of the Review Conducted by PMDA

5.1 Single-dose toxicity

A single-dose toxicity study was not conducted with cemiplimab. The acute toxicity of cemiplimab was assessed based on the data after the first dose in 4-week (CTD 4.2.3.2-1) and 26-week (CTD 4.2.3.2-2) repeated IV dose toxicity studies in cynomolgus monkeys (Table 9). The approximate lethal dose was determined to be >50 mg/kg. Although acute symptoms associated with anti-drug antibody (ADA) formation were observed following administration of cemiplimab, there were no symptoms related to PD-1 blockade.

5.2 Repeated-dose toxicity

Four-week and 26-week repeated IV dose toxicity studies in cynomolgus monkeys were conducted (Table 9). The findings observed following administration of cemiplimab were considered to be abnormal findings associated with ADA formation, PD-1 blockade-related increases in the counts of blood T-lymphocytes, and increased antibody response. Thus, these findings were not considered adverse. Based on the above, the no-observed-adverse-effect level (NOAEL) following 4-week and 26-week IV administration was determined to be 50 mg/kg/week. PMDA's conclusion on T-cell activation related to PD-1 blockade by cemiplimab and human effects associated with ADA formation will be described in Sections "6.R.1 Effect of anti-cemiplimab antibodies on PK of cemiplimab" and "7.R.3 Safety," taking account of the PK and safety of cemiplimab in clinical studies.

Table 9. Repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Doses (mg/kg/week)	Noteworthy findings	NOAEL (mg/kg/week)	Attached document CTD
Male and female cynomolgus monkeys	IV	4 weeks (QW) + 8-week recovery period	0,[*1] 2, 10, 50	[Systemic toxicity evaluation] ≥2: ADA formation in blood (male and female), vacuolization[*2]/hypertrophy[*2] of zona fasciculata of the adrenal cortex, splenic red pulp and hemosiderin deposition in Kupffer cells in the liver,[*3] increased number/size of germinal centers of mandibular lymph node,[*3, *5] increased granular deposits containing C3 in Kupffer cells in the liver[*3] (male) ≥10: increased adrenal weight[*2] (male), lymphocytic infiltration in the lamina propria of the stomach mucosa[*3] (female) 50: increased number/size of germinal centers of lymphoid follicle in the spleen[*3] (male and female), arterial hypertrophy/hyperplasia in the spleen,[*3] vascular/perivascular inflammation/necrosis in the spleen,[*3] deposits of monkey Ig and/or C3 in the spleen[*3] (female) 10: vacuolization/hypertrophy of zona fasciculata of the adrenal cortex,[*2] enlarged paracortex of axillary lymph node,[*3] vascular hypertrophy/hyperplasia[*3]/deposits of monkey Ig and/or C3[*3] in axillary lymph node 2: acute hemorrhage[*3]/vascular dilatation [*3] in zona fasciculata of the adrenal cortex, increased granular deposits containing C3 in adrenal cortical epithelial cells,[*3] arterial hypertrophy/hyperplasia in the spleen,[*3] deposits of monkey Ig and/or C3 in the spleen[*3] (male) [Immunotoxicity evaluation] ≥2: increases in the absolute counts and frequency of proliferating T-lymphocytes/T-helper lymphocytes/T-cytotoxic lymphocytes in blood, increased blood anti-KLH IgG titers[*4, *5] (male and female) These findings were reversible.	50	4.2.3.2-1
Male and female cynomolgus monkeys	IV	26 weeks (QW) + 12-week recovery period	0,[*1] 2, 10, 50	[Mortalities] 10: 1 of 5 animals (female), 50: 1 of 5 animals (male) 10: ADA formation in blood, lethargy,[*3] weakness,[*3] dyspnea,[*3] increases in prothrombin time[*3]/APTT,[*3] decreased fibrinogen,[*3] decreases in blood albumin[*3]/calcium,[*3] increases in inorganic phosphate[*3]/magnesium,[*3] pulmonary hemorrhage [*3] and edema,[*3] hemorrhage in the thymus[*3] 50: ADA formation in blood, decreased activity,[*3] prepuce swelling,[*3] increased platelet count,[*3] pulmonary hemorrhage[*3] and edema,[*3] hemorrhage [*3] and vascular/perivascular necrosis/inflammation in the kidney,[*3] hemorrhage [*3] and vascular/perivascular necrosis/inflammation in the skin,[*3] hemorrhage[*3] and edema[*3] in the urinary bladder [Surviving animals] ≥2: ADA formation in blood (male and female) These findings were reversible.	50	4.2.3.2-2

*1: 10 mM histidine, 5% sucrose, and 0.1% polysorbate 80 (pH6.0) solution, *2: The applicant discussed that these were stress-related secondary effects.
*3: The applicant discussed that these were abnormal findings associated with ADA formation. *4: Males and females were evaluated together.
*5: Excluding the 10 mg/kg group

5.3 Genotoxicity

Since cemiplimab is an antibody drug, and it is not expected that cemiplimab would interact directly with DNA or other chromosomal material, no genotoxicity studies were conducted.

5.4 Carcinogenicity

Since cemiplimab is an anti-neoplastic drug intended to treat patients with advanced cancer, no carcinogenicity studies were conducted.

5.5 Reproductive and developmental toxicity

A 13-week intravenous toxicology fertility assessment study in sexually mature cynomolgus monkeys was conducted (Table 10). There were no toxicological changes in male testicular tissue and function, female ovarian tissue and menstrual cycle, etc., and the NOAEL for fertility was determined to be 50 mg/kg/week.

The applicant's explanation about the use of cemiplimab in pregnant women:

For the following reasons etc., when administered to pregnant women, cemiplimab may affect the maintenance of maternal immunological tolerance to the fetus and disrupt the maintenance of pregnancy. In addition, cemiplimab has the potential to cross the placenta [see Section 4.3]. Therefore, the package insert will advise that females with reproductive potential should be advised to use effective contraception during treatment with cemiplimab and for a certain period of time after the last dose of cemiplimab, and that cemiplimab may be administered to pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks.

- In a study using allogeneic pregnant mice, blockade of PD-L1 or PD-L1 deficiency resulted in an increased incidence of abortion or fetal loss (*J Exp Med*. 2005; 202: 231-7).
- In allogeneic pregnant mice, PD-L1 blockade abrogated the protective effect of regulatory T cells, resulting in higher rates of abortion and fetal resorption (*J Immunol*. 2007; 179: 5211-9, *Am J Reprod Immunol*. 2009; 62: 283-92).

Table 10. Reproductive and developmental toxicity study

Test system	Route of administration	Duration of dosing	Doses (mg/kg/week)	Noteworthy findings	NOAEL (mg/kg/week)	Attached document CTD
Male and female cynomolgus monkeys	IV	13 weeks (QW) + 12-week recovery period	0,[*1] 10, 50	≥10: ADA formation (male and female) 10: ecchymotic hemorrhage in the scrotum and legs[*2] (male) After recovery period None	50	4.2.3.5.1-1

*1: 10 mM histidine, 5% sucrose, and 0.1% polysorbate 80 solution (pH6.0)
*2: The applicant discussed that these were abnormal findings associated with ADA formation.

5.6 Local tolerance

The local tolerance of cemiplimab was evaluated in 4-week (CTD 4.2.3.2-1) and 26-week (CTD 4.2.3.2-2) repeated IV dose toxicity studies in monkeys. There were no cemiplimab-related abnormal findings at the sites of administration at doses up to 50 mg/kg (25 mg/mL).

5.7 Tissue cross-reactivity

The applicant's explanation about the tissue cross-reactivity of cemiplimab:

A tissue cross-reactivity study with normal human and cynomolgus monkey tissues was conducted. Biotinylated cemiplimab stained mononuclear leukocytes and glial cells (Table 11), and biotinylated cemiplimab staining was similar between human and cynomolgus monkey tissues. The pattern of observed biotinylated cemiplimab staining was also consistent with reported PD-1 expression in mononuclear leukocytes and glial cells (*J Biol Chem*. 2013; 288: 11771-85, *Proc Natl Acad Sci USA*. 2008; 105: 10483-8, *J Virol*. 2013;

87: 11538-51, *Ocul Immunol Inflamm*. 2009; 17: 47-55, etc.). There should be little safety concern about positive staining of the cytoplasm of glial cells because the monoclonal antibody cannot access the cytoplasm of the cells *in vivo*.

Table 11. Tissue cross-reactivity study

Test system	Test method	Tissues/cells stained	Attached document CTD
Normal human and cynomolgus monkey tissues	Biotinylated cemiplimab 2 or 15 μg/mL was applied to cryosections of normal tissues, and binding in a panel of tissues (36 tissues) was detected by immunohistochemical staining.	[Human tissues] cytoplasm/cytoplasmic processes of glial cells in the cerebral cortex/cerebellum, cytoplasm/cytoplasmic processes of glial cells in the eye (retina)/pituitary gland/spinal cord, cytoplasm of mononuclear leucocytes in the kidney (glomerulus, tubule)/thymus, cytoplasm/plasma membrane of mononuclear leucocytes in the lymph node/spleen/tonsil	4.2.3.7.7-1
		[Cynomolgus monkey tissues] cytoplasm/cytoplasmic processes of glial cells in the cerebral cortex/cerebellum/eye (optic disc), cytoplasm of mononuclear leucocytes in the stomach/small intestine GALT/kidney (glomerulus, tubule)/lung BALT/salivary gland/thymus/bladder/large intestine, cytoplasm/plasma membrane of mononuclear leucocytes in the lymph node/spleen/thyroid gland/tonsil, cytoplasm/cytoplasmic processes of glial cells in the pituitary gland/spinal cord	

5.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the toxicity of cemiplimab is acceptable.

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 method

6.1.1.1 Cemiplimab assay

Cemiplimab in human serum was quantified by an ELISA using solid phased human PD-1 extracellular domain, biotinylated mouse anti-human IgG4 monoclonal antibody, and HRP-conjugated NeutrAvidin (lower limit of quantification [LLOQ], 1.56 ng/mL).

6.1.1.2 Anti-cemiplimab antibody assay

Anti-cemiplimab antibodies in human serum were detected by an ECL assay using ruthenium-labeled cemiplimab (detection sensitivity, approximately 2.4 and 6.6 ng/mL[10)]).

The applicant's explanation about the potential interference of cemiplimab in samples with anti-cemiplimab antibody assay:

Up to approximately 734 and 626 μg/mL[10)] of cemiplimab in samples did not interfere with the above anti-cemiplimab antibody assay. In the clinical studies in which this assay method was used, the serum cemiplimab concentrations in the samples collected were <626 μg/mL. Given this finding, the presence of cemiplimab in

[10)] Calculated using positive controls, anti-cemiplimab monoclonal antibody and anti-cemiplimab polyclonal antibody.

the samples obtained from the clinical studies in which this assay method was used did not interfere with the assay.

6.2 Clinical pharmacology

The PK of cemiplimab as monotherapy were studied in patients with cancer.

6.2.1 Japanese study

6.2.1.1 Japanese phase I study (CTD 5.3.5.2-2, Study 1622, Part 1 [ongoing since June 2017 (data cutoff date of May 1, 2021)])

An open-label, uncontrolled study was conducted in 13 patients with advanced solid malignancies (13 included in PK analysis) to investigate the PK etc. of cemiplimab. Cemiplimab 250 or 350 mg Q3W was to be administered intravenously, and serum cemiplimab concentrations were determined.

Table 12 shows the PK parameters of cemiplimab after the first dose of cemiplimab.

Table 12. PK parameters of cemiplimab

Dose (mg)	N	C_{max} (mg/L)	C_{trough} (mg/L)	AUC_{3week} (mg·day/L)	$t_{1/2}$ (day)
250	6	144 ± 24.4	31.3 ± 7.14	1,077 ± 86.3	18.2 ± 6.04
350	7	157 ± 21.9	41.0 ± 6.91*	1,345 ± 99.7*	17.6 ± 3.32*

Mean ± SD, *: N = 6

6.2.2 Global study

6.2.2.1 Global phase III study (CTD 5.3.5.1-1, Study 1676 [ongoing since September 2017 (data cutoff date of January 4, 2021)])

A randomized, open-label study was conducted in 608 patients with advanced or recurrent cervical cancer previously treated with chemotherapy (295 in the cemiplimab group included in PK analysis) to compare the efficacy and safety of cemiplimab versus the investigator's choice of chemotherapy. Each cycle was 6 weeks, and cemiplimab 350 mg Q3W was to be administered intravenously. Serum cemiplimab concentrations were determined.

Table 13 shows the PK parameters of cemiplimab.

Table 13. PK parameters of cemiplimab

Sampling time point	N	C_{max} (mg/L)	N	C_{trough} (mg/L)
Day 1 of Cycle 1	284	134 ± 58.7	—	—
Day 1 of Cycle 4	112	186 ± 60.8	113	65.6 ± 30.0

Mean ± SD, —: Not measured.

6.2.3 Foreign study

6.2.3.1 Foreign phase I study (CTD 5.3.5.2-1, Study 1423, dose escalation cohorts [February 2015 to November 2019])

An open-label, uncontrolled study was conducted in 60 patients with advanced solid malignancies (60 patients included in PK analysis, including 18 patients who received cemiplimab monotherapy) to investigate the PK etc. of cemiplimab. Cemiplimab 1, 3, or 10 mg/kg Q2W was to be administered intravenously, and serum cemiplimab concentrations were determined.

Table 14 shows the PK parameters of cemiplimab after the first dose of cemiplimab. Cemiplimab exposure increased almost dose-proportionally over the dose range tested.

Table 14. PK parameters of cemiplimab

Dose (mg/kg)	N	C_{max} (mg/L)	AUC_{2week} (mg·day/L)	$t_{1/2}$ (day)
1	6	22.7 ± 4.62	144 ± 28.0	8.27 ± 1.53
3	6	68.3 ± 18.3	467 ± 136	12.4 ± 4.04
10	6	264 ± 84.2	1,811 ± 234	12.9 ± 4.10

Mean ± SD

6.2.4 PPK analysis

Based on cemiplimab PK data (17,312 PK samples in 1,063 patients) obtained from foreign clinical studies (Studies 1423, 1540, 1620, and 1624), a PPK analysis was performed by non-linear mixed-effects modeling (software used: NONMEM version 7.4). The PK of cemiplimab were described by a 2-compartment model with first-order elimination and time-dependent CL.

Table 15 shows the PK parameters and covariates assessed in this analysis.

Table 15. Covariates tested

PK parameters	Covariates
CL	body weight, age, sex, albumin, baseline ALT, baseline AST, baseline total bilirubin, baseline CrCL, baseline creatinine, baseline ECOG PS, ethnicity (Hispanic or Latino, Not Hispanic or Latino, unknown), race (White, others, unknown), tumor type (CSCC, BCC, NSCLC, others)
V1	body weight, age, sex, baseline albumin, race
EMAX	body weight, albumin, baseline albumin, tumor type
T50	albumin, baseline albumin, tumor type

As significant covariates on (1) CL, (2) V1, (3) EMAX, and (4) T50 of cemiplimab, (1) body weight, sex, albumin, tumor type (cutaneous squamous cell carcinoma [CSCC] and basal cell carcinoma [BCC]), and baseline ALT, (2) sex and baseline albumin, (3) tumor type (BCC), and (4) tumor type (others) were identified. The applicant explained that since the magnitude of these covariate effects on cemiplimab exposure was limited, these covariates are unlikely to have a clinically significant impact on the PK of cemiplimab.

6.2.5 Exposure-efficacy/safety relationship

6.2.5.1 Exposure-efficacy relationship

Based on the results of a global phase III study (Study 1676), subjects were divided into 4 quartiles[11] according to cemiplimab exposures (the C_{trough} after the first dose[12]) to evaluate the relationship between cemiplimab exposure and overall survival (OS)/progression-free survival (PFS)/objective response rate/duration of response. There was no clear relationship between cemiplimab exposure and the above efficacy endpoints.

6.2.5.2 Exposure-safety relationship

Based on the results of a global phase III study (Study 1676), subjects were divided into 4 quartiles[13] according to cemiplimab exposures (the C_{max} after the first dose[12]) to evaluate the relationship between cemiplimab exposure and the incidences of all immune-related adverse events and Grade ≥3 immune-related adverse events. There was no clear relationship between cemiplimab exposure and the above adverse events.

6.2.6 Effects of decreased renal or hepatic function on PK of cemiplimab

No clinical studies to investigate the PK of cemiplimab in patients with renal or hepatic impairment have been conducted. However, the applicant explained that given the following points, decreased renal or hepatic function is unlikely to affect the PK of cemiplimab.

- Cemiplimab is considered to be cleared through catabolism.
- The PPK analysis showed no clear differences in cemiplimab exposure between patients with mild, moderate, or severe renal impairment and patients with normal renal function and between patients with mild or moderate hepatic impairment and patients with normal hepatic function.

6.2.7 Differences in PK of cemiplimab between Japanese and non-Japanese populations

The applicant's explanation:

Since there were no clear differences in the C_{max} or C_{trough} of cemiplimab between Japanese and non-Japanese patients in Study 1676 (Table 16), no clear differences in the PK of cemiplimab have been observed between Japanese and non-Japanese populations.

Table 16. PK parameters of cemiplimab

	Sampling time point	N	C_{max} (mg/L)	C_{trough} (mg/L)
Japanese patients	Day 1 of Cycle 1	28	144 ± 32.1	—
	Day 1 of Cycle 4	12	211 ± 36.8	78.4 ± 29.8*
Non-Japanese patients	Day 1 of Cycle 1	256	133 ± 60.9	—
	Day 1 of Cycle 4	100	183 ± 62.5	63.9 ± 29.8

Mean ± SD, *: N = 13, —: Not measured.

6.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the applicant's explanation about the clinical pharmacology etc. of cemiplimab is acceptable, except for the considerations in the following section.

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[11] The ranges of C_{trough} (mg/L) in the quartiles were ≥4.3 and ≤22.3; >22.3 and ≤27.3; >27.3 and ≤32.8; and >32.8 and ≤51.4.

[12] Predicted values from the PPK analysis [see Section 6.2.4].

[13] The ranges of C_{max} (mg/L) in the quartiles were ≥61.6 and ≤115; >115 and ≤128.6; >128.6 and ≤145.1; and >145.1 and ≤242.6.

6.R.1 Effect of anti-cemiplimab antibodies on PK of cemiplimab

The applicant's explanation about the effect of anti-cemiplimab antibodies on the PK of cemiplimab:

The incidence of anti-cemiplimab antibodies was determined in Studies 1423, 1540, 1620, 1624, and 1676. Anti-cemiplimab antibodies were detected in 22 of 1,029 patients evaluable for anti-cemiplimab antibodies (2.1%).

Based on the time-matched PK/anti-cemiplimab antibody assay data from patients treated with the proposed dosing regimen of cemiplimab in Study 1676, there were no clear differences in the serum cemiplimab concentration between anti-cemiplimab antibody-positive and -negative patients (Table 17). Similar results were obtained also from Studies 1620 and 1624. Given these findings, anti-cemiplimab antibodies are unlikely to affect the PK of cemiplimab.

Table 17. Serum cemiplimab concentrations in anti-cemiplimab antibody-positive and -negative patients (μg/mL)

Sampling time point	N	Anti-cemiplimab antibody-positive patients	N	Anti-cemiplimab antibody-negative patients
Pre-dose on Day 1 of Cycle 3	1	103	139	57.7 (1.95, 292)
30 days after the last dose of cemiplimab	3	39.9 (4.23, 40.1)	85	38.4 (1.81, 151)

Median (Min., Max.) (Individual value is listed for N = 1)

PMDA's discussion:

Given that the number of anti-cemiplimab antibody-positive patients was limited, it is difficult to draw a definitive conclusion on the effect of anti-cemiplimab antibodies on the PK of cemiplimab. Thus, it is necessary to continue to collect information on the effect of anti-cemiplimab antibodies on the PK of cemiplimab, and if a new finding is obtained, the information should be provided appropriately to healthcare professionals in clinical practice.

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 the results from a total of 3 studies presented in Table 18: a Japanese phase I study, a global phase III study, and a foreign phase I study. The applicant also submitted reference data, in the form of the results from a total of 3 studies presented in Table 18: two foreign phase II studies and 1 foreign phase III study.

Table 18. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	No. of patients enrolled	Dosing regimen	Main endpoints
Evaluation	Japan	1622	I	[Part 1[*1]] Patients with advanced solid malignancies	13 (1) 6 (2) 7	(1) Cemiplimab 250 mg Q3W IV (2) Cemiplimab 350 mg Q3W IV	Tolerability Safety PK
	Global	1676	III	Patients with advanced or recurrent cervical cancer previously treated with chemotherapy	608 (1) 304 (2) 304	(1) Cemiplimab 350 mg Q3W IV (2) Investigator's choice of chemotherapy: • PEM 500 mg/m^2 Q3W IV • NGT 1 mg/m^2 IV on Days 1-5 of each 3-week cycle • IRI 100 mg/m^2 IV on Days 1, 8, 15, and 22 of each 6-week cycle • GEM 1,000 mg/m^2 IV on Days 1 and 8 of each 3-week cycle • VNR 30 mg/m^2 IV on Days 1 and 8 of each 3-week cycle	Efficacy Safety
	Foreign	1423[*2]	I	[Dose escalation cohorts] (1)-(4) Patients with advanced solid tumors [Expansion cohorts] (5)(6) Patients with NSCLC (7) Patients with head and neck squamous cell carcinoma (8) Patients with breast cancer (9) Patients with advanced solid tumors (10) Patients with advanced solid tumors excluding (5)-(8) (11) Patients with metastatic CSCC (12) Patients with unresectable locally advanced CSCC (13) Patients with advanced/recurrent colorectal cancer with MSI-High (14) Patients with advanced/recurrent endometrial cancer with MSI-High (15) Patients with castration-resistance prostate cancer with MSI-High (16) Patients with advanced solid tumors with MSI-High excluding (13)-(15) (17) Patients with unresectable hepatocellular carcinoma (18)(19) Patients with advanced solid tumors (20) Patients with unresectable colorectal cancer with MSI-High (21)(25) Patients with advanced/recurrent NSCLC (22) Patients with GBM (23) Patients with recurrent GBM (24) Patients with advanced solid tumors with HIV infection (26) Patients with advanced/recurrent NSQ-NSCLC (27)(28) Patients with advanced or recurrent cervical cancer (29) Patients with BCC	Dose escalation cohorts: 60 Expansion cohorts: 338	[Dose escalation cohorts] (1) Cemiplimab 1, 3, or 10 mg/kg Q2W IV (2) Cemiplimab 1 or 3 mg/kg Q2W IV + radiotherapy (3) Cemiplimab 3 mg/kg Q2W IV + CPA (4) Cemiplimab 3 mg/kg Q2W IV + radiotherapy + CPA [Expansion cohorts] (5) Cemiplimab 200 mg Q2W IV (6)(28) Cemiplimab 3 mg/kg Q2W IV + radiotherapy (7)-(10) Cemiplimab 3 mg/kg Q2W IV + radiotherapy + CPA etc. (11)-(17), (20)(24)(27)(29) Cemiplimab 3 mg/kg Q2W IV (18)(21) Cemiplimab 3 mg/kg Q2W IV + CBDCA + DTX (19) Cemiplimab 3 mg/kg Q2W IV + DTX (22)(23) Cemiplimab 1 or 3 mg/kg Q2W IV + radiotherapy (25) Cemiplimab 3 mg/kg Q3W IV + CBDCA + PTX (26) Cemiplimab 3 mg/kg Q3W IV + CBDCA + PEM	Tolerability Safety PK
Reference	Foreign	1540	II	(1) Patients with metastatic CSCC (2) Patients with locally advanced CSCC (3) Patients with metastatic CSCC	193 (1) 59 (2) 78 (3) 56	(1)(2) Cemiplimab 3 mg/kg Q2W IV (3) Cemiplimab 350 mg Q3W IV	Efficacy Safety PK
		1620	II	Patients with advanced BCC	132	Cemiplimab 350 mg Q3W IV	Efficacy Safety
		1624[*2]	III	Patients with PD-L1-positive, unresectable, advanced/recurrent NSCLC	710 (1) 356 (2) 354	(1) Cemiplimab 350 mg Q3W IV (2) Investigator's choice: platinum agent + PTX, platinum agent + GEM, or platinum agent + PEM	Efficacy Safety

*1: Part 2 (to assess the efficacy and safety of cemiplimab alone or in combination with chemotherapy in chemotherapy-naïve patients with unresectable advanced/recurrent NSCLC) is currently ongoing, and the results from Part 1 only were submitted for the present application. This review report describes Part 1 only.

*2: The dosing regimens of concomitant medications are omitted.

These clinical studies are summarized below.

The main adverse events other than deaths observed in the clinical studies are described in Section "7.3 Adverse events etc. observed in clinical studies," and PK study results are described in Sections "6.1 Summary of biopharmaceutic studies and associated analytical methods" and "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 1622, Part 1 [ongoing since June 2017 (data cutoff date of May 1, 2021)])

An open-label, uncontrolled study was conducted at 1 site in Japan to investigate the tolerability, safety, PK, etc. of cemiplimab in patients with advanced solid malignancies (target sample size, 14 subjects).

Cemiplimab 250 or 350 mg Q3W was to be administered intravenously until disease progression or a criterion for study withdrawal was met.

All of 13 subjects enrolled in the study (6 in the 250 mg group, 7 in the 350 mg group) received cemiplimab and were included in the safety analysis set.

The dose-limiting toxicity (DLT) assessment period was until 21 days after the start of cemiplimab. No DLTs were observed. Cemiplimab was considered tolerable in Japanese patients, and the recommended dose of cemiplimab was 350 mg Q3W.

Regarding safety, there were no deaths during the cemiplimab treatment period or within 90 days after the last dose of cemiplimab.

7.1.2 Global study

7.1.2.1 Global phase III study (CTD 5.3.5.1-1, Study 1676 [ongoing since September 2017 (data cutoff date of January 4, 2021)])

A randomized, open-label study was conducted at 97 sites in 14 countries or regions including Japan to compare the efficacy and safety of cemiplimab versus the investigator's choice of chemotherapy (IC) in patients with advanced or recurrent cervical cancer[14)] previously treated with chemotherapy[15)] (target sample size, 590 patients including 460 patients with SCC).

[14)] Patients with SCC or adenocarcinoma (including adenosquamous carcinoma) were enrolled in the study.
[15)] Patients after treatment with platinum-containing chemotherapy, with or without BV, used to treat advanced or recurrent cervical cancer, were enrolled in the study.

Subjects in the cemiplimab group were to receive cemiplimab 350 mg Q3W IV. Subjects in the IC group were to receive pemetrexed sodium hydrate (PEM) (500 mg/m^2 Q3W), nogitecan hydrochloride (NGT) (1 mg/m^2 on Days 1-5 of each 3-week cycle), irinotecan hydrochloride (IRI) (100 mg/m^2 on Days 1, 8, 15, and 22 of each 6-week cycle), gemcitabine hydrochloride (GEM) (1,000 mg/m^2 on Days 1 and 8 of each 3-week cycle), or vinorelbine ditartrate (VNR) (30 mg/m^2 on Days 1 and 8 of each 3-week cycle) IV. Treatment was to be continued until disease progression or a criterion for study withdrawal was met.

All of 608 subjects who were enrolled in the study and randomized (304 in the cemiplimab group, 304 in the IC group) were included in the full analysis set (FAS), which was used for efficacy analyses (including 29 Japanese patients in the cemiplimab group and 27 Japanese patients in the IC group). After excluding 18 subjects who did not receive study drug (5 in the cemiplimab group, 13 in the IC group) from the FAS, 590 subjects (300 in the cemiplimab group,[16)] 290 in the IC group) were included in the safety analysis set (including 29 Japanese patients in the cemiplimab group and 27 Japanese patients in the IC group).

The primary endpoint for the study was overall survival (OS). The hypothesis testing of OS was to be performed with a hierarchical order of the SCC population, then the FAS. The major changes to the study plan are described below.

- At the start of the study, the target sample size was approximately 436 patients in the FAS, and patients with SCC or adenocarcinoma (including adenosquamous carcinoma) were enrolled in the study. However, as the results of Study 1423 etc. suggested that the efficacy of cemiplimab may be associated with SCC histology, only patients with SCC were eligible for enrollment in the study, starting with Protocol Amendment 5 (as of March 8, 2019).[17)]
- Although SCC has been reported to account for approximately 85% of all cervical cancers (*Int J Cancer*. 2006; 118: 1481-95), as the proportion of patients with SCC histology in the total study population [17)] as of Protocol Amendment 5 was lower than the above report, a new target enrollment of 436 SCC patients was chosen, and the target total enrollment was changed to 534 patients to mimic the real world distribution of cervical cancer histologies (Protocol Amendment 5 [as of March 8, 2019]).
- Although no interim analysis for efficacy evaluation had been planned at the start of the study, 2 interim analyses were added for earlier efficacy assessment. Two interim analyses and the final analysis were to be performed when approximately 238, 289, and 340 OS events had been observed in the SCC population, respectively. With these changes, the target enrollment for SCC and the target total enrollment were changed to 460 and 590 patients, respectively, to maintain 90% power with 2 interim analyses (Protocol Amendment 6 [as of May 26, 2020]). Lan-DeMets O'Brien-Fleming alpha spending function was to be used to control the type I error rate for the interim analyses of OS.

The results of the second interim analysis of the primary efficacy endpoint of OS (data cutoff date of January 4, 2021) and the Kaplan-Meier curves are shown in Table 19 and Figure 1 and Figure 2, and the superiority of

[16)] One subject who was assigned to the IC group, but mistakenly received cemiplimab was handled as the cemiplimab group in the safety analysis set.
[17)] As of Protocol Amendment 5, 198 patients (133 SCC patients, 65 adenocarcinoma patients) had been enrolled in the study.

cemiplimab to IC was demonstrated in both the SCC population and the FAS. Based on these results, the independent data monitoring committee (IDMC) recommended early termination of the study for efficacy on March 8, 2021.

Table 19. Results of second interim analysis of OS (Data cutoff date of January 4, 2021)

	SCC population		FAS	
	Cemiplimab	IC	Cemiplimab	IC
N	239	238	304	304
Number of events (%)	143 (59.8)	161 (67.6)	184 (60.5)	211 (69.4)
Median [95% CI] (months)	11.1 [9.2, 13.4]	8.8 [7.6, 9.8]	12.0 [10.3, 13.5]	8.5 [7.5, 9.6]
Hazard ratio [95% CI]	0.727 [0.579, 0.914][*1]		0.685 [0.560, 0.838][*2]	
P-value[*3] (one-sided level of significance)	0.00306 (0.01508)		0.00011 (0.025)	

*1: Stratified Cox proportional hazards model using geographic region (North America versus Asia-Pacific versus the rest of the world) as a stratification factor

*2: Stratified Cox proportional hazards model using geographic region (North America versus Asia-Pacific versus the rest of the world) and histology (SCC versus adenocarcinoma) as stratification factors, *3: Stratified log-rank test (the same stratification factors as those for Cox proportional hazards model)

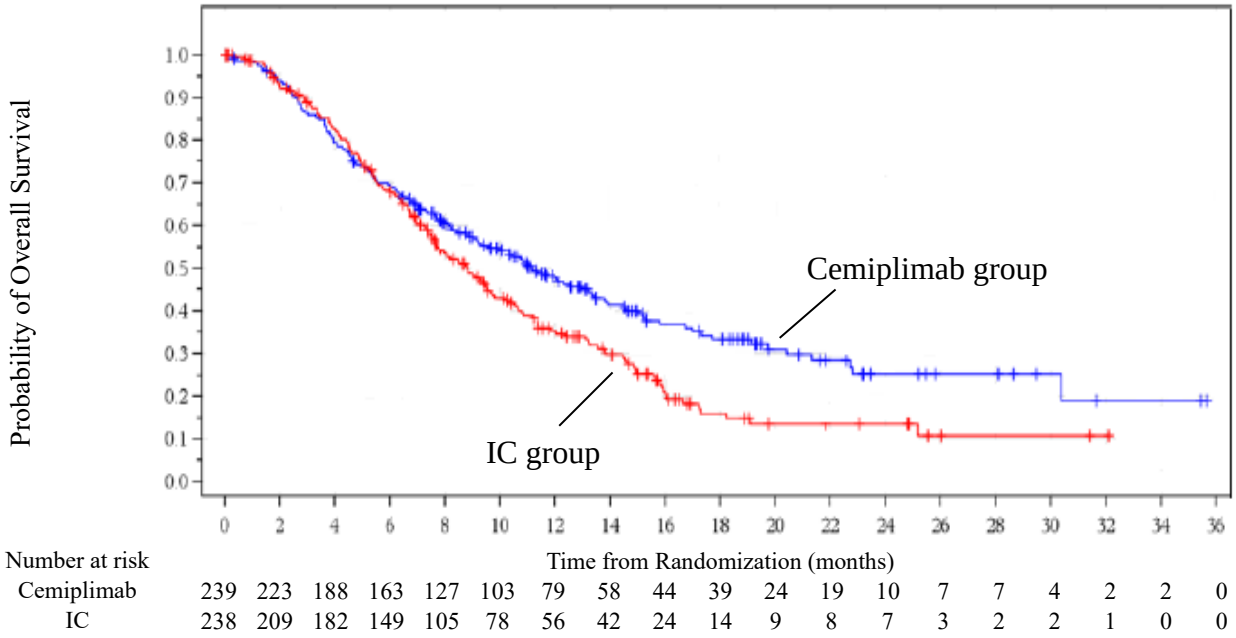


Figure 1. Kaplan-Meier curves for OS at the second interim analysis (SCC population, Data cutoff date of January 4, 2021)

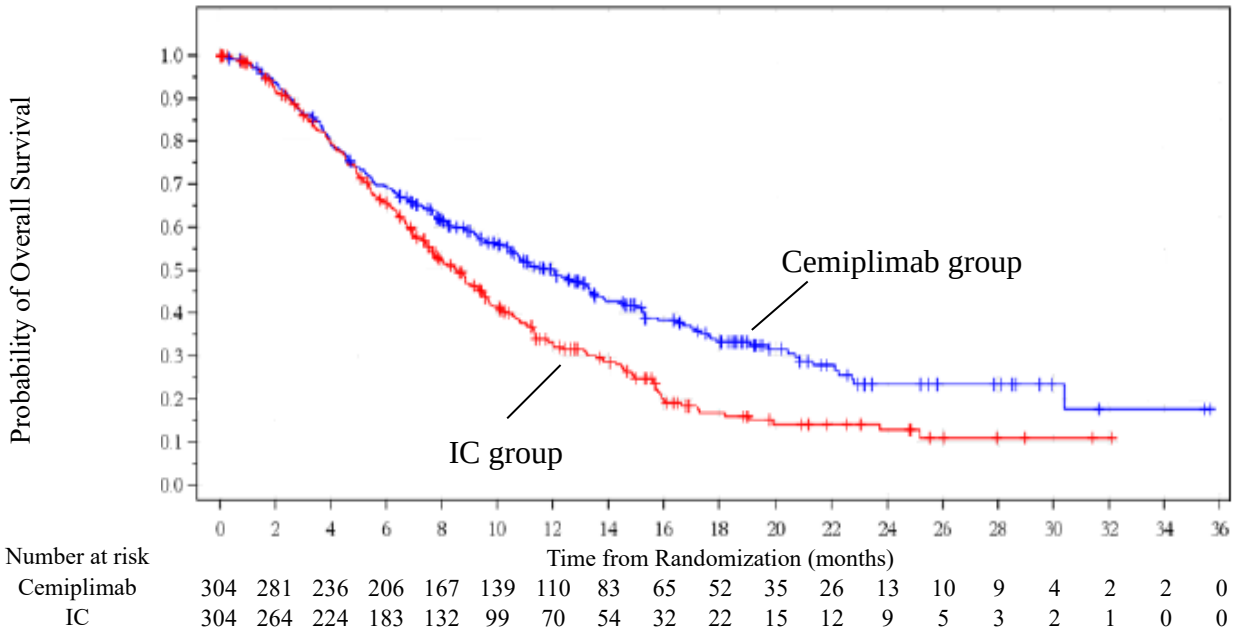


Figure 2. Kaplan-Meier curves for OS at the second interim analysis (FAS, Data cutoff date of January 4, 2021)

Regarding safety, 76 of 300 subjects (25.3%) in the cemiplimab group and 70 of 290 subjects (24.1%) in the IC group died during the study treatment period or within 90 days after the last dose of study drug (7 of 29 Japanese patients in the cemiplimab group and 8 of 27 Japanese patients in the IC group died). The causes of deaths other than disease progression (67 in the cemiplimab group, 66 in the IC group) were unknown (2 subjects); and cerebrovascular accident; pulmonary embolism; respiratory failure; ischaemic stroke; pneumonia; death; and sudden death (1 subject each) in the cemiplimab group and unknown (2 subjects); and performance status decreased; and multiple organ dysfunction syndrome and neutropenic sepsis (1 subject each) in the IC group, and a causal relationship to study drug could not be ruled out for performance status decreased; and multiple organ dysfunction syndrome and neutropenic sepsis (1 subject each) in the IC group (The causes of deaths of Japanese patients were all disease progression).

7.1.3 Foreign study

7.1.3.1 Foreign phase I study (CTD 5.3.5.2-1, Study 1423 [February 2015 to November 2019 (data cutoff date of April 30, 2019)])

An open-label, uncontrolled study was conducted at 38 sites overseas to investigate the tolerability, safety, etc. of cemiplimab as monotherapy or in combination with other anti-cancer treatments etc. in patients with advanced solid malignancies etc. (target sample size, 60 subjects in dose escalation cohorts, 323 subjects in expansion cohorts).

The dosing regimens for dose escalation and expansion cohorts are shown below, and treatment was to be continued until disease progression or a criterion for study withdrawal was met.

[Dose escalation cohorts]

(1) Cemiplimab 1, 3, or 10 mg/kg Q2W IV

(2) Cemiplimab 1 or 3 mg/kg Q2W IV + radiotherapy

(3) Cemiplimab 3 mg/kg Q2W IV + cyclophosphamide hydrate (CPA)
(4) Cemiplimab 3 mg/kg Q2W IV + radiotherapy + CPA
[Expansion cohorts]
(5) Cemiplimab 200 mg Q2W IV
(6)(28) Cemiplimab 3 mg/kg Q2W IV + radiotherapy
(7)-(10) Cemiplimab 3 mg/kg Q2W IV + radiotherapy + CPA, etc.
(11)-(17), (20)(24)(27)(29) Cemiplimab 3 mg/kg Q2W IV
(18)(21) Cemiplimab 3 mg/kg Q2W IV + carboplatin (CBDCA) + docetaxel hydrate (DTX)
(19) Cemiplimab 3 mg/kg Q2W IV + DTX
(22)(23) Cemiplimab 1 or 3 mg/kg Q2W IV + radiotherapy
(25) Cemiplimab 3 mg/kg Q3W IV + CBDCA + PTX
(26) Cemiplimab 3 mg/kg Q3W IV + CBDCA + PEM

The safety analysis set included 398 subjects who were enrolled in the study and received study drug (60 subjects in dose escalation cohorts [18 subjects received 1 mg/kg cemiplimab, 36 subjects received 3 mg/kg cemiplimab, 6 subjects received 10 mg/kg cemiplimab], 338 subjects in expansion cohorts).

Regarding safety, 9 of 130 subjects (6.9%) in the cemiplimab monotherapy group (0 in the 1 mg/kg Q2W group, 7 of 98 subjects [7.1%] in the 3 mg/kg Q2W group, 0 in the 10 mg/kg Q2W group, 2 of 20 subjects [10.0%] in the 200 mg Q2W group), 1 of 64 subjects (1.6%) in the cemiplimab + chemotherapy group, 5 of 86 subjects (5.8%) in the cemiplimab + radiotherapy group, and 8 of 118 subjects (6.8%) in the cemiplimab + chemotherapy + radiotherapy group died during the study treatment period or within 30 days after the last dose of study drug. The causes of deaths other than disease progression (7 in the cemiplimab monotherapy group [5 in the 3 mg/kg Q2W group, 2 in the 200 mg Q2W group], 1 in the cemiplimab + chemotherapy group, 3 in the cemiplimab + radiotherapy group, 8 in the cemiplimab + chemotherapy + radiotherapy group) were acute kidney injury; and pulmonary embolism (1 subject each) in the cemiplimab monotherapy group and pneumonitis (2 subjects) in the cemiplimab + radiotherapy group. A causal relationship to study drug could not be ruled out for pneumonitis (2 subjects) in the cemiplimab + radiotherapy group.

7.2 Reference data

7.2.1 Foreign studies

7.2.1.1 Foreign phase II study (CTD 5.3.5.2-3, Study 1540 [ongoing since August 2016 (data cutoff date of September 20, 2018 for Groups 1 and 3, data cutoff date of October 10, 2018 for Group 2)])

An open-label, uncontrolled study was conducted at 35 sites overseas to assess the efficacy and safety of cemiplimab in patients with locally advanced or metastatic cutaneous squamous cell carcinoma (CSCC) (target sample size, approximately 182 subjects).

Patients with metastatic CSCC in Group 1 and patients with locally advanced CSCC in Group 2 were to receive cemiplimab 3 mg/kg Q2W IV, and patients with metastatic CSCC in Group 3 were to receive cemiplimab 350

mg Q3W IV. Treatment was to be continued until disease progression or a criterion for study withdrawal was met.

All of 193 subjects enrolled in the study (59 in Group 1, 78 in Group 2, 56 in Group 3) received cemiplimab and were included in the safety analysis set.

Regarding safety, 9 of 59 subjects (15.3%) in Group 1, 3 of 78 subjects (3.8%) in Group 2, and 8 of 56 subjects (14.3%) in Group 3 died during the cemiplimab treatment period or within 105 days after the last dose of cemiplimab. The causes of deaths other than disease progression (6 in Group 1, 7 in Group 3) were death; acute respiratory distress syndrome; and others (1 subject each) in Group 1, death; pneumonia; and others (1 subject each) in Group 2, and arterial haemorrhage (1 subject) in Group 3, and a causal relationship to cemiplimab could not be ruled out for death (1 subject) in Group 2.

7.2.1.2 Foreign phase II study (CTD 5.3.5.2-4, Study 1620 [ongoing since July 2017 (data cutoff date of February 17, 2020)])

An open-label, uncontrolled study was conducted at 50 sites overseas to assess the efficacy and safety of cemiplimab in patients with locally advanced or metastatic basal cell carcinoma (BCC) (target sample size, approximately 137 subjects).

Cemiplimab 350 mg Q3W was to be administered intravenously. Treatment was to be continued until disease progression or a criterion for study withdrawal was met.

All of 132 subjects enrolled in the study received cemiplimab and were included in the safety analysis set.

Regarding safety, 8 of 132 subjects (6.1%) died during the cemiplimab treatment period or within 105 days after the last dose of cemiplimab. The causes of deaths other than disease progression (2 subjects) were others (2 subjects); and staphylococcal pneumonia; brain neoplasm malignant; acute kidney injury; and cachexia (1 subject each), and a causal relationship to cemiplimab was denied for all those cases.

7.2.1.3 Foreign phase III study (CTD 5.3.5.1-2, Study 1624 [ongoing since May 2017 (data cutoff date of March 1, 2020)])

A randomized, open-label study was conducted at 138 sites overseas to compare the efficacy and safety of cemiplimab versus platinum-containing chemotherapy in chemotherapy-naïve patients with PD-L1-positive (≥50%), unresectable, advanced or recurrent non-small cell lung cancer (NSCLC) (target sample size, 700 subjects).

The dosing regimens are shown below. Treatment was to be continued until disease progression or a criterion for study withdrawal was met.

- Cemiplimab group: cemiplimab 350 mg Q3W IV[18)]
- IC group: platinum agent in combination with PTX, GEM, or PEM IV for 4 to 6 3-week cycles

The safety analysis set included 697 subjects who were enrolled in the study and received study drug (355 in the cemiplimab group, 342 in the IC group).

Regarding safety, 79 of 355 subjects (22.3%) in the cemiplimab group and 77 of 342 subjects (22.5%) in the IC group died during the study treatment period or within 90 days after the last dose of study drug. The causes of deaths other than disease progression (43 in the cemiplimab group, 40 in the IC group) were death (7 subjects); respiratory failure (4 subjects); pulmonary embolism (3 subjects); septic shock (2 subjects); and bronchospasm; completed suicide; sepsis; cerebral infarction; autoimmune myocarditis; cerebral ischaemia; embolism; cardiopulmonary failure; cardiac failure; multiple organ dysfunction syndrome; haemorrhagic shock; hypoxia; pneumonia; cardio-respiratory arrest; acute myocardial infarction; myocardial infarction; nephritis; tumour hyperprogression; dyspnoea; and pulmonary haemorrhage (1 subject each) in the cemiplimab group and pneumonia (8 subjects); cardiac arrest (3 subjects); cardio-respiratory arrest; respiratory failure; sudden death; death; pulmonary embolism; dyspnoea; myocardial infarction; and unknown (2 subjects each); and pulmonary tuberculosis; lung abscess; septic shock; cerebrovascular accident; pulmonary haemorrhage; myocardial ischaemia; bronchitis; ischaemic cerebral infarction, pneumonia, and sepsis; completed suicide; and acute cardiac failure (1 subject each) in the IC group. A causal relationship to study drug could not be ruled out for septic shock; autoimmune myocarditis; cardiopulmonary failure; cardiac failure; death; cardio-respiratory arrest; nephritis; tumour hyperprogression; and respiratory failure (1 subject each) in the cemiplimab group and pulmonary embolism; and pneumonia (2 subjects each); and lung abscess; cardiac arrest; and myocardial infarction (1 subject each) in the IC group.

7.R Outline of the review conducted by PMDA

7.R.1 Review strategy

PMDA review strategy:

Among the evaluation data submitted, the pivotal clinical study to evaluate the efficacy and safety of cemiplimab is a global phase III study in patients with advanced or recurrent cervical cancer previously treated with chemotherapy (Study 1676). PMDA decided to focus its review on this study. The efficacy of cemiplimab in Japanese patients is evaluated systematically based on Study 1676 etc., in accordance with "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), partial revision of "Basic Principles on Global Clinical Trials (Reference Cases)"(Administrative Notice dated December 10, 2021), "Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018), etc.

7.R.2 Efficacy

Based on the following considerations, PMDA concluded that the efficacy of cemiplimab in patients with

[18)] Planned treatment duration was up to 108 weeks.

advanced or recurrent cervical cancer previously treated with chemotherapy was demonstrated.

7.R.2.1 Choice of control group

The applicant's explanation about the reason for choosing PEM, NGT, IRI, GEM, and VNR as chemotherapy options in the control group of Study 1676:

Although no standard of care had been established for the patient population of Study 1676, i.e., patients with advanced or recurrent cervical cancer previously treated with chemotherapy, at the time of planning Study 1676, given that PEM, NGT, IRI, GEM, and VNR were included as possible second-line treatment options in the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Cervical Cancer (the NCCN guidelines) (ver.1.2017) etc., PEM, NGT, IRI, GEM, or VNR was to be chosen by the investigator in the control group of Study 1676.

PMDA's discussion:

PMDA largely accepted the applicant's explanation. However, the possibility that the chemotherapy choices in the IC group affected the efficacy assessment of cemiplimab needs to be assessed based on the results of efficacy evaluation of the chemotherapy choices in the IC group versus cemiplimab [see Section 7.R.2.2].

7.R.2.2 Efficacy endpoint and evaluation results

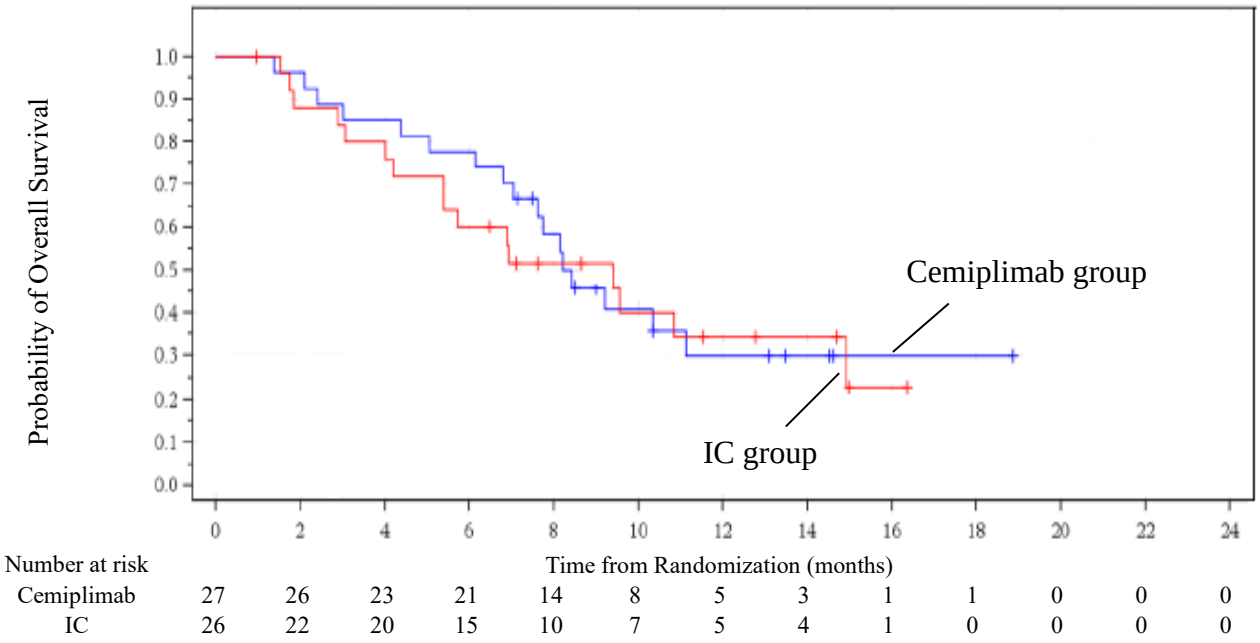
Study 1676 demonstrated the superiority of cemiplimab to IC in the primary endpoint of OS in both the SCC population and the FAS [see Section 7.1.2.1]. In the FAS, the hazard ratios of OS for cemiplimab versus IC [95% confidence interval (CI)] in the subgroups according to the control therapy determined before randomization by the investigator from PEM, NGT, IRI, GEM, and VNR were 0.711 [0.515, 0.981], 0.781 [0.312, 1.955], 0.689 [0.279, 1.702], 0.757 [0.539, 1.062], and 0.767 [0.399, 1.477], respectively. There were no differences affecting the efficacy assessment of cemiplimab among the chemotherapy choices in the IC group.

The results of the second interim analysis of OS (data cutoff date of January 4, 2021) and the Kaplan-Meier curves in the Japanese subgroup are shown in Table 20 and Figure 3 and Figure 4.

Table 20. Results of second interim analysis of OS in Japanese subgroup (Data cutoff date of January 4, 2021)

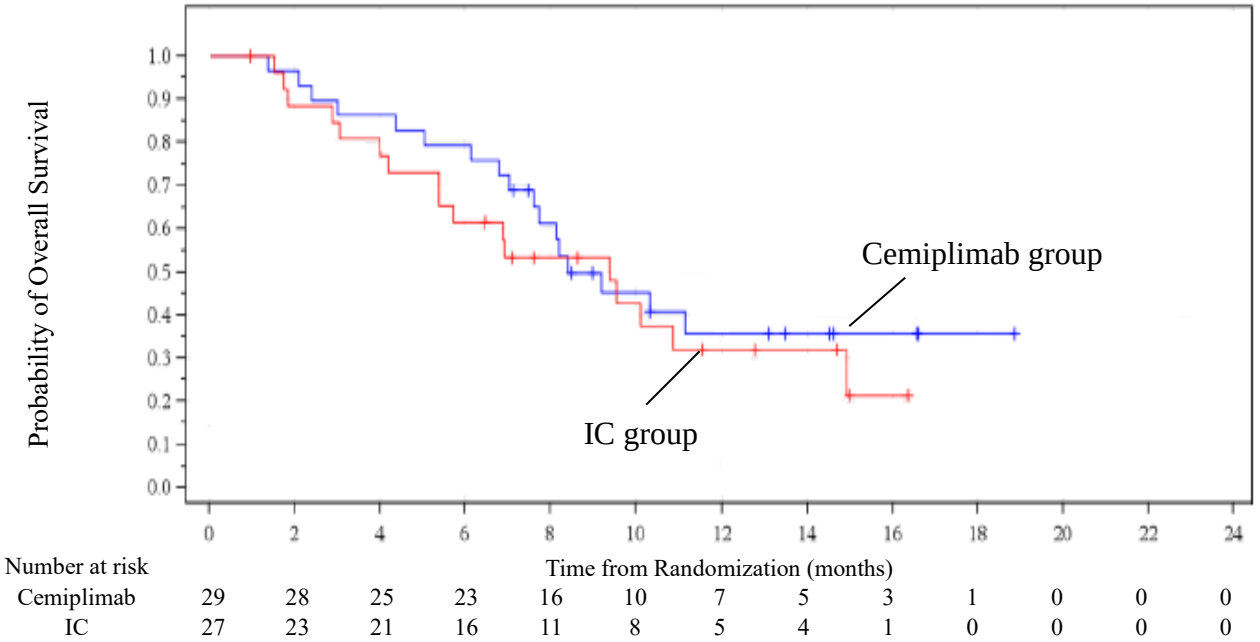
	SCC population		FAS	
	Cemiplimab	IC	Cemiplimab	IC
N	27	26	29	27
Number of events (%)	17 (63.0)	16 (61.5)	17 (58.6)	17 (63.0)
Median [95% CI] (months)	8.3 [6.8, 11.1]	9.4 [5.4, 14.9]	8.4 [7.0, －]	9.4 [5.4, 14.9]
Hazard ratio [95% CI]*	0.924 [0.464, 1.838]		0.855 [0.434, 1.684]	

－: Not estimable, *: Stratified Cox proportional hazards model using histology (SCC versus adenocarcinoma) as a stratification factor



Number at risk													
Cemiplimab	27	26	23	21	14	8	5	3	1	1	0	0	0
IC	26	22	20	15	10	7	5	4	1	0	0	0	0

Figure 3. Kaplan-Meier curves for OS at the second interim analysis in the Japanese subgroup (SCC population, Data cutoff date of January 4, 2021)



Number at risk													
Cemiplimab	29	28	25	23	16	10	7	5	3	1	0	0	0
IC	27	23	21	16	11	8	5	4	1	0	0	0	0

Figure 4. Kaplan-Meier curves for OS at the second interim analysis in the Japanese subgroup (FAS, Data cutoff date of January 4, 2021)

PMDA's discussion:

For the following reasons etc., the efficacy of cemiplimab in patients with advanced or recurrent cervical cancer previously treated with chemotherapy was demonstrated.

- Study 1676 demonstrated the superiority of cemiplimab to IC in the primary endpoint of OS in both the SCC population and the FAS.
- The number of Japanese patients and the number of events in Japanese patients in Study 1676 were limited, and there are limitations to evaluating the efficacy of cemiplimab in Japanese patients based on the results

from the Japanese subgroup. Nonetheless, there was no trend towards clear differences in the efficacy results between the Japanese subgroup and the overall population.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies"]

PMDA's conclusion:

Based on the following considerations, adverse events that require particular attention following administration of cemiplimab are infusion reactions, colitis/diarrhoea, myositis, rhabdomyolysis/myasthenia gravis, myocarditis/pericarditis, renal disorders, endocrine dysfunction, type 1 diabetes mellitus, skin disorders, peripheral neuropathies (including Guillain-Barre syndrome), encephalitis/meningitis, hepatic dysfunction, interstitial lung disease (ILD), transplant-related adverse events, venous thromboembolism, febrile neutropenia, immune thrombocytopenia, pancreatitis, and uveitis.

Although attention should be paid to the possible occurrence of the above adverse events during the use of cemiplimab, cemiplimab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate actions, such as monitoring of adverse events, differential diagnosis and management in anticipation of adverse drug reactions due to excessive immune response, and interruption of cemiplimab.

7.R.3.1 Safety profile of cemiplimab

The applicant's explanation about the safety profile of cemiplimab based on cemiplimab safety information from Study 1676:

Safety data from Study 1676 are summarized in Table 21.

Table 21. Summary of safety data (Study 1676)

	n (%)	
	Cemiplimab N = 300	IC N = 290
All adverse events	265 (88.3)	265 (91.4)
Grade ≥3 adverse events	135 (45.0)	155 (53.4)
Adverse events leading to death	5 (1.7)	2 (0.7)
Serious adverse events	89 (29.7)	78 (26.9)
Adverse events leading to treatment discontinuation	26 (8.7)	15 (5.2)
Adverse events leading to dose interruption/delay	75 (25.0)	114 (39.3)
Adverse events leading to dose reduction	0	58 (20.0)

In Study 1676, adverse events of any grade reported at a ≥5% higher incidence in the cemiplimab group than in the IC group were arthralgia (31 subjects [10.3%] in the cemiplimab group, 8 subjects [2.8%] in the IC group) and hypothyroidism (18 subjects [6.0%], 0 subjects). Grade ≥3 adverse events reported at a ≥2% higher incidence in the cemiplimab group than in the IC group were urinary tract infection (15 subjects [5.0%], 8 subjects [2.8%]). There were no adverse events leading to death, serious adverse events, or adverse events

leading to treatment discontinuation or dose interruption/delay that were reported at a ≥2% higher incidence in the cemiplimab group than in the IC group.[19)]

PMDA's discussion:
Since adverse events of any grade and Grade ≥3 adverse events that were reported at a higher incidence in the cemiplimab group than in the IC group in Study 1676 are likely to occur following administration of cemiplimab, patients should be monitored closely for these events, considering their possible relationship to cemiplimab. Meanwhile, most of these events were manageable with dose interruption/delay of cemiplimab etc. Given the above points, cemiplimab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate actions, such as monitoring of adverse events, differential diagnosis and management in anticipation of adverse drug reactions due to excessive immune response, and interruption of cemiplimab.

7.R.3.2 Differences in safety between Japanese and non-Japanese populations

The applicant's explanation about differences in the safety of cemiplimab between Japanese and non-Japanese populations, based on safety information from Study 1676:
Safety data from Japanese and non-Japanese patients in the cemiplimab group of Study 1676 are summarized in Table 22.

Table 22. Summary of safety data from Japanese and non-Japanese patients (the cemiplimab group of Study 1676)

	n (%)	
	Japanese patients N = 29	Non-Japanese patients N = 271
All adverse events	23 (79.3)	242 (89.3)
Grade ≥3 adverse events	11 (37.9)	124 (45.8)
Adverse events leading to death	0	5 (1.8)
Serious adverse events	9 (31.0)	80 (29.5)
Adverse events leading to treatment discontinuation	1 (3.4)	25 (9.2)
Adverse events leading to dose interruption/delay	5 (17.2)	70 (25.8)

Adverse events of any grade reported at a ≥10% higher incidence in Japanese patients than in non-Japanese patients were pyrexia (6 Japanese patients [20.7%], 29 non-Japanese patients [10.7%]) and insomnia (5 Japanese patients [17.2%], 14 non-Japanese patients [5.2%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients were anaemia (4 Japanese patients [13.8%], 32 non-Japanese patients [11.8%]), urinary tract infection (2 Japanese patients [6.9%], 13 non-Japanese patients [4.8%]), bacteraemia (1 Japanese patient [3.4%], 0 non-Japanese patients), pyelonephritis (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), sepsis (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), skin infection (1 Japanese patient [3.4%], 0 non-Japanese patients), aphthous ulcer (1 Japanese patient [3.4%], 0 non-Japanese patients), duodenal ulcer (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), ileus (1 Japanese patient [3.4%], 0 non-Japanese patients), amylase increased (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), neutrophil count decreased (1 Japanese patient [3.4%], 0 non-Japanese patients),

[19)] Since no patients had their dose of cemiplimab reduced in Study 1676, the results of analyses for adverse events leading to dose reduction are omitted thereafter.

platelet count decreased (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), decreased appetite (1 Japanese patient [3.4%], 0 non-Japanese patients), haemorrhagic cystitis (1 Japanese patient [3.4%], 0 non-Japanese patients), cataract (1 Japanese patient [3.4%], 0 non-Japanese patients), hepatic function abnormal (1 Japanese patient [3.4%], 0 non-Japanese patients), cystitis radiation (1 Japanese patient [3.4%], 0 non-Japanese patients), and subclavian vein thrombosis (1 Japanese patient [3.4%], 0 non-Japanese patients). Serious adverse events reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients were pyelonephritis (1 Japanese patient [3.4%], 2 non-Japanese patients [0.7%]), sepsis (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), skin infection (1 Japanese patient [3.4%], 0 non-Japanese patients), cataract (1 Japanese patient [3.4%], 0 non-Japanese patients), duodenal ulcer (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), hepatic function abnormal (1 Japanese patient [3.4%], 0 non-Japanese patients), cystitis radiation (1 Japanese patient [3.4%], 0 non-Japanese patients), arthritis (1 Japanese patient [3.4%], 0 non-Japanese patients), device occlusion (1 Japanese patient [3.4%], 0 non-Japanese patients), haemorrhagic cystitis (1 Japanese patient [3.4%], 0 non-Japanese patients), and subclavian vein thrombosis (1 Japanese patient [3.4%], 0 non-Japanese patients). Adverse events leading to treatment discontinuation reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients were anaemia (1 Japanese patient [3.4%], 0 non-Japanese patients), disseminated intravascular coagulation (1 Japanese patient [3.4%], 0 non-Japanese patients), hypothyroidism (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), hepatic function abnormal (1 Japanese patient [3.4%], 0 non-Japanese patients), amylase increased (1 Japanese patient [3.4%], 0 non-Japanese patients), platelet count decreased (1 Japanese patient [3.4%], 0 non-Japanese patients), and decreased appetite (1 Japanese patient [3.4%], 0 non-Japanese patients). Adverse events leading to dose interruption/delay reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients were malaise (1 Japanese patient [3.4%], 0 non-Japanese patients), pyrexia (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), skin infection (1 Japanese patient [3.4%], 0 non-Japanese patients), rash (1 Japanese patient [3.4%], 1 non-Japanese patient [0.4%]), and subclavian vein thrombosis (1 Japanese patient [3.4%], 0 non-Japanese patients). There were no adverse events leading to death that were reported at a ≥2% higher incidence in Japanese patients than in non-Japanese patients.

PMDA's discussion:

Although there are limitations to comparison of the safety profile of cemiplimab between Japanese and non-Japanese populations due to the limited number of Japanese patients treated with cemiplimab, some events were reported at a higher incidence in Japanese patients than in non-Japanese patients in Study 1676, and attention should be paid to the possible occurrence of these events during treatment with cemiplimab. However, there were no adverse events leading to death for which a causal relationship to cemiplimab could not be ruled out, and there was no trend towards a clearly higher incidence of serious adverse events in Japanese patients than in non-Japanese patients. In addition, cemiplimab will be used under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy. Given these points, cemiplimab is considered tolerable also in Japanese patients.

In the following sections, based on the safety results from Study 1676 etc., PMDA conducted its safety review, focusing on adverse events reported at a higher incidence in the cemiplimab group, adverse events predicted by the mechanism of action of cemiplimab, adverse events that require attention following administration of other PD-1 inhibitors, nivolumab and pembrolizumab, etc.

7.R.3.3 Infusion reactions

The applicant's explanation about infusion reactions associated with cemiplimab:

The following events were counted as infusion reactions.

- Events coded to the following MedDRA PTs that occurred on the day of infusion or the day after infusion: "infusion related reaction," "drug hypersensitivity," "hypersensitivity," "type I hypersensitivity," "anaphylactic reaction," "anaphylactic shock," "anaphylactoid reaction," "anaphylactoid shock," "shock," "respiratory failure," and "respiratory arrest"
- Events coded to the following MedDRA PTs that occurred on the day of infusion or the day after infusion and resolved within 2 days: "abdominal pain," "allergic oedema," "angioedema," "back pain," "blood pressure decreased," "bronchial oedema," "bronchospasm," "cardiac arrest," "cardio-respiratory arrest," "chest pain," "chills," "choking," "choking sensation," "circulatory collapse," "cough," "dyspnoea," "erythema," "flushing," "hypotension," "hyperhidrosis," "laryngeal oedema," "laryngospasm," "lip oedema," "lip swelling," "mouth swelling," "nausea," "oedema," "oedema mouth," "oropharyngeal oedema," "oropharyngeal spasm," "oropharyngeal swelling," "pruritus," "pruritus allergic," "pyrexia," "rash," "rash erythematous," "rash pruritic," "respiratory distress," "respiratory dyskinesia," "skin reaction," "shock symptom," "skin swelling," "sneezing," "stridor," "swelling," "swelling face," "swollen tongue," "tachycardia," "tachypnoea," "tongue oedema," "tracheal obstruction," "tracheal oedema," "upper airway obstruction," "urticaria," "urticaria papular," "vomiting," and "wheezing"

Table 23 shows the incidence of infusion reactions in Study 1676.

Table 23. Infusion reactions reported by ≥1% of subjects in either group (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Infusion reactions[*2]	33 (11.0)	0	48 (16.6)	5 (1.7)
Infusion related reaction	8 (2.7)	0	13 (4.5)	1 (0.3)
Pyrexia	8 (2.7)	0	7 (2.4)	0
Nausea	7 (2.3)	0	16 (5.5)	0
Vomiting	7 (2.3)	0	11 (3.8)	0
Abdominal pain	1 (0.3)	0	4 (1.4)	2 (0.7)

*1: MedDRA ver.23.1, *2: Any event of infusion reaction

In Study 1676, a serious infusion reaction was not reported in the cemiplimab group, but occurred in 1 of 290 subjects (0.3%) (hypersensitivity [1 subject]) in the IC group, and its causal relationship to study drug was denied. No infusion reactions leading to treatment discontinuation were reported in the cemiplimab group, and infusion reactions leading to treatment discontinuation occurred in 3 of 290 subjects (1.0%) (infusion related

reaction [2 subjects]; and anaphylactic reaction [1 subject]) in the IC group. Infusion reactions leading to dose interruption/delay occurred in 5 of 300 subjects (1.7%) (infusion related reaction [5 subjects]) in the cemiplimab group and 9 of 290 subjects (3.1%) (infusion related reaction [9 subjects]) in the IC group. There were no infusion reactions leading to death.

In Study 1676, the median time to the first onset of infusion reaction (min., max.) (days) in the cemiplimab group was 2 (1, 450).

Table 24 shows the details of patients with serious infusion reactions for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application.

Table 24. Listing of patients with serious infusion reactions (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT*	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1624	7[redacted]	F	None	Infusion related reaction	2	22	1	Interrupted	Resolved
1423	6[redacted]	M	Radiotherapy	Infusion related reaction	3	1	2	Discontinued	Resolved
	8[redacted]	M	CBDCA, PTX	Infusion related reaction	2	64	1	Interrupted	Resolved
	7[redacted]	F	CBDCA, PTX	Pyrexia	1	24	3	None	Resolved
1620	9[redacted]	F	None	Infusion related reaction	2	24	2	Interrupted	Resolved

*: MedDRA ver.22.1 for Studies 1624 and 1620, MedDRA ver.20.0 for Study 1423

PMDA's discussion:
Given that multiple cases of serious infusion reactions for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted, etc., attention should be paid to the possible occurrence of infusion reactions following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of infusion reactions in the clinical studies, using the package insert etc.

7.R.3.4 Enterocolitis/diarrhea

The applicant's explanation about enterocolitis/diarrhea associated with cemiplimab:
Events in the MedDRA SMQs "noninfectious diarrhoea (broad)," "pseudomembranous colitis (broad)," "gastrointestinal perforation (narrow)," and "gastrointestinal obstruction (narrow)" and events coded to the MedDRA PTs "acute haemorrhagic ulcerative colitis," "autoimmune colitis," "colitis," "colitis erosive," "colitis microscopic," "colitis ulcerative," "enteritis," "enterocolitis," "enterocolitis haemorrhagic," "necrotising colitis," "proctitis," and "proctitis haemorrhagic" were counted as enterocolitis/diarrhea.

Table 25 shows the incidence of enterocolitis/diarrhea in Study 1676.

Table 25. Incidence of enterocolitis/diarrhea (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Enterocolitis/diarrhea[*2]	44 (14.7)	12 (4.0)	48 (16.6)	12 (4.1)
Diarrhoea	32 (10.7)	3 (1.0)	39 (13.4)	4 (1.4)
Colitis	5 (1.7)	1 (0.3)	0	0
Gastroenteritis	3 (1.0)	0	2 (0.7)	1 (0.3)
Ileus	2 (0.7)	1 (0.3)	3 (1.0)	3 (1.0)
Intestinal obstruction	2 (0.7)	2 (0.7)	2 (0.7)	1 (0.3)
Anal fistula	1 (0.3)	0	0	0
Anal stenosis	1 (0.3)	1 (0.3)	0	0
Change of bowel habit	1 (0.3)	1 (0.3)	0	0
Clostridium difficile infection	1 (0.3)	1 (0.3)	0	0
Colonic fistula	1 (0.3)	1 (0.3)	0	0
Large intestinal obstruction	1 (0.3)	0	0	0
Oesophageal obstruction	1 (0.3)	0	0	0
Peritonitis	1 (0.3)	1 (0.3)	1 (0.3)	1 (0.3)
Proctitis	1 (0.3)	1 (0.3)	0	0
Radiation proctitis	1 (0.3)	0	0	0
Rectal perforation	1 (0.3)	1 (0.3)	0	0
Anal incontinence	0	0	1 (0.3)	0
Diverticular perforation	0	0	1 (0.3)	1 (0.3)
Intestinal fistula infection	0	0	1 (0.3)	1 (0.3)
Post procedural diarrhoea	0	0	1 (0.3)	0
Small intestinal obstruction	0	0	1 (0.3)	1 (0.3)

*1: MedDRA ver.23.1, *2: Any event of enterocolitis/diarrhea

In Study 1676, serious enterocolitis/diarrhea occurred in 8 of 300 subjects (2.7%) (diarrhoea [2 subjects]; and Clostridium difficile infection; colitis; colonic fistula; intestinal obstruction; peritonitis; and rectal perforation [1 subject each]) in the cemiplimab group and 8 of 290 subjects (2.8%) (diarrhoea; and ileus [2 subjects each]; and intestinal obstruction; peritonitis; diverticular perforation; and gastroenteritis [1 subject each]) in the IC group, and a causal relationship to study drug could not be ruled out for 2 cases (diarrhoea; and colitis [1 subject each]) in the cemiplimab group and 2 cases (diarrhoea [2 subjects]) in the IC group. Enterocolitis/diarrhea leading to treatment discontinuation occurred in 3 of 300 subjects (1.0%) (colitis; gastroenteritis; and peritonitis [1 subject each]) in the cemiplimab group and 2 of 290 subjects (0.7%) (peritonitis; and diverticular perforation [1 subject each]) in the IC group. Enterocolitis/diarrhea leading to dose interruption/delay occurred in 6 of 300 subjects (2.0%) (diarrhoea [5 subjects]; and large intestinal obstruction [1 subject]) in the cemiplimab group and 8 of 290 subjects (2.8%) (diarrhoea [3 subjects]; ileus [2 subjects]; and gastroenteritis; intestinal fistula infection; intestinal obstruction; and small intestinal obstruction [1 subject each] [some subjects had more than 1 event]) in the IC group. There was no enterocolitis/diarrhea leading to death.

In Study 1676, the median time to the first onset of enterocolitis/diarrhea (min., max.) (days) in the cemiplimab group was 30 (1, 211).

Table 26 shows the details of patients with serious enterocolitis/diarrhea for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application.

Table 26. Listing of patients with serious enterocolitis/diarrhea (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT*	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	5[redacted]	F	None	Colitis	3	49	80	Not applicable	Resolved
	5[redacted]	F	None	Diarrhoea	2	327	12	Interrupted	Resolved
1622	6[redacted]	F	None	Autoimmune colitis	3	79	Unknown	Interrupted	Resolving
1624	6[redacted]	M	None	Diarrhoea	3	10	3	None	Resolved
	5[redacted]	F	None	Colitis	2	331	7	None	Resolved
1423	7[redacted]	M	DTX	Diarrhoea	3	8	9	None	Resolved
	8[redacted]	F	DTX	Colitis	3	15	4	Discontinued	Resolved
1540	8[redacted]	F	None	Proctitis	3	372	97	Discontinued	Resolved
1620	7[redacted]	F	None	Colitis	3	61	23	Interrupted	Resolved
	9[redacted]	F	None	Colitis	3	109	6	None	Resolved
	7[redacted]	M	None	Colitis	3	400	41	Interrupted	Resolved
	7[redacted]	M	None	Colitis	3	305	8	Discontinued	Resolved
	8[redacted]	M	None	Autoimmune colitis	3	472	Unknown	Not applicable	Not resolved

*: MedDRA ver.23.1 for Studies 1676 and 1622, MedDRA ver.22.1 for Studies 1624 and 1620, MedDRA ver.20.0 for Studies 1423 and 1540

PMDA's discussion:

Given that multiple cases of serious colitis and diarrhoea for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted, etc., attention should be paid to the possible occurrence of colitis and diarrhoea following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of colitis and diarrhoea in the clinical studies, using the package insert, etc.

7.R.3.5 Myositis (including myasthenia gravis)

The applicant's explanation about myositis (including myasthenia gravis) associated with cemiplimab:

Events in the MedDRA SOC "musculoskeletal and connective tissue disorders" were counted as myositis (including myasthenia gravis).

Table 27 shows the incidence of myositis (including myasthenia gravis) in Study 1676.

Table 27. Myositis (including myasthenia gravis) reported by ≥1% of subjects in either group (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Myositis (including myasthenia gravis)[*2]	83 (27.7)	10 (3.3)	65 (22.4)	6 (2.1)
Back pain	33 (11.0)	4 (1.3)	25 (8.6)	2 (0.7)
Arthralgia	31 (10.3)	1 (0.3)	8 (2.8)	0
Pain in extremity	18 (6.0)	2 (0.7)	7 (2.4)	2 (0.7)
Myalgia	10 (3.3)	0	9 (3.1)	0
Flank pain	6 (2.0)	0	4 (1.4)	1 (0.3)
Muscle spasms	6 (2.0)	0	2 (0.7)	0
Neck pain	5 (1.7)	0	2 (0.7)	0
Groin pain	3 (1.0)	1 (0.3)	1 (0.3)	0
Muscular weakness	3 (1.0)	1 (0.3)	6 (2.1)	1 (0.3)
Musculoskeletal chest pain	2 (0.7)	0	3 (1.0)	0
Bone pain	1 (0.3)	0	4 (1.4)	0
Musculoskeletal pain	1 (0.3)	0	4 (1.4)	0

*1: MedDRA ver.23.1, *2: Any event of myositis (including myasthenia gravis)

In Study 1676, serious myositis (including myasthenia gravis) occurred in 6 of 300 subjects (2.0%) (arthritis; back pain; groin pain; muscular weakness; pathological fracture; and spondylolisthesis [1 subject each]) in the cemiplimab group and 3 of 290 subjects (1.0%) (muscular weakness; pathological fracture; and flank pain [1 subject each]) in the IC group, and a causal relationship to study drug could not be ruled out for 1 case (arthritis [1 subject]) in the cemiplimab group and 1 case (muscular weakness [1 subject]) in the IC group. Myositis (including myasthenia gravis) leading to treatment discontinuation occurred in 1 of 300 subjects (0.3%) (polyarthritis [1 subject]) in the cemiplimab group and 1 of 290 subjects (0.3%) (muscular weakness [1 subject]) in the IC group. Myositis (including myasthenia gravis) leading to dose interruption/delay occurred in 4 of 300 subjects (1.3%) (back pain [2 subjects]; and groin pain; and spondylolisthesis [1 subject each]) in the cemiplimab group and 1 of 290 subjects (0.3%) (back pain [1 subject]) in the IC group. There was no myositis (including myasthenia gravis) leading to death.

In Study 1676, the median time to the first onset of myositis (including myasthenia gravis) (range) (min., max.) (days) in the cemiplimab group was 38 (1, 684).

Table 28 shows the details of patients with serious myositis (including myasthenia gravis) for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and the foreign marketing experience.

Table 28. Listing of patients with serious myositis (including myasthenia gravis) (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT[*1, 2]	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	5[redacted]	F	None	Arthritis	2	2	Unknown	None	Resolving
1624	7[redacted]	M	None	Pain in extremity	3	35	88	None	Resolved
1423	6[redacted]	F	Radiotherapy, CPA	Myasthenia gravis	2	38	6	None	Sequelae
Foreign marketing experience	7[redacted]	M	None	Polymyalgia rheumatica	Unknown	Unknown	Unknown	Discontinued	Unknown
	8[redacted]	M	None	Autoimmune myositis	Unknown	23	Unknown	Discontinued	Fatal
				Myositis	Unknown	27	Unknown	Discontinued	Resolving
	Unknown	Unknown	None	Myositis	Unknown	Unknown	Unknown	Unknown	Resolving
				Myositis	Unknown	Unknown	Unknown	Unknown	Unknown
	8[redacted]	M	None	Myositis	3	17	Unknown	Discontinued	Not resolved
	9[redacted]	M	None	Immune-mediated myositis	Unknown	Unknown	Unknown	Not applicable	Fatal
				Rhabdomyolysis	Unknown	Unknown	Unknown	Not applicable	Fatal
	7[redacted]	M	None	Myositis	Unknown	16	Unknown	Discontinued	Not resolved
				Rhabdomyolysis	Unknown	16	Unknown	Discontinued	Not resolved
	9[redacted]	M	None	Myositis	Unknown	36	14	Discontinued	Fatal
	Unknown	Unknown	None	Rhabdomyolysis	Unknown	Unknown	Unknown	Unknown	Unknown
	7[redacted]	M	None	Autoimmune myositis	Unknown	135	Unknown	Discontinued	Resolving
	8[redacted]	M	None	Myositis	Unknown	Unknown	Unknown	Not applicable	Unknown
	9[redacted]	F	None	Autoimmune myositis	Unknown	20	Unknown	Not applicable	Resolved
	7[redacted]	M	None	Polymyalgia rheumatica	2	Unknown	Unknown	Unknown	Resolved
	7[redacted]	M	None	Myositis	Unknown	Unknown	Unknown	Discontinued	Unknown
	8[redacted]	F	None	Myositis	Unknown	41	Unknown	Not applicable	Resolving
	8[redacted]	M	None	Polymyalgia rheumatica	Unknown	209	Unknown	Discontinued	Resolved
	7[redacted]	M	None	Polymyalgia rheumatica	2	Unknown	Unknown	Unknown	Unknown
	8[redacted]	M	None	Myositis	Unknown	Unknown	Unknown	Not applicable	Fatal
	8[redacted]	M	None	Myositis	Unknown	30	Unknown	Discontinued	Resolving
	8[redacted]	M	None	Myositis	Unknown	Unknown	Unknown	Unknown	Unknown
	8[redacted]	F	None	Myositis	Unknown	128	Unknown	Discontinued	Resolved
	7[redacted]	Unknown	None	Polymyalgia rheumatica	Unknown	Unknown	Unknown	Discontinued	Unknown

*1: MedDRA ver.23.1 for Study 1676, MedDRA ver.22.1 for Study 1624, MedDRA ver.20.0 for Study 1423
*2: As events reported in the foreign marketing experience, events coded to the MedDRA PTs "myositis," "autoimmune myositis," "immune-mediated myositis," "polymyositis," "rhabdomyolysis," and "polymyalgia rheumatica" only are listed in the table.

PMDA's discussion:

Multiple cases of serious or fatal myositis and rhabdomyolysis for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience. Serious myasthenia gravis for which a causal relationship to cemiplimab could not be ruled out was reported in the clinical studies, and myasthenia gravis is a known risk associated with other anti-PD-1 antibodies (nivolumab and pembrolizumab). Given these findings, attention should be paid to the possible occurrence of myositis, rhabdomyolysis, and myasthenia gravis following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of myositis, rhabdomyolysis, and myasthenia gravis in the clinical studies, using the package insert, etc.

7.R.3.6 Cardiac disorders (including myocarditis)

The applicant's explanation about cardiac disorders (including myocarditis) associated with cemiplimab:
Events in the MedDRA SOC "cardiac disorders" were counted as cardiac disorders (including myocarditis).

Table 29 shows the incidence of cardiac disorders (including myocarditis) in Study 1676.

Table 29. Incidence of cardiac disorders (including myocarditis) (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Cardiac disorders[*2]	13 (4.3)	1 (0.3)	9 (3.1)	1 (0.3)
Pericardial effusion	3 (1.0)	1 (0.3)	0	0
Sinus tachycardia	3 (1.0)	0	1 (0.3)	0
Tachycardia	3 (1.0)	0	2 (0.7)	0
Autoimmune pericarditis	1 (0.3)	0	0	0
Left ventricular dysfunction	1 (0.3)	0	1 (0.3)	0
Myocardial ischaemia	1 (0.3)	0	0	0
Palpitations	1 (0.3)	0	3 (1.0)	0
Pericarditis	1 (0.3)	0	0	0
Angina pectoris	0	0	1 (0.3)	0
Cardiac failure	0	0	1 (0.3)	1 (0.3)

*1: MedDRA ver.23.1, *2: Any event of cardiac disorder (including myocarditis)

In Study 1676, serious cardiac disorders (including myocarditis) occurred in 2 of 300 subjects (0.7%) (autoimmune pericarditis; and pericardial effusion [1 subject each]) in the cemiplimab group and 1 of 290 subjects (0.3%) (cardiac failure [1 subject]) in the IC group, and a causal relationship to study drug could not be ruled out for 1 case (autoimmune pericarditis [1 subject]) in the cemiplimab group and 1 case (cardiac failure [1 subject]) in the IC group. Cardiac disorders (including myocarditis) leading to treatment discontinuation occurred in 1 of 300 subjects (0.3%) (autoimmune pericarditis [1 subject]) in the cemiplimab group and 1 of 290 subjects (0.3%) (cardiac failure [1 subject]) in the IC group. Cardiac disorders (including myocarditis) leading to dose interruption/delay occurred in 3 of 300 subjects (1.0%) (pericardial effusion; pericarditis; and sinus tachycardia [1 subject each]) in the cemiplimab group, but not in the IC group. There were no cardiac disorders (including myocarditis) leading to death.

In Study 1676, the median time to the first onset of cardiac disorder (including myocarditis) (range) (min., max.) (days) in the cemiplimab group was 55 (8, 210).

Table 30 shows the details of patients with serious cardiac disorders (including myocarditis) for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and the foreign marketing experience.

Table 30. Listing of patients with serious cardiac disorders (including myocarditis) (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT[*1, 2]	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	5[redacted]	F	None	Autoimmune pericarditis	2	156	Unknown	Discontinued	Not resolved
1624	6[redacted]	M	None	Autoimmune myocarditis	5	40	4	Discontinued	Fatal
	6[redacted]	M	None	Atrial tachycardia	3	303	Unknown	None	Unknown
	7[redacted]	M	None	Cardiopulmonary failure	5	581	1	None	Fatal
	7[redacted]	M	None	Cardiac failure	5	28	2	None	Fatal
	6[redacted]	M	None	Myocarditis	2	230	66	Interrupted	Resolved
	6[redacted]	M	None	Cardio-respiratory arrest	5	238	10	Not applicable	Fatal
	5[redacted]	F	None	Ventricular extrasystoles	3	85	89	None	Resolved
1540	8[redacted]	F	None	Myocarditis	3	58	9	Not applicable	Resolved
	8[redacted]	M	None	Pericarditis	3	218	67	Interrupted	Resolved
1620	7[redacted]	M	None	Autoimmune myocarditis	3	113	15	Interrupted	Resolved
	4[redacted]	F	None	Autoimmune pericarditis	3	115	Unknown	Discontinued	Unknown
				Immune-mediated myocarditis	3	115	Unknown	Discontinued	Unknown
Foreign marketing experience	Unknown	Unknown	None	Myocarditis	Unknown	Unknown	Unknown	Unknown	Unknown
	Unknown	Unknown	None	Myocarditis	Unknown	Unknown	Unknown	Unknown	Unknown
	7[redacted]	M	None	Perimyocarditis	Unknown	16	Unknown	Discontinued	Not resolved
	9[redacted]	M	None	Myocarditis	Unknown	34	16	Discontinued	Fatal
	7[redacted]	F	None	Myocarditis	Unknown	14	Unknown	Discontinued	Resolved
	8[redacted]	M	None	Myocarditis	Unknown	Unknown	Unknown	Not applicable	Unknown
	Unknown	M	None	Autoimmune myocarditis	Unknown	22	Unknown	Unknown	Unknown
	9[redacted]	F	None	Myocarditis	Unknown	22	Unknown	Not applicable	Resolved
	Unknown	Unknown	None	Myocarditis	Unknown	Unknown	Unknown	Not applicable	Fatal
	7[redacted]	M	None	Myocarditis	Unknown	39	Unknown	Unknown	Resolved
	8[redacted]	F	None	Myocarditis	Unknown	41	Unknown	Not applicable	Resolving
	Unknown	Unknown	None	Myocarditis	Unknown	Unknown	Unknown	Unknown	Unknown
	8[redacted]	M	None	Immune-mediated myocarditis	Unknown	Unknown	Unknown	Not applicable	Fatal
	8[redacted]	F	None	Immune-mediated myocarditis	Unknown	Unknown	Unknown	Not applicable	Fatal
	Unknown	F	None	Myocarditis	Unknown	Unknown	Unknown	Unknown	Unknown
	8[redacted]	M	None	Myocarditis	Unknown	Unknown	Unknown	Unknown	Unknown
	8[redacted]	M	None	Pericarditis	Unknown	Unknown	Unknown	Discontinued	Unknown
	7[redacted]	M	None	Myocarditis	Unknown	Unknown	Unknown	Unknown	Not resolved
	7[redacted]	M	None	Myocarditis	Unknown	2	Unknown	Unknown	Resolving
	8[redacted]	F	None	Myocarditis	Unknown	Unknown	Unknown	Unknown	Unknown
	7[redacted]	M	None	Myocarditis	Unknown	55	Unknown	Unknown	Resolved
	5[redacted]	M	Plerixafor	Pericarditis	3	42	Unknown	Discontinued	Not resolved

*1: MedDRA ver.23.1 for Study 1676, MedDRA ver.22.1 for Studies 1624 and 1620, MedDRA ver.20.0 for Study 1540
*2: As events reported in the foreign marketing experience, events coded to the MedDRA PTs "myocarditis," "autoimmune myocarditis," "immune-mediated myocarditis," "myopericarditis," and "pericarditis" only are listed in the table.

PMDA's discussion:

Given that multiple cases of serious or fatal myocarditis and pericarditis for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience, etc., attention should be paid to the possible occurrence of myocarditis and pericarditis among cardiac disorders, following administration of cemiplimab. Thus, it is necessary to appropriately advise

healthcare professionals in clinical practice about the incidence and management of myocarditis and pericarditis in the clinical studies, using the package insert, etc.

7.R.3.7 Renal disorders

The applicant's explanation about renal disorders associated with cemiplimab:
Events in the MedDRA HLGTs "nephropathies" and "renal disorders (excl nephropathies)" were counted as renal disorders.

Table 31 shows the incidence of renal disorders in Study 1676.

Table 31. Incidence of renal disorders (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Renal disorders[*2]	24 (8.0)	13 (4.3)	21 (7.2)	9 (3.1)
Hydronephrosis	9 (3.0)	7 (2.3)	4 (1.4)	2 (0.7)
Acute kidney injury	8 (2.7)	3 (1.0)	7 (2.4)	1 (0.3)
Pyelonephritis	4 (1.3)	2 (0.7)	4 (1.4)	3 (1.0)
Chronic kidney disease	3 (1.0)	2 (0.7)	2 (0.7)	2 (0.7)
Kidney infection	2 (0.7)	2 (0.7)	0	0
Acute pyelonephritis	2 (0.7)	1 (0.3)	2 (0.7)	1 (0.3)
Renal failure	2 (0.7)	0	3 (1.0)	1 (0.3)
Nephritis	1 (0.3)	0	0	0
Renal impairment	1 (0.3)	0	1 (0.3)	0
Renal injury	1 (0.3)	0	0	0
Renal vein thrombosis	1 (0.3)	0	0	0
Azotaemia	0	0	1 (0.3)	0
Oliguria	0	0	1 (0.3)	0
Renal artery stenosis	0	0	1 (0.3)	0

*1: MedDRA ver.23.1, *2: Any event of renal disorder

In Study 1676, serious renal disorders occurred in 12 of 300 subjects (4.0%) (acute kidney injury [5 subjects]; hydronephrosis; and pyelonephritis [3 subjects each]; kidney infection; and acute pyelonephritis [2 subjects each]; and renal failure [1 subject] [some subjects had more than 1 event]) in the cemiplimab group and 11 of 290 subjects (3.8%) (acute kidney injury; and pyelonephritis [3 subjects each]; acute pyelonephritis; and renal failure [2 subjects each]; and chronic kidney disease; and renal impairment [1 subject each] [some subjects had more than 1 event]) in the IC group, and a causal relationship to study drug could not be ruled out for the events reported by 2 subjects in the cemiplimab group (acute kidney injury [2 subjects]; and kidney infection [1 subject] (one subject had more than 1 event]) and the events reported by 4 subjects in the IC group (acute kidney injury [2 subjects]; and pyelonephritis; and renal failure [1 subject each]). Renal disorders leading to treatment discontinuation occurred in 1 of 300 subjects (0.3%) (acute kidney injury [1 subject]) in the cemiplimab group and 1 of 290 subjects (0.3%) (renal failure [1 subject]) in the IC group. Renal disorders leading to dose interruption/delay occurred in 9 of 300 subjects (3.0%) (acute kidney injury [3 subjects]; chronic kidney disease; and kidney infection [2 subjects each]; and hydronephrosis; pyelonephritis; and renal failure [1 subject each] [some subjects had more than 1 event]) in the cemiplimab group and 8 of 290 subjects (2.8%) (acute kidney injury; chronic kidney disease; and pyelonephritis acute [2 subjects each]; and

hydronephrosis; pyelonephritis; and renal failure [1 subject each] [some subjects had more than 1 event]) in the IC group. There were no renal disorders leading to death.

In Study 1676, the median time to the first onset of renal disorder (range) (min., max.) (days) in the cemiplimab group was 64 (15, 613).

Table 32 shows the details of patients with serious renal disorders for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and the foreign marketing experience.

Table 32. Listing of patients with serious renal disorders (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT[*1, 2]	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	5[redacted]	F	None	Acute kidney injury	1	25	5	None	Resolved
	4[redacted]	F	None	Kidney infection	3	156	7	Interrupted	Resolved
				Acute kidney injury	1	177	Unknown	Interrupted	Not resolved
1624	5[redacted]	M	None	Nephritis	5	76	26	None	Fatal
1423	6[redacted]	M	PEM, CBDCA	Acute kidney injury	3	126	18	Discontinued	Resolved
1620	8[redacted]	M	None	Acute kidney injury	2	421	3	Discontinued	Resolved
Foreign marketing experience	8[redacted]	M	None	Immune-mediated renal disorder	Unknown	Unknown	Unknown	Discontinued	Unknown
				Immune-mediated nephritis	Unknown	Unknown	Unknown	Discontinued	Unknown
	8[redacted]	M	None	Immune-mediated nephritis	Unknown	Unknown	Unknown	Not applicable	Resolving
	7[redacted]	M	None	Tubulointerstitial nephritis	Unknown	41	Unknown	Discontinued	Fatal
	8[redacted]	M	None	Intercapillary glomerulosclerosis	Unknown	Unknown	Unknown	Unknown	Resolved
				Glomerulonephritis membranous	Unknown	Unknown	Unknown	Unknown	Resolved
	7[redacted]	M	None	Tubulointerstitial nephritis	Unknown	Unknown	Unknown	Not applicable	Resolving
	Unknown	F	None	Nephritis	Unknown	Unknown	Unknown	Unknown	Unknown
	5[redacted]	M	None	Glomerulosclerosis	Unknown	Unknown	Unknown	Unknown	Unknown
				Glomerulonephritis	Unknown	Unknown	Unknown	Unknown	Unknown
	7[redacted]	M	None	Tubulointerstitial nephritis	Unknown	329	Unknown	Discontinued	Resolving
	Unknown	F	None	Immune-mediated nephritis	3	Unknown	Unknown	Discontinued	Not resolved

*1: MedDRA ver.23.1 for Study 1676, MedDRA ver.22.1 for Studies 1624 and 1620, MedDRA ver.20.0 for Study 1423
*2: As events reported in the foreign marketing experience, events coded to the MedDRA PTs "immune-mediated nephritis," "immune-mediated renal disorder," "nephritis," "glomerulonephritis," "glomerulonephritis membranous," "glomerulosclerosis," "intercapillary glomerulosclerosis," and "tubulointerstitial nephritis" only are listed in the table.

PMDA's discussion:

Given that multiple cases of fatal or serious renal disorders for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience, etc., attention should be paid to the possible occurrence of renal disorders following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of renal disorders in the clinical studies, using the package insert, etc.

7.R.3.8 Endocrine dysfunction (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction)

The applicant's explanation about endocrine dysfunction associated with cemiplimab:

Events in the MedDRA SMQ "thyroid dysfunction (narrow)," events in the MedDRA HLGTs "adrenal gland disorders" and "hypothalamus and pituitary gland disorders," and events coded to the MedDRA PT "thyroid disorder" were counted as endocrine dysfunction.

Table 33 shows the incidence of endocrine dysfunction in Study 1676.

Table 33. Incidence of endocrine dysfunction (Study 1676)

PT*1	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Endocrine dysfunction *2	24 (8.0)	1 (0.3)	1 (0.3)	0
Hypothyroidism	18 (6.0)	1 (0.3)	0	0
Hyperthyroidism	9 (3.0)	0	0	0
Adrenal insufficiency	0	0	1 (0.3)	0

*1: MedDRA ver.23.1, *2: Any event of endocrine dysfunction

In Study 1676, serious endocrine dysfunction occurred in 1 of 300 subjects (0.3%) (hypothyroidism [1 subject]) in the cemiplimab group, but not in the IC group, and a causal relationship to study drug could not be ruled out for the event reported by 1 subject (hypothyroidism [1 subject]) in the cemiplimab group. Endocrine dysfunction leading to treatment discontinuation occurred in 2 of 300 subjects (0.7%) (hypothyroidism [2 subjects]) in the cemiplimab group, but not in the IC group. Endocrine dysfunction leading to dose interruption/delay occurred in 2 of 300 subjects (0.7%) (hyperthyroidism [2 subjects]) in the cemiplimab, but not in the IC group. There was no endocrine dysfunction leading to death.

In Study 1676, the median time to the first onset of endocrine dysfunction (min., max.) (days) in the cemiplimab group was 85 (21, 171).

Table 34 shows the details of patients with serious endocrine dysfunction for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application.

Table 34. Listing of patients with serious endocrine dysfunction (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT*	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	7[redacted]	F	None	Hypothyroidism	3	159	63	Not applicable	Resolved
1423	5[redacted]	F	Radiotherapy, CPA	Hyperthyroidism	3	53	Unknown	Interrupted Dose reduced	Not resolved
	7[redacted]	F	DTX, CBDCA	Hypothyroidism	3	113	18	Not applicable	Resolved
1540	7[redacted]	M	None	Hypophysitis	3	225	9	Interrupted	Sequelae
1620	8[redacted]	M	None	Hypophysitis	3	141	47	Discontinued	Resolved
	7[redacted]	M	None	Adrenal insufficiency	3	557	Unknown	None	Not resolved
	7[redacted]	F	None	Adrenal insufficiency	3	127	Unknown	Discontinued	Resolving

*: MedDRA ver.23.1 for Study 1676, MedDRA ver.20.0 for Studies 1423 and 1540, MedDRA ver.22.1 for Study 1620

PMDA's discussion:

Given that multiple cases of serious endocrine dysfunction for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted, etc., attention should be paid to the possible occurrence of endocrine dysfunction following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of endocrine dysfunction in the clinical studies, using the package insert, etc.

7.R.3.9 Type 1 diabetes mellitus

The applicant's explanation about type 1 diabetes mellitus associated with cemiplimab:

Events coded to the MedDRA PTs "type 1 diabetes mellitus, " "diabetes mellitus inadequate control," "fulminant type 1 diabetes mellitus," "diabetic ketoacidosis," "diabetic neuropathy," "diabetic eye disease," "diabetic vascular disorder," "diabetic hyperosmolar coma," and "diabetic nephropathy" were counted as type 1 diabetes mellitus.

Table 35 shows the incidence of type 1 diabetes mellitus in Study 1676.

Table 35. Incidence of type 1 diabetes mellitus (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Type 1 diabetes mellitus[*2]	1 (0.3)	0	0	0
Diabetic neuropathy	1 (0.3)	0	0	0

*1: MedDRA ver.23.1, *2: Any event of type 1 diabetes mellitus

In Study 1676, there was no type 1 diabetes mellitus leading to death, serious type 1 diabetes mellitus, or type 1 diabetes mellitus leading to treatment discontinuation or dose interruption/delay.

Table 36 shows the details of patients with serious type 1 diabetes mellitus for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and the foreign marketing experience.

Table 36. Listing of patients with serious type 1 diabetes mellitus (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT*	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1423	6[redacted]	M	None	Diabetic ketoacidosis	4	41	5	Interrupted	Sequelae
	5[redacted]	F	Radiotherapy, CPA	Diabetic ketoacidosis	4	28	3	Interrupted	Resolved
Foreign marketing experience	Unknown	M	None	Type 1 diabetes mellitus	Unknown	Unknown	Unknown	Unknown	Unknown
	8[redacted]	M	None	Diabetic ketoacidosis	Unknown	41	Unknown	Not applicable	Fatal
	Unknown	F	None	Type 1 diabetes mellitus	Unknown	Unknown	Unknown	None	Unknown
				Diabetic ketoacidosis	Unknown	Unknown	Unknown	None	Unknown
	6[redacted]	M	None	Diabetic ketoacidosis	Unknown	99	Unknown	Not applicable	Resolving
	6[redacted]	M	None	Type 1 diabetes mellitus	Unknown	32	Unknown	Unknown	Unknown
	7[redacted]	F	None	Type 1 diabetes mellitus	Unknown	79	Unknown	Not applicable	Not resolved
				Diabetic ketoacidosis	Unknown	79	Unknown	Not applicable	Resolved
	Unknown	Unknown	Unknown	Type 1 diabetes mellitus	Unknown	Unknown	Unknown	Unknown	Sequelae
	7[redacted]	F	None	Type 1 diabetes mellitus	Unknown	Unknown	Unknown	Discontinued	Resolved
				Diabetic ketoacidosis	Unknown	Unknown	Unknown	Discontinued	Resolved
	8[redacted]	F	None	Type 1 diabetes mellitus	Unknown	87	Unknown	Unknown	Unknown
	7[redacted]	F	None	Type 1 diabetes mellitus	Unknown	81	Unknown	Not applicable	Not resolved

*: MedDRA ver.20.0 for Study 1423

PMDA's discussion:

Given that multiple cases of fatal or serious type 1 diabetes mellitus for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience, etc., attention should be paid to the possible occurrence of type 1 diabetes mellitus following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of type 1 diabetes mellitus in the clinical studies, using the package insert, etc.

7.R.3.10 Skin disorders

The applicant's explanation about skin disorders associated with cemiplimab:

Events in the MedDRA SOC "skin and subcutaneous tissue disorders" were counted as skin disorders.

Table 37 shows the incidence of skin disorders in Study 1676.

Table 37. Skin disorders reported by ≥1% of subjects in either group (Study 1676)

PT*1	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Skin disorders*2	60 (20.0)	5 (1.7)	57 (19.7)	1 (0.3)
Rash	18 (6.0)	3 (1.0)	19 (6.6)	0
Pruritus	16 (5.3)	0	15 (5.2)	1 (0.3)
Dry skin	10 (3.3)	0	0	0
Rash maculo-papular	7 (2.3)	0	0	0
Alopecia	0	0	9 (3.1)	0

*1: MedDRA ver.23.1, *2: Any event of skin disorder

In Study 1676, serious skin disorder occurred in 1 of 300 subjects (0.3%) (rash [1 subject]) in the cemiplimab group, but not in the IC group, and a causal relationship to cemiplimab was denied for the 1 case in the cemiplimab group. Skin disorders leading to dose interruption/delay occurred in 4 of 300 subjects (1.3%) (rash [2 subjects]; and dermatitis allergic; and rash maculo-papular [1 subject each]) in the cemiplimab group, but not in the IC group. There were no skin disorders leading to death or treatment discontinuation.

In Study 1676, the median time to the first onset of skin disorder (min., max.) (days) in the cemiplimab group was 33 (1, 475).

Table 38 shows the details of patients with serious skin disorders for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and the foreign marketing experience.

Table 38. Listing of patients with serious skin disorders (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT[*1, 2]	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1624	6[redacted]	M	None	Rash	3	45	28	None	Resolved
	4[redacted]	F	None	Rash maculo-papular	3	16	34	Interrupted	Resolved
	4[redacted]	M	None	Dermatomyositis	2	126	30	Discontinued	Resolved
1423	6[redacted]	F	Radiotherapy, CPA, GM-CSF	Pemphigoid	3	4	46	Interrupted Dose reduced	Resolved
	6[redacted]	F	Radiotherapy, CPA	Erythema multiforme	3	47	25	None	Resolved
1540	7[redacted]	M	None	Rash maculo-papular	3	72	52	Interrupted Dose reduced	Resolved
Foreign marketing experience	8[redacted]	F	None	TEN	5	14	8	Not applicable	Fatal
	8[redacted]	F	None	SJS	Unknown	Unknown	Unknown	Not applicable	Unknown
	Unknown	M	Unknown	SJS	Unknown	Unknown	Unknown	Unknown	Unknown
	Unknown	Unknown	None	TEN	5	Unknown	Unknown	Not applicable	Fatal
	8[redacted]	M	Unknown	SJS	Unknown	12	Unknown	Unknown	Not resolved
	Unknown	M	Unknown	TEN	Unknown	Unknown	Unknown	Unknown	Unknown
	5[redacted]	M	None	TEN	5	7	14	Not applicable	Fatal
				SJS-TEN overlap	Unknown	7	14	Not applicable	Fatal
	Unknown	F	Unknown	TEN	5	Unknown	Unknown	Not applicable	Fatal

*1: MedDRA ver.22.1 for Study 1624, MedDRA ver.20.0 for Studies 1423 and 1540
*2: As events reported in the foreign marketing experience, events coded to the MedDRA PTs "TEN," "SJS," and "SJS-TEN overlap" only are listed in the table.

PMDA's discussion:

Given that fatal or serious skin disorders for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience, etc., attention should be paid to the possible occurrence of severe skin disorders following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of skin disorders in the clinical studies, using the package insert, etc.

7.R.3.11 Peripheral neuropathies (including Guillain-Barre syndrome)

The applicant's explanation about peripheral neuropathies (including Guillain-Barre syndrome) associated with cemiplimab:

Events in the MedDRA SMQs "peripheral neuropathy (broad)" and "Guillain-Barre syndrome (broad)" were counted as peripheral neuropathies (including Guillain-Barre syndrome).

Table 39 shows the incidence of peripheral neuropathies (including Guillain-Barre syndrome) in Study 1676.

Table 39. Incidence of peripheral neuropathies (including Guillain-Barre syndrome) (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Peripheral neuropathies (including Guillain-Barre syndrome)[*2]	49 (16.3)	8 (2.7)	60 (20.7)	5 (1.7)
Asthenia	33 (11.0)	7 (2.3)	44 (15.2)	3 (1.0)
Muscular weakness	3 (1.0)	1 (0.3)	6 (2.1)	1 (0.3)
Peripheral neuropathy	3 (1.0)	0	2 (0.7)	0
Paraesthesia	3 (1.0)	0	5 (1.7)	0
Peripheral sensory neuropathy	3 (1.0)	0	2 (0.7)	0
Hypoaesthesia	2 (0.7)	0	1 (0.3)	0
Balance disorder	1 (0.3)	0	0	0
Dysphagia	1 (0.3)	0	0	0
Peripheral motor neuropathy	1 (0.3)	0	0	0
Gait disturbance	0	0	1 (0.3)	0
Neurotoxicity	0	0	4 (1.4)	1 (0.3)
Skin burning sensation	0	0	1 (0.3)	0

*1: MedDRA ver.23.1, *2: Any event of peripheral neuropathy (including Guillain-Barre syndrome)

In Study 1676, serious peripheral neuropathies (including Guillain-Barre syndrome) occurred in 2 of 300 subjects (0.7%) (asthenia; and muscular weakness [1 subject each]) in the cemiplimab group and 1 of 290 subjects (0.3%) (muscular weakness [1 subject]) in the IC group, and a causal relationship to study drug could not be ruled out for 1 case (asthenia [1 subject]) in the cemiplimab group and 1 case (muscular weakness [1 subject]) in the IC group. No peripheral neuropathies (including Guillain-Barre syndrome) leading to treatment discontinuation were reported in the cemiplimab group, and peripheral neuropathies (including Guillain-Barre syndrome) leading to treatment discontinuation occurred in 2 of 290 subjects (0.7%) (muscular weakness; and neurotoxicity [1 subject each]) in the IC group. Peripheral neuropathies (including Guillain-Barre syndrome) leading to dose interruption/delay occurred in 1 of 300 subjects (0.3%) (asthenia [1 subject]) in the cemiplimab group and 3 of 290 subjects (1.0%) (asthenia [2 subjects]; and peripheral neuropathy [1 subject]) in the IC group. There were no peripheral neuropathies (including Guillain-Barre syndrome) leading to death.

In Study 1676, the median time to the first onset of peripheral neuropathy (including Guillain-Barre syndrome) (min., max.) (days) in the cemiplimab group was 44 (1, 686).

Table 40 shows the details of patients with serious peripheral neuropathies (including Guillain-Barre syndrome) for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and the foreign marketing experience.

Table 40. Listing of patients with serious peripheral neuropathies (including Guillain-Barre syndrome) (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT[*1, 2]	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	5[redacted]	F	None	Asthenia	2	22	6	None	Resolved
1624	4[redacted]	M	None	Respiratory failure	5	3	4	None	Fatal
1423	7[redacted]	F	CBDCA, DTX	Guillain-Barre syndrome	3	116	15	Not applicable	Resolved
1620	6[redacted]	M	None	Facial paralysis	2	31	Unknown	Interrupted	Not resolved
Foreign marketing experience	Unknown	M	Unknown	Polyneuropathy	Unknown	Unknown	Unknown	Unknown	Unknown
	9[redacted]	M	Radiotherapy	Polyneuropathy	Unknown	35	15	Not applicable	Fatal
	8[redacted]	M	None	Immune-mediated neuropathy	Unknown	97	Unknown	Discontinued	Unknown
	8[redacted]	M	None	Guillain-Barre syndrome	Unknown	Unknown	Unknown	Discontinued	Resolving
				Miller Fisher syndrome	Unknown	Unknown	Unknown	Discontinued	Resolving
				Peripheral sensorimotor neuropathy	Unknown	Unknown	Unknown	Discontinued	Resolving
	8[redacted]	M	None	Miller Fisher syndrome	Unknown	Unknown	Unknown	Discontinued	Resolving
	Unknown	M	Unknown	Guillain-Barre syndrome	Unknown	Unknown	Unknown	Unknown	Unknown
	6[redacted]	M	Unknown	Guillain-Barre syndrome	Unknown	Unknown	Unknown	Discontinued	Unknown

*1: MedDRA ver.23.1 for Study 1676, MedDRA ver.22.1 for Studies 1624 and 1620, MedDRA ver.20.0 for Study 1423
*2: As events reported in the foreign marketing experience, events coded to the MedDRA PTs "polyneuropathy," "immune-mediated neuropathy," "peripheral sensorimotor neuropathy," "Miller Fisher syndrome," and "Guillain-Barre syndrome" only are listed in the table.

PMDA's discussion:

Given that multiple cases of fatal or serious peripheral neuropathies (including Guillain-Barre syndrome) for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience, etc., attention should be paid to the possible occurrence of peripheral neuropathies (including Guillain-Barre syndrome) following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of peripheral neuropathies (including Guillain-Barre syndrome) in the clinical studies, using the package insert, etc.

7.R.3.12 Encephalitis/meningitis

The applicant's explanation about encephalitis/meningitis associated with cemiplimab:

Events in the MedDRA SMQs "noninfectious encephalitis (narrow)" and "noninfectious meningitis (narrow)" were counted as encephalitis/meningitis.

No encephalitis or meningitis was reported in Study 1676.

Table 41 shows the details of patients with serious encephalitis/meningitis for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and the foreign marketing experience.

Table 41. Listing of patients with serious encephalitis/meningitis (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT*[1, 2]	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1423	4[redacted]	M	None	Paraneoplastic encephalomyelitis	5	59	79	Discontinued	Fatal
	7[redacted]	F	Radiotherapy	Meningitis	4	131	26	Discontinued	Sequelae
	6[redacted]	F	Radiotherapy	Noninfective encephalitis	3	26	34	Interrupted	Resolved
1540	7[redacted]	M	None	Meningitis aseptic	3	14	4	Discontinued	Resolved
	7[redacted]	M	None	Encephalitis	3	11	48	Discontinued	Resolved
Foreign marketing experience	7[redacted]	M	None	Encephalitis	Unknown	Unknown	Unknown	Unknown	Resolved
	7[redacted]	M	None	Encephalitis	Unknown	238	Unknown	Not applicable	Not resolved
	Unknown	M	None	Encephalitis	Unknown	Unknown	Unknown	Unknown	Unknown
	8[redacted]	M	None	Encephalitis	5	Unknown	Unknown	Not applicable	Fatal
	Unknown	M	None	Encephalitis	4	Unknown	Unknown	Discontinued	Resolving
	Unknown	M	None	Encephalitis autoimmune	Unknown	Unknown	Unknown	Discontinued	Unknown
	4[redacted]	M	None	Encephalitis	Unknown	6	Unknown	Discontinued	Unknown
				Meningitis aseptic	Unknown	6	Unknown	Discontinued	Unknown
	4[redacted]	M	None	Encephalitis	Unknown	8	Unknown	Discontinued	Resolving
	7[redacted]	M	None	Encephalitis	Unknown	120	Unknown	Discontinued	Resolving
				Encephalitis allergic	Unknown	120	Unknown	Discontinued	Resolving
	Unknown	M	None	Encephalitis	Unknown	Unknown	Unknown	Unknown	Unknown

*1: MedDRA ver.20.0 for Studies 1430 and 1540
*2: As events reported in the foreign marketing experience, events coded to the MedDRA PTs "encephalitis," "encephalitis autoimmune," "encephalitis allergic," and "meningitis aseptic" only are listed in the table.

PMDA's discussion:

Given that multiple cases of fatal or serious encephalitis/meningitis for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience, etc., attention should be paid to the possible occurrence of encephalitis/meningitis following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of encephalitis/meningitis in the clinical studies, using the package insert, etc.

7.R.3.13 Hepatic dysfunction

The applicant's explanation about hepatic dysfunction associated with cemiplimab:

Events in the MedDRA SMQs "drug related hepatic disorders - severe events only (broad)," "cholestasis and jaundice of hepatic origin (narrow)," and "liver related investigations, signs and symptoms (broad)" were counted as hepatic dysfunction.

Table 42 shows the incidence of hepatic dysfunction in Study 1676.

Table 42. Hepatic dysfunction reported by ≥1% of subjects in either group (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Hepatic dysfunction[*2]	51 (17.0)	19 (6.3)	49 (16.9)	12 (4.1)
Hypoalbuminaemia	21 (7.0)	4 (1.3)	18 (6.2)	4 (1.4)
ALT increased	13 (4.3)	2 (0.7)	20 (6.9)	2 (0.7)
AST increased	12 (4.0)	2 (0.7)	19 (6.6)	0
Blood ALP increased	12 (4.0)	4 (1.3)	14 (4.8)	2 (0.7)
GGT increased	7 (2.3)	0	6 (2.1)	1 (0.3)
Autoimmune hepatitis	4 (1.3)	3 (1.0)	0	0
Immune-mediated hepatitis	4 (1.3)	4 (1.3)	0	0

*1: MedDRA ver.23.1, *2: Any event of hepatic dysfunction

In Study 1676, serious hepatic dysfunction occurred in 8 of 300 subjects (2.7%) (autoimmune hepatitis [4 subjects]; immune-mediated hepatitis [3 subjects]; and hepatic function abnormal [1 subject]) in the cemiplimab group, but not in the IC group, and a causal relationship to cemiplimab could not be ruled out for the 8 cases in the cemiplimab group. Hepatic dysfunction leading to treatment discontinuation occurred in 8 of 300 subjects (2.7%) (autoimmune hepatitis; and immune-mediated hepatitis [3 subjects each]; and ALT increased; hepatic function abnormal; and hepatitis [1 subject each] [some subjects had more than 1 event]), but not in the IC group. Hepatic dysfunction leading to dose interruption/delay occurred in 8 of 300 subjects (2.7%) (ALT increased; AST increased; and immune-mediated hepatitis [2 subjects each]; and autoimmune hepatitis; blood ALP increased; GGT increased; and hepatotoxicity [1 subject each] [some subjects had more than 1 event]) in the cemiplimab group and 5 of 290 subjects (1.7%) (ALT increased; GGT increased; drug-induced liver injury; hepatic enzyme increased; hepatocellular injury; cholestasis; and hyperbilirubinaemia [1 subject each] [some subjects had more than 1 event]) in the IC group. There was no hepatic dysfunction leading to death.

In Study 1676, the median time to the first onset of hepatic dysfunction (min., max.) (days) in the cemiplimab group was 43 (8, 683).

Table 43 shows the details of patients with serious hepatic dysfunction for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application.

Table 43. Listing of patients with serious hepatic dysfunction (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT*	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	5[redacted]	F	None	Autoimmune hepatitis	3	149	Unknown	Discontinued	Unknown
	3[redacted]	F	None	Autoimmune hepatitis	3	148	3	Discontinued	Resolved
	3[redacted]	F	None	Immune-mediated hepatitis	3	63	5	Discontinued	Resolved
	3[redacted]	F	None	Immune-mediated hepatitis	3	84	5	Discontinued	Resolved
	6[redacted]	F	None	Autoimmune hepatitis	3	150	Unknown	Discontinued	Unknown
	6[redacted]	F	None	Hepatic function abnormal	4	21	Unknown	Discontinued	Resolving
	5[redacted]	F	None	Autoimmune hepatitis	2	295	15	Interrupted	Resolved
	6[redacted]	F	None	Immune-mediated hepatitis	3	65	Unknown	Interrupted	Not resolved
1624	7[redacted]	F	None	Hepatitis	3	84	Unknown	Discontinued	Resolving
	6[redacted]	M	None	Immune-mediated hepatitis	4	39	Unknown	None	Not resolved
	5[redacted]	M	None	Immune-mediated hepatitis	4	685	26	Discontinued	Resolved
1423	5[redacted]	F	Radiotherapy, CPA	Transaminases increased	3	29	8	Interrupted	Resolved
	8[redacted]	M	None	ALT increased	3	71	Unknown	None	Not resolved
				AST increased	3	71	Unknown	None	Not resolved
	6[redacted]	M	None	Hepatic failure	5	148	9	Discontinued	Fatal
	4[redacted]	M	None	Autoimmune hepatitis	3	31	83	Discontinued	Resolved
	5[redacted]	M	None	Autoimmune hepatitis	3	99	10	Discontinued	Resolved
1540	8[redacted]	F	None	Autoimmune hepatitis	3	4	35	Interrupted	Resolved
1620	7[redacted]	M	None	Autoimmune hepatitis	2	127	14	Discontinued	Resolved
	7[redacted]	F	None	Immune-mediated hepatitis	3	105	160	Discontinued	Resolved

*: MedDRA ver.23.1 for Study 1676, MedDRA ver.22.1 for Studies 1624 and 1620, MedDRA ver.20.0 for Studies 1423 and 1540

In the clinical studies submitted for the present application and other cemiplimab clinical studies,[20)] although there were no Hy's law cases of drug-induced liver injury (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), 3 cases of MedDRA PT "drug-induced liver injury" were reported, and a causal relationship to cemiplimab could not be ruled out for all those cases.

PMDA's discussion:

Given that multiple cases of serious hepatic dysfunction and autoimmune hepatitis for which a causal relationship to cemiplimab could not be ruled out were reported, and fatal hepatic failure also occurred in the clinical studies submitted, etc., attention should be paid to the possible occurrence of hepatic dysfunction following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of hepatic dysfunction in the clinical studies, using the package insert, etc.

7.R.3.14 ILD

The applicant's explanation about ILD associated with cemiplimab:

Events in the MedDRA SMQ "interstitial lung disease (broad)" were counted as ILD.

Table 44 shows the incidence of ILD in Study 1676.

[20)] Besides the clinical studies submitted for the present application, the following clinical studies are included.
Study R1979-ONC-1504, Study R2810-ONC-1606, Study R2810-ONC-16111, Part 2 of Study R2810-ONC-16113, Study R2810-ONC-1655, Study R2810-ONC-1690, Study R2810-ONC-1763, Study R2810-ONC-1787, Study R2810-ONC-1866, and Study R2810-ONC-1901

Table 44. Incidence of ILD (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
ILD[*2]	7 (2.3)	2 (0.7)	2 (0.7)	1 (0.3)
Pneumonitis	6 (2.0)	2 (0.7)	2 (0.7)	1 (0.3)
Bronchiolitis	1 (0.3)	0	0	0
ILD	1 (0.3)	0	0	0

*1: MedDRA ver.23.1, *2: Any event of ILD

In Study 1676, serious ILD occurred in 3 of 300 subjects (1.0%) (pneumonitis [3 subjects]) in the cemiplimab group and 1 of 290 subjects (0.3%) (pneumonitis [1 subject]) in the IC group, and a causal relationship to study drug could not be ruled out for all those events. ILD leading to treatment discontinuation occurred in 5 of 300 subjects (1.7%) (pneumonitis [5 subjects]) in the cemiplimab group and 1 of 290 subjects (0.3%) (pneumonitis [1 subject]) in the IC group. ILD leading to dose interruption/delay occurred in 2 of 300 subjects (0.7%) (pneumonitis [2 subjects]) in the cemiplimab group, but not in the IC group. There was no ILD leading to death.

In Study 1676, the median time to the first onset of ILD (min., max.) (days) in the cemiplimab group was 47 (24, 694).

Table 45 shows the details of patients with serious ILD for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application.

Table 45. Listing of patients with serious ILD (causally related to cemiplimab)

Study ID	Age	Sex	Race	Concomitant therapy	PT*	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	4[redacted]	F	Non-Japanese	None	Pneumonitis	3	24	Unknown	Discontinued	Not resolved
	3[redacted]	F	Non-Japanese	None	Pneumonitis	2	159	25	Discontinued	Resolved
	5[redacted]	F	Non-Japanese	None	Pneumonitis	3	47	33	Discontinued	Resolved
1624	6[redacted]	M	Non-Japanese	None	Pneumonitis	4	60	Unknown	Discontinued	Not resolved
	6[redacted]	M	Non-Japanese	None	Immune-mediated pneumonitis	4	38	Unknown	None	Not resolved
	7[redacted]	M	Non-Japanese	None	Interstitial lung disease	3	563	14	Interrupted	Resolved
	6[redacted]	M	Non-Japanese	None	Pneumonitis	2	162	88	Interrupted	Resolved
	6[redacted]	M	Non-Japanese	None	Pneumonitis	2	51	Unknown	Interrupted	Not resolved
	6[redacted]	M	Non-Japanese	None	Pneumonitis	2	337	Unknown	Discontinued	Not resolved
	7[redacted]	M	Non-Japanese	None	Pneumonitis	2	74	17	Interrupted	Resolved
	7[redacted]	M	Non-Japanese	None	Pneumonitis	2	35	14	Interrupted	Resolved
1423	6[redacted]	M	Non-Japanese	None	Pneumonitis	2	24	10	Interrupted	Resolved
	7[redacted]	M	Non-Japanese	None	Pneumonitis	3	29	15	Discontinued	Sequelae
	5[redacted]	M	Non-Japanese	Radiotherapy	Pneumonitis	5	91	8	Discontinued	Fatal
	6[redacted]	M	Non-Japanese	Radiotherapy	Pneumonitis	2	170	25	Discontinued	Resolved
	7[redacted]	F	Non-Japanese	Radiotherapy, CPA, GM-CSF	Pneumonitis	3	22	Unknown	Discontinued	Not resolved
	2[redacted]	F	Non-Japanese	Radiotherapy	Pneumonitis	3	239	52	Interrupted	Resolved
	5[redacted]	F	Non-Japanese	Radiotherapy	Pneumonitis	5	234	14	Interrupted	Fatal
1540	6[redacted]	M	Non-Japanese	None	Pneumonitis	3	7	10	Discontinued	Resolved
	6[redacted]	M	Non-Japanese	None	Pneumonitis	3	41	Unknown	Discontinued	Unknown
	8[redacted]	M	Non-Japanese	None	Pneumonitis	2	226	27	Interrupted	Resolved
					Pneumonitis	2	281	Unknown	Discontinued	Not resolved
	6[redacted]	M	Non-Japanese	None	Pneumonitis	3	516	4	Discontinued	Resolved
	8[redacted]	M	Non-Japanese	None	Pneumonitis	2	19	Unknown	Interrupted	Not resolved
	8[redacted]	F	Non-Japanese	None	Pneumonitis	4	133	7	Discontinued	Resolved
					Pneumonitis	3	153	9	Not applicable	Resolved
	7[redacted]	M	Non-Japanese	None	Pneumonitis	4	130	9	Discontinued	Resolved
	6[redacted]	M	Non-Japanese	None	Pneumonitis	2	56	7	Interrupted	Resolved
1620	8[redacted]	M	Non-Japanese	None	Pneumonitis	3	274	28	Interrupted	Resolved
	5[redacted]	M	Non-Japanese	None	Sarcoidosis	2	90	43	None	Resolved
					Sarcoidosis	2	133	Unknown	None	Not resolved

*: MedDRA ver.23.1 for Study 1676, MedDRA ver.22.1 for Studies 1624 and 1620, MedDRA ver.20.0 for Studies 1423 and 1540

PMDA's discussion:

Given that multiple cases of fatal or serious ILD for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted, etc., attention should be paid to the possible occurrence of ILD following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence and management of ILD in the clinical studies, using the package insert, etc.

7.R.3.15 Transplant-related adverse events

The applicant's explanation about transplant-related adverse events associated with cemiplimab:
Events in the MedDRA HLTs "transplant rejections" and "transplantation complications" were counted as transplant-related adverse events.

In the clinical studies submitted for the present application and other cemiplimab clinical studies,[20)] no solid organ transplant-related events for which a causal relationship to cemiplimab could not be ruled out were reported.

Table 46 shows the details of patients with serious transplant-related adverse events for which a causal relationship to cemiplimab could not be ruled out in the foreign marketing experience.

Table 46. Listing of patients with serious transplant-related adverse events (causally related to cemiplimab)

	Age	Sex	PT	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
Foreign marketing experience	7[redacted]	M	Transplant rejection	Unknown	38	Unknown	Not applicable	Resolving
	8[redacted]	M	Kidney transplant rejection	Unknown	13	15	None	Resolved
	6[redacted]	M	Transplant rejection	Unknown	Unknown	Unknown	Discontinued	Resolving
	Unknown	Unknown	Solid organ transplant rejection	Unknown	Unknown	Unknown	Unknown	Unknown
	5[redacted]	F	Transplant rejection	Unknown	Unknown	Unknown	Discontinued	Not resolved
	5[redacted]	F	Kidney transplant rejection	Unknown	Unknown	Unknown	Unknown	Unknown
	8[redacted]	M	Renal transplant failure	Unknown	Unknown	Unknown	Not applicable	Unknown
	5[redacted]	M	Transplant rejection	Unknown	Unknown	Unknown	Unknown	Unknown
	Unknown	Unknown	Transplant rejection	Unknown	Unknown	Unknown	Unknown	Unknown
	4[redacted]	F	Renal transplant failure	Unknown	50	Unknown	Discontinued	Not resolved
	5[redacted]	M	Chronic allograft nephropathy	Unknown	Unknown	Unknown	Unknown	Unknown

PMDA's discussion:
Transplant-related adverse events for which a causal relationship to cemiplimab could not be ruled out were reported in the foreign marketing experience. These events can be caused by immune system activation. Transplant-related adverse events such as graft versus host disease following allogeneic hematopoietic stem cell transplantation are known risks associated with other anti-PD-1 antibodies (nivolumab and pembrolizumab). Given these findings, attention should be paid to the possible occurrence of transplant-related adverse events following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about this point, using the package insert, etc.

7.R.3.16 Venous thromboembolism

The applicant's explanation about venous thromboembolism associated with cemiplimab:
Events in the MedDRA SMQ "embolic and thrombotic events, venous (narrow)" were counted as venous thromboembolism.

Table 47 shows the incidence of venous thromboembolism in Study 1676.

Table 47. Incidence of venous thromboembolism (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Venous thromboembolism[*2]	13 (4.3)	2 (0.7)	5 (1.7)	3 (1.0)
Deep vein thrombosis	4 (1.3)	0	2 (0.7)	1 (0.3)
Brachiocephalic vein thrombosis	2 (0.7)	1 (0.3)	0	0
Jugular vein thrombosis	1 (0.3)	0	0	0
Pulmonary embolism	1 (0.3)	0	2 (0.7)	2 (0.7)
Renal vein thrombosis	1 (0.3)	0	0	0
Subclavian vein thrombosis	1 (0.3)	1 (0.3)	0	0
Superior vena cava syndrome	1 (0.3)	0	0	0
Superficial thrombophlebitis	1 (0.3)	0	0	0
Venous thrombosis	1 (0.3)	0	0	0
Venous thrombosis limb	0	0	1 (0.3)	0

*1: MedDRA ver.23.1, *2: Any event of venous thromboembolism

In Study 1676, serious venous thromboembolism occurred in 2 of 300 subjects (0.7%) (deep vein thrombosis; and subclavian vein thrombosis [1 subject each]) in the cemiplimab group and 3 of 290 subjects (1.0%) (pulmonary embolism [2 subjects]; and deep vein thrombosis [1 subject]) in the IC group, and a causal relationship to study drug was denied for all those events. Venous thromboembolism leading to treatment discontinuation occurred in 1 of 300 subjects (0.3%) (superior vena cava syndrome [1 subject]) in the cemiplimab group and 1 of 290 subjects (0.3%) (deep vein thrombosis [1 subject]) in the IC group. Venous thromboembolism leading to dose interruption/delay occurred in 2 of 300 subjects (0.7%) (pulmonary embolism; and subclavian vein thrombosis [1 subject each]) in the cemiplimab group and 1 of 290 subjects (0.3%) (pulmonary embolism [1 subject]) in the IC group. There was no venous thromboembolism leading to death.

In Study 1676, the median time to the first onset of venous thromboembolism (min., max.) (days) in the cemiplimab group was 64 (16, 225).

Table 48 shows the details of patients with serious venous thromboembolism for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and the foreign marketing experience.

Table 48. Listing of patients with serious venous thromboembolism (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT[*1]	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1624	5[redacted]	M	None	Pulmonary embolism	4	63	64	Interrupted	Resolved
Foreign marketing experience	Unknown	M	None	Pulmonary embolism	Unknown	5	Unknown	Unknown	Unknown
	7[redacted]	M	None	Pulmonary embolism	Unknown	Unknown[*2]	Unknown	Discontinued	Resolved
	6[redacted]	M	None	Pulmonary embolism	Unknown	Unknown	Unknown	Discontinued	Fatal[*3]
	Unknown	Unknown	None	Pulmonary embolism	Unknown	Unknown	Unknown	Unknown	Fatal
	7[redacted]	M	None	Pulmonary embolism	Unknown	21	Unknown	Unknown	Fatal
	8[redacted]	M	None	Deep vein thrombosis	Unknown	Unknown	Unknown	Discontinued	Fatal

*1: MedDRA ver.22.1 for Study 1624, *2: The event occurred within 90 days after the start of cemiplimab. *3: The patient died 35 days after the start of cemiplimab.

PMDA's discussion:

Given that multiple cases of fatal or serious venous thromboembolism for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience, and that venous thromboembolism has been reported with another anti-PD-1 antibody (nivolumab), attention should be paid to the possible occurrence of venous thromboembolism following administration of cemiplimab. Thus, it is necessary to appropriately advise healthcare professionals in clinical practice about the incidence of venous thromboembolism in the clinical studies, using the package insert etc.

7.R.3.17 Blood disorders

The applicant's explanation about blood disorders associated with cemiplimab:

Events in the MedDRA HLGTs "white blood cell disorders," "platelet disorders," "haemolyses and related conditions," and "haematological disorders NEC" and events coded to the MedDRA PTs "white blood cell count decreased," "neutrophil count decreased," "platelet count decreased," "lymphocyte count decreased," "haemoglobin decreased," "anaemia," and "pancytopenia" were counted as blood disorders.

Table 49 shows the incidence of blood disorders in Study 1676.

Table 49. Incidence of blood disorders (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Blood disorders[*2]	91 (30.3)	43 (14.3)	169 (58.3)	114 (39.3)
Anaemia	75 (25.0)	36 (12.0)	129 (44.5)	78 (26.9)
Neutropenia	6 (2.0)	3 (1.0)	44 (15.2)	26 (9.0)
Leukopenia	4 (1.3)	1 (0.3)	13 (4.5)	7 (2.4)
Febrile neutropenia	3 (1.0)	2 (0.7)	5 (1.7)	5 (1.7)
Platelet count decreased	3 (1.0)	2 (0.7)	14 (4.8)	5 (1.7)
Eosinophilia	2 (0.7)	0	0	0
Lymphocyte count decreased	2 (0.7)	0	5 (1.7)	2 (0.7)
Lymphopenia	2 (0.7)	1 (0.3)	2 (0.7)	2 (0.7)
Neutrophil count decreased	2 (0.7)	1 (0.3)	26 (9.0)	12 (4.1)
Thrombocytopenia	2 (0.7)	1 (0.3)	16 (5.5)	9 (3.1)
White blood cell count decreased	2 (0.7)	0	14 (4.8)	6 (2.1)
Haemoglobin decreased	1 (0.3)	0	0	0
Thrombocytosis	1 (0.3)	0	2 (0.7)	0
Hyperbilirubinaemia	0	0	1 (0.3)	1 (0.3)
Leukocytosis	0	0	1 (0.3)	0
Neutropenic sepsis	0	0	1 (0.3)	1 (0.3)
Pancytopenia	0	0	3 (1.0)	3 (1.0)
Transfusion reaction	0	0	2 (0.7)	1 (0.3)

*1: MedDRA ver.23.1, *2: Any event of blood disorder

In Study 1676, no blood disorders leading to death were reported in the cemiplimab group. Blood disorder leading to death occurred in 1 of 290 subjects (0.3%) (neutropenic sepsis [1 subject]) in the IC group, and its causal relationship to study drug could not be ruled out. Serious blood disorders occurred in 6 of 300 subjects (2.0%) (febrile neutropenia [3 subjects]; anaemia [2 subjects]; and platelet count decreased [1 subject]) in the cemiplimab group and 23 of 290 subjects (7.9%) (anaemia [14 subjects]; febrile neutropenia [5 subjects]; thrombocytopenia [3 subjects]; pancytopenia; and transfusion reaction [2 subjects each]; and lymphocyte count

decreased; neutropenia; neutropenic sepsis; and neutrophil count decreased [1 subject each] [some subjects had more than 1 event]) in the IC group, and a causal relationship to study drug could not be ruled out for the events reported by 4 subjects in the cemiplimab group (febrile neutropenia [2 subjects]; and anaemia; and platelet count decreased [1 subject each]) and the events reported by 21 subjects in the IC group (anaemia [12 subjects]; febrile neutropenia [5 subjects]; thrombocytopenia [3 subjects]; pancytopenia [2 subjects]; and lymphocyte count decreased; neutropenia; neutropenic sepsis; and neutrophil count decreased [1 subject each] [some subjects had more than 1 event]). Blood disorders leading to treatment discontinuation occurred in 2 of 300 subjects (0.7%) (anaemia; febrile neutropenia; and platelet count decreased [1 subject each] [some subjects had more than 1 event]) in the cemiplimab group and 2 of 290 subjects (0.7%) (anaemia; neutropenia; and thrombocytopenia [1 subject each] [some subjects had more than 1 event]) in the IC group. Blood disorders leading to dose interruption/delay occurred in 11 of 300 subjects (3.7%) (anaemia [10 subjects]; and neutropenia [1 subject]) in the cemiplimab group and 63 of 290 subjects (21.7%) (anaemia [32 subjects]; neutropenia [19 subjects]; neutrophil count decreased [9 subjects]; platelet count decreased [7 subjects]; leukopenia; and thrombocytopenia [5 subjects each]; white blood cell count decreased [3 subjects]; and febrile neutropenia; hyperbilirubinaemia; lymphocyte count decreased; and transfusion reaction [1 subject each] [some subjects had more than 1 event]) in the IC group.

In Study 1676, the median time to the first onset of blood disorder (min., max.) (days) in the cemiplimab group was 43 (1, 703).

Table 50 shows the details of patients with serious blood disorders for which a causal relationship to cemiplimab could not be ruled out in the clinical studies submitted for the present application and in the foreign marketing experience.

Table 50. Listing of patients with serious blood disorders (causally related to cemiplimab)

Study ID	Age	Sex	Concomitant therapy	PT[*1, 2]	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
1676	6[redacted]	F	None	Febrile neutropenia	3	69	28	Discontinued	Resolved
	4[redacted]	F	None	Febrile neutropenia	3	30	3	None	Resolved
	6[redacted]	F	None	Platelet count decreased	4	52	Unknown	None	Not resolved
	3[redacted]	F	None	Anaemia	2	29	2	Interrupted	Resolved
1624	6[redacted]	M	None	Neutropenia	4	213	16	Interrupted	Resolved
	7[redacted]	M	None	Anaemia	3	133	4	None	Resolved
1423	7[redacted]	F	CBDCA, PTX	Neutropenia	4	8	8	None	Resolved
1540	6[redacted]	M	None	Anaemia	3	42	4	Interrupted	Resolved
1620	7[redacted]	F	None	Pancytopenia	4	65	25	Interrupted	Resolved
Foreign marketing experience	6[redacted]	F	None	Immune thrombocytopenia	3	40	Unknown	Not applicable	Unknown
	6[redacted]	M	None	Immune thrombocytopenia	Unknown	Unknown	Unknown	Discontinued	Unknown

*1: MedDRA ver.23.1 for Study 1676, MedDRA ver.22.1 for Study 1624, MedDRA ver.20.0 for Study 1423
*2: As events reported in the foreign marketing experience, events coded to the MedDRA PT "immune thrombocytopenia" only are listed in the table.

PMDA's discussion:

Although febrile neutropenia and immune thrombocytopenia for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and in the foreign marketing experience, as the number of reported cases, including serious cases, was limited, it is difficult at present to draw a definitive conclusion on the risk of febrile neutropenia and immune thrombocytopenia associated with cemiplimab. However, given that febrile neutropenia and immune thrombocytopenia have been reported with other anti-PD-1 antibodies (nivolumab or pembrolizumab), it is necessary to collect post-marketing information on febrile neutropenia and immune thrombocytopenia, and if new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

7.R.3.18 Pancreatitis

The applicant's explanation about pancreatitis associated with cemiplimab:

Events in the MedDRA HLT "acute and chronic pancreatitis" and events coded to the MedDRA PT "pancreatic enzymes increased" were counted as pancreatitis.

In Study 1676, pancreatitis of any grade or Grade ≥3 pancreatitis occurred in 1 of 300 subjects (0.3%) (chronic pancreatitis [1 subject]) in the cemiplimab group, but not in the IC group. Pancreatitis leading to treatment discontinuation occurred in 1 of 300 subjects (0.3%) (chronic pancreatitis [1 subject]) in the cemiplimab group, but not in the IC group. There was no pancreatitis leading to death, serious pancreatitis, or pancreatitis leading to dose interruption/delay.

In the clinical studies submitted for the present application including Study 1676, there was no serious pancreatitis for which a causal relationship to cemiplimab could not be ruled out. Table 51 shows the details of patients with serious pancreatitis for which a causal relationship to cemiplimab could not be ruled out in the foreign marketing experience.

Table 51. Listing of patients with serious pancreatitis (causally related to cemiplimab)

	Age	Sex	Concomitant therapy	PT	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
Foreign marketing experience	8[redacted]	F	None	Immune-mediated pancreatitis	Unknown	Unknown	Unknown	Unknown	Unknown
	Unknown	Unknown	None	Pancreatitis	Unknown	Unknown	Unknown	Unknown	Unknown

PMDA's discussion:

Although serious pancreatitis for which a causal relationship to cemiplimab could not be ruled out was reported in the foreign marketing experience, the clinical course is unknown, and it is difficult at present to draw a definitive conclusion on the risk of pancreatitis associated with cemiplimab. However, given that pancreatitis is a known risk associated with other anti-PD-1 antibodies (nivolumab and pembrolizumab), etc., it is necessary to collect post-marketing information on pancreatitis, and if new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

7.R.3.19 Eye disorders (including uveitis)

The applicant's explanation about eye disorders (including uveitis) associated with cemiplimab:
Events in the MedDRA SOC "eye disorders" were counted as eye disorders (including uveitis).

Table 52 shows the incidence of eye disorders (including uveitis) in Study 1676.

Table 52. Incidence of eye disorders (including uveitis) (Study 1676)

PT[*1]	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Eye disorders[*2]	8 (2.7)	1 (0.3)	9 (3.1)	0
Vision blurred	4 (1.3)	0	0	0
Dry eye	2 (0.7)	0	0	0
Cataract	1 (0.3)	1 (0.3)	0	0
Eye pruritus	1 (0.3)	0	1 (0.3)	0
Lacrimation increased	1 (0.3)	0	6 (2.1)	0
Corneal perforation	0	0	1 (0.3)	0
Eyelid oedema	0	0	1 (0.3)	0
Vitreous floaters	0	0	1 (0.3)	0

*1: MedDRA ver.23.1, *2: Any event of eye disorder

In Study 1676, serious eye disorder (including uveitis) occurred in 1 of 300 subjects (0.3%) (cataract [1 subject]) in the cemiplimab group, but not in the IC group, and a causal relationship to cemiplimab was denied for the 1 case in the cemiplimab group. Eye disorder (including uveitis) leading to dose interruption/delay occurred in 1 of 300 subjects (0.3%) (eye pruritus [1 subject]) in the cemiplimab group, but not in the IC group. There were no eye disorders (including uveitis) leading to death or treatment discontinuation.

In Study 1676, the median time to the first onset of eye disorder (including uveitis) (min., max.) (days) in the cemiplimab group was 95.5 (8, 316).

In the clinical studies submitted for the present application including Study 1676, no serious eye disorders (including uveitis) for which a causal relationship to cemiplimab could not be ruled out were reported. Table 53 shows the details of patients with serious eye disorders (including uveitis) for which a causal relationship to cemiplimab could not be ruled out in the foreign marketing experience.

Table 53. Listing of patients with serious eye disorders (including uveitis) (causally related to cemiplimab)

	Age	Sex	Concomitant therapy	PT*	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
Foreign marketing experience	6[redacted]	F	None	Vision blurred	Unknown	Unknown	Unknown	None	Resolving
				Vogt-Koyanagi-Harada disease	Unknown	Unknown	Unknown	None	Unknown
	7[redacted]	M	None	Uveitis	Unknown	212	Unknown	Discontinued	Not resolved
	8[redacted]	M	None	Vision blurred	Unknown	Unknown	Unknown	Discontinued	Resolving
	6[redacted]	M	None	Retinal vasculitis	Unknown	Unknown	Unknown	Discontinued	Resolving
				Vision blurred	Unknown	Unknown	Unknown	Discontinued	Resolving
	4[redacted]	M	None	Iridocyclitis	Unknown	Unknown	Unknown	Discontinued	Resolving
				Vision blurred	Unknown	Unknown	Unknown	Discontinued	Resolving
	8[redacted]	M	None	Vision blurred	Unknown	91	Unknown	Discontinued	Not resolved
	9[redacted]	F	None	Vision blurred	Unknown	Unknown	Unknown	Discontinued	Resolved
	Unknown	M	None	Retinal tear	Unknown	Unknown	Unknown	Discontinued	Unknown
	Unknown	Unknown	None	Vogt-Koyanagi-Harada disease	Unknown	Unknown	Unknown	Unknown	Resolved
				Vision blurred	Unknown	Unknown	Unknown	Unknown	Resolved

*: Events coded to the MedDRA PTs "Vogt-Koyanagi-Harada disease," "uveitis," "retinal tear," "retinal vasculitis," "iridocyclitis," and "vision blurred" only are listed in the table.

PMDA's discussion:

Although serious eye disorders (including uveitis) for which a causal relationship to cemiplimab could not be ruled out were reported in the foreign marketing experience, the clinical course is unknown, and it is difficult at present to draw a definitive conclusion on the risk of eye disorders associated with cemiplimab. However, given that uveitis (including iritis and iridocyclitis) has been reported with another anti-PD-1 antibody (pembrolizumab), it is necessary to collect post-marketing information on uveitis, and if new information becomes available, the information should be provided appropriately to healthcare professionals in clinical practice.

7.R.3.20 Others

(1) Gastritis

Events in the MedDRA HLT "gastritis (excl infective)" were counted as gastritis.

In Study 1676, gastritis of any grade occurred in 2 of 300 subjects (0.7%) (gastritis [2 subjects]) in the cemiplimab group and 2 of 290 subjects (0.7%) (gastritis [2 subjects]) in the IC group. Grade ≥3 gastritis occurred in 1 of 300 subjects (0.3%) (gastritis [1 subject]) in the cemiplimab group, but not in the IC group. Serious gastritis occurred in 1 of 300 subjects (0.3%) (gastritis [1 subject]) in the cemiplimab group, but not in the IC group, and a causal relationship to study drug was denied for the 1 case in the cemiplimab group. Gastritis leading to treatment discontinuation occurred in 1 of 300 subjects (0.3%) (gastritis [1 subject]) in the cemiplimab group, but not in the IC group. There was no gastritis leading to death or dose interruption/delay.

In the clinical studies submitted for the present application including Study 1676, no serious gastritis for which a causal relationship to cemiplimab could not be ruled out was reported. Table 54 shows the details of patients with serious gastritis for which a causal relationship to cemiplimab could not be ruled out in the foreign marketing experience.

Table 54. Listing of patients with serious gastritis (causally related to cemiplimab)

	Age	Sex	Concomitant therapy	PT	Grade	Time to onset (days)	Duration (days)	Action taken with cemiplimab	Outcome
Foreign marketing experience	5[redacted]	M	Cancer peptide vaccine	Gastritis	Unknown	Unknown	Unknown	None	Resolving
	6[redacted]	M	Cancer peptide vaccine	Gastritis	3	114	Unknown	None	Not resolved

(2) Tuberculosis

Events in the MedDRA HLT "tuberculous infections" were counted as tuberculosis.

In the clinical studies submitted for the present application and other cemiplimab clinical studies,[20)] tuberculosis was not reported.

In the foreign marketing experience, 1 case of serious lymph node tuberculosis for which a causal relationship to cemiplimab could not be ruled out was reported, but the details such as the severity, time to onset, duration, action taken with cemiplimab, and outcome were unknown.

PMDA's discussion:

As to (1) and (2), although the events for which a causal relationship to cemiplimab could not be ruled out were reported in the clinical studies submitted and the foreign marketing experience, as the number of reported cases, including serious cases, was limited, no special precautionary statement is needed at present, on the premise that post-marketing information on the incidence of these events will be collected, and that if new information becomes available, the information will be provided to healthcare professionals in clinical practice.

7.R.4 Clinical positioning and indication

The proposed indication for cemiplimab was "recurrent or metastatic cervical cancer that has progressed during or after chemotherapy," and no statements were included in the PRECAUTIONS CONCERNING INDICATION section.

PMDA's conclusion:

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the considerations in the following sections, the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section, and then the proposed indication should be modified to "advanced or recurrent cervical cancer that has progressed after chemotherapy."

- The efficacy and safety of cemiplimab as first-line treatment have not been established.
- The efficacy and safety of cemiplimab as postoperative adjuvant therapy have not been established.

7.R.4.1 Clinical positioning of cemiplimab and target population

There is no description of cemiplimab for patients with cervical cancer previously treated with chemotherapy in the Japanese and foreign clinical practice guidelines and the major textbooks of clinical oncology.

The applicant's explanation about the clinical positioning of cemiplimab:
Since Study 1676 in patients with advanced or recurrent cervical cancer previously treated with platinum-containing chemotherapy showed the clinical usefulness of cemiplimab [see Sections 7.R.2 and 7.R.3], cemiplimab is recommended in these patients. On the other hand, as no clinical studies have evaluated the efficacy and safety of cemiplimab in chemotherapy-naïve patients, cemiplimab is not recommended in these patients. In addition, as no clinical studies have evaluated the efficacy and safety of cemiplimab as postoperative adjuvant therapy, the use of cemiplimab as postoperative adjuvant therapy is not recommended.

Although patients with SCC or adenocarcinoma were initially enrolled in Study 1676, as the results of Study 1423 etc. suggested that the efficacy of cemiplimab may be associated with SCC histology, the protocol was amended during the study to enroll patients with SCC only [see Section 7.1.2.1]. Given this change, PMDA asked the applicant to explain the efficacy of cemiplimab in patients with adenocarcinoma and the target population for cemiplimab.

The applicant's response:
Study 1676 enrolled 131 patients with adenocarcinoma (65 in the cemiplimab group, 66 in the IC group). The median OS [95% CI] (months) in the cemiplimab and IC groups among the patients with adenocarcinoma were 13.3 [9.6, 17.6] and 7.0 [5.1, 9.7], respectively, and the hazard ratio of OS for cemiplimab versus IC [95% CI] was 0.556 [0.363, 0.853]. There were no clear differences from the results in patients with SCC (the hazard ratio [95% CI], 0.727 [0.579, 0.914]). Thus, the efficacy of cemiplimab is expected in patients with cervical cancer previously treated with chemotherapy, including those with adenocarcinoma.

Based on the above, the applicant proposed the indication of "recurrent or metastatic cervical cancer that has progressed during or after chemotherapy."

PMDA's discussion:
PMDA largely accepted the applicant's explanation. However, the PRECAUTIONS CONCERNING INDICATION section should advise that no clinical studies have evaluated the efficacy and safety of cemiplimab as first-line treatment or postoperative adjuvant therapy.

Based on the above, the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section, and then the proposed indication should be modified to "advanced or recurrent cervical cancer that has progressed after chemotherapy."

- The efficacy and safety of cemiplimab as first-line treatment have not been established.
- The efficacy and safety of cemiplimab as postoperative adjuvant therapy have not been established.

7.R.4.2 Efficacy and safety of cemiplimab by PD-L1 expression status and target population

Since cemiplimab is an antibody drug directed against human PD-1, PMDA asked the applicant to explain the efficacy and safety of cemiplimab by expression status of its ligand, PD-L1, and the target population.

The applicant's response:

Since PD-L1 testing was not mandatory in Study 1676 for the following reasons, (1) the efficacy and (2) safety of cemiplimab by PD-L1 expression status (cutoff value, TC 1%) were evaluated exploratorily in a subset of patients with tumor samples assessable for PD-L1 expression (126 of 304 patients [41.4%] in the cemiplimab group, 128 of 304 patients [42.1%] in the IC group). Roche Diagnostics' "VENTANA OptiView PD-L1 (SP263)" was used to analyze available tumor samples for their PD-L1 expression.

- Given that collection of adequate tumor samples for the PD-L1 assay may lead to complications such as fistula formation in the patient population of Study 1676, it was difficult to collect new tumor samples. Thus, it was considered difficult to determine PD-L1 expression levels in all patients.
- Patients with advanced or recurrent cervical cancer previously treated with chemotherapy have a poor prognosis, and there is a need for rapid treatment initiation for these patients.
- At the time of planning Study 1676, there were no findings suggesting that PD-L1 expression status affects the efficacy of cemiplimab in patients with advanced or recurrent cervical cancer previously treated with chemotherapy.

(1) Efficacy

The results of the second interim analysis of OS (data cutoff date of January 4, 2021) and the Kaplan-Meier curves by PD-L1 expression status in Study 1676 are shown in Table 55 and Figure 5, respectively.

Table 55. Results of second interim analysis of OS by PD-L1 expression status (FAS, Data cutoff date of January 4, 2021)

PD-L1 expression	Treatment group	N	OS		
			Median [95% CI] (months)	Hazard ratio[*1] [95% CI]	*P*-value for interaction[*2]
TC <1%	Cemiplimab	44	7.7 [4.3, 12.3]	0.976 [0.588, 1.617]	0.1884
	IC	48	6.7 [3.9, 9.5]		
TC ≥1%	Cemiplimab	82	13.9 [9.6, －]	0.698 [0.463, 1.053]	
	IC	80	9.3 [7.0, 11.4]		

－: Not estimable

*1: Stratified Cox proportional hazards model using geographic region (North America versus Asia-Pacific versus the rest of the world) and histology (SCC versus adenocarcinoma) as stratification factors

*2: Stratified Cox proportional hazards model with (1) treatment, (2) PD-L1 level, and (3) treatment by PD-L1 level interaction as covariates and geographic region (North America versus Asia-Pacific versus the rest of the world) and histology (squamous cell carcinoma versus adenocarcinoma) as stratification factors

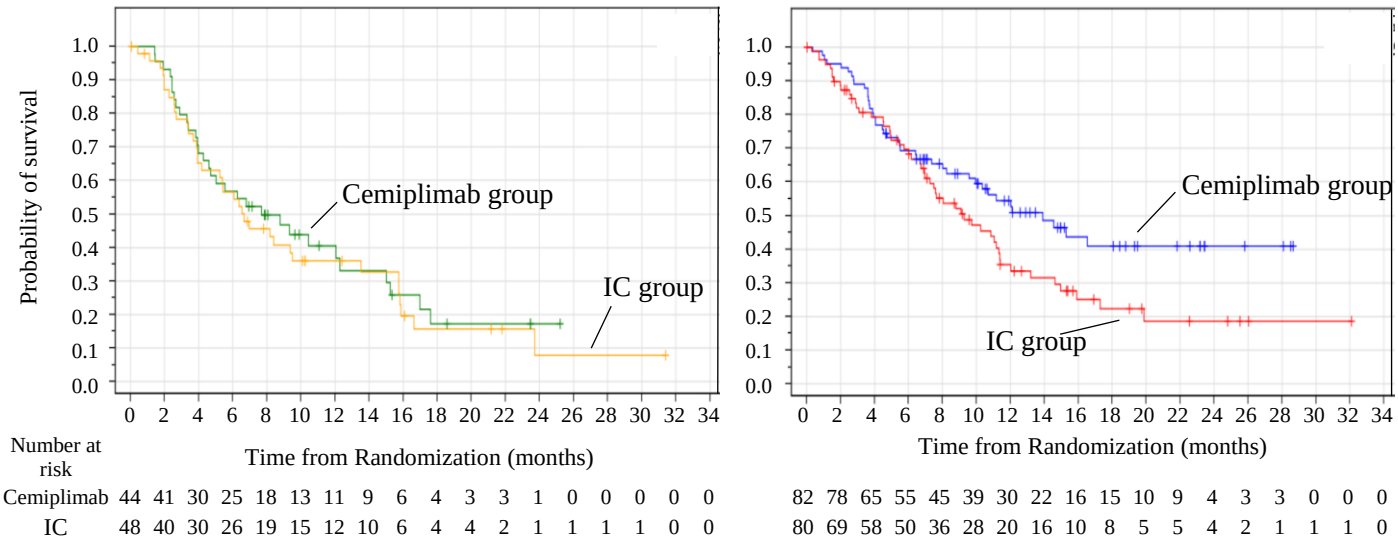


Figure 5. Kaplan-Meier curves for OS at the second interim analysis by PD-L1 expression status (FAS, Data cutoff date of January 4, 2021)
(Left figure: TC <1%, Right figure: TC ≥1%)

Given that there was a trend towards differences in the results of OS between the TC <1% and TC ≥1% subgroups as shown in the above, an adjusted analysis was performed using the stratified Cox hazards model with Eastern Cooperative Oncology Group Performance Status (ECOG PS)[21)] as a covariate because among histology (SCC versus adenocarcinoma) and ECOG PS (0 versus 1) that were considered to impact OS in patients with cervical cancer, ECOG PS was imbalanced between the treatment groups. The hazard ratio of OS for cemiplimab versus IC [95% CI] in the TC<1% subgroup was 0.898 [0.533, 1.516]. Although an analysis was performed to account for the effect of the post-treatment therapy in the TC <1% subgroup,[22)] the analysis results suggested no effects of the post-treatment therapy.

Based on the above, only a subset of patients in the FAS were evaluable for PD-L1 expression in Study 1676, and there are limitations to evaluating the efficacy of cemiplimab by PD-L1 expression status. However, given the following points, a certain level of efficacy of cemiplimab is expected, regardless of PD-L1 expression status.

- In the TC <1% subgroup, an imbalance in patient characteristics between the treatment groups may have affected the results of OS.
- According to an additional analysis performed 1 year after the second interim analysis of OS (data cutoff date of January 4, 2022), the median OS [95% CI] (months) in the cemiplimab and IC groups in the TC <1% subgroup were 8.2 [4.3, 12.3] and 6.7 [3.9, 11.8] respectively, and the hazard ratio of OS for cemiplimab versus IC [95% CI] was 0.846 [0.527, 1.357].

21) As a factor imbalanced (a ≥5% difference) between the treatment groups in the TC <1% subgroup, ECOG PS (0: 17 of 44 subjects [38.6%] in the cemiplimab group and 25 of 48 subjects [52.1%] in the IC group; 1: 27 of 44 subjects [61.4%] in the cemiplimab group and 23 of 48 subjects [47.9%] in the IC group) was chosen.

22) According to a sensitivity analysis of OS by censoring patients on the start date of post-treatment therapy, the hazard ratio of OS for cemiplimab versus IC [95% CI] was 0.972 [0.518, 1.821].

(2) Safety

In the cemiplimab group, the incidences of adverse events of any grade in the TC <1% and TC ≥1% subgroups were 88.9% and 87.7%, respectively. The incidences of Grade ≥3 adverse events were 44.4% and 40.7%, respectively, and the incidences of serious adverse events were 35.6% and 24.7%, respectively.

Regarding the safety of cemiplimab by PD-L1 expression status, as there were no clear differences in the safety of cemiplimab between the TC <1% and TC ≥1% subgroups, cemiplimab is tolerable, regardless of PD-L1 expression status.

Given the above (1) and (2) and the following point, the clinical usefulness of cemiplimab is expected also in the TC <1% subpopulation. Thus, cemiplimab is recommended in patients with advanced or recurrent cervical cancer previously treated with chemotherapy, regardless of PD-L1 expression status.

- In patients with advanced or recurrent cervical cancer, rectovaginal fistula associated with a local lesion, colostomy due to gastrointestinal obstruction, etc., are expected, and the use of existing treatments such as irinotecan hydrochloride (IRI) may cause exacerbation of gastrointestinal disorders and a marked decrease in quality of life (QOL) due to the known risk of diarrhoea etc.

PMDA's discussion:

In Study 1676, the results of analysis of tumor cell PD-L1 expression were available in only a subset of patients, and there are limitations to evaluation based on the presented results. However, the applicant's explanation that an imbalance in patient characteristics between the treatment groups may have affected the results of OS is understandable to some extent, and given the following point, the results of the additional analysis of OS, and the medical need based on the risks associated with existing treatments, offering cemiplimab as a treatment option for patients with advanced or recurrent cervical cancer previously treated with chemotherapy, including those with TC <1%, is clinically meaningful.

- There is no treatment whose efficacy has been demonstrated based on the OS benefit in patients with advanced or recurrent cervical cancer that has progressed after platinum-containing chemotherapy.

7.R.5 Dosage and administration

The proposed dosage and administration statement was "The usual adult dosage is 350 mg of Cemiplimab (Genetical Recombination) administered as an intravenous infusion over 30 minutes every 3 weeks." The following statements were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section. However, after the submission of the present application, the applicant explained that the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section will also advise that the efficacy and safety of cemiplimab in combination with other anti-neoplastic drugs have not been established.

- Treatment may be continued until symptomatic disease progression or unacceptable toxicity.
- Recommended dosage modifications for cemiplimab for adverse reactions

PMDA's conclusion:

Based on Sections "7.R.2 Efficacy" and "7.R.3 Safety" and the considerations in the following sections, the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement of "The usual adult dosage is 350 mg of Cemiplimab (Genetical Recombination) administered as an intravenous infusion over 30 minutes every 3 weeks." is appropriate.

- The efficacy and safety of cemiplimab in combination with other anti-neoplastic drugs have not been established.
- Recommended dosage modifications for cemiplimab for adverse reactions [see Section 7.R.5.2].

7.R.5.1 Dosing regimen of cemiplimab

The applicant's explanation about the rationale for the proposed dosing regimen of cemiplimab:

The dosing regimen for Study 1676 was selected based on the following clinical study results etc., and Study 1676 showed the clinical usefulness of cemiplimab in patients with advanced or recurrent cervical cancer that has progressed after chemotherapy [see Sections 7.R.2 and 7.R.3]. Thus, the dosing regimen of cemiplimab was proposed based on Study 1676, and then "Treatment may be continued until disease progression or unacceptable toxicity" was included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

- A foreign phase I study in patients with advanced solid malignancies (Study 1423) demonstrated the tolerability of cemiplimab 3 mg/kg Q2W [see Section 7.1.3.1].
- The results of the PPK analyses indicated that a 350 mg Q3W dose resulted in similar exposure as compared to a 3 mg/kg Q2W dose.
- In a Japanese phase I study (Study 1622), no DLTs were observed in the 350 mg Q3W group (N = 7), and cemiplimab 350 mg Q3W was tolerable also in Japanese patients [see Section 7.1.1.1].

Since no clinical studies have evaluated the efficacy and safety of cemiplimab in combination with other anti-neoplastic drugs at present, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section will advise that the efficacy and safety of cemiplimab in combination with other anti-neoplastic drugs have not been established.

PMDA's discussion:

PMDA largely accepted the applicant's explanation. However, the precautionary statement of "Treatment may be continued until disease progression or unacceptable toxicity." is unnecessary because this is not a matter that should be specifically noted, given that cemiplimab will be used under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy.

Based on the above, the following statement should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and then the proposed dosage and administration statement of

"The usual adult dosage is 350 mg of Cemiplimab (Genetical Recombination) administered as an intravenous infusion over 30 minutes every 3 weeks." is appropriate.

- The efficacy and safety of cemiplimab in combination with other anti-neoplastic drugs have not been established.

7.R.5.2 Recommended dosage modifications

The applicant's explanation about the recommended dosage modifications for cemiplimab:

Study 1676 was conducted according to the cemiplimab dosage modification guidelines for adverse reactions and showed the clinical usefulness of cemiplimab. Thus, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section included a revised version of these guidelines.

PMDA's discussion:

PMDA largely accepted the applicant's explanation and concluded that the following recommended dosage modifications for cemiplimab for adverse reactions should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

- In the event of adverse reactions to cemiplimab, dosage modifications should be considered based on the table below.

Table 56. Recommended dosage modifications for cemiplimab for adverse reactions

Adverse reaction	Severity*	Dosage modifications
ILD	Grade 2	Withhold until resolution to Grade ≤1
	Grade ≥3 or recurrent Grade 2	Permanently discontinue
Colitis/Diarrhea	Grade 2 or 3	Withhold until resolution to Grade ≤1
	Grade 4 or recurrent Grade 3	Permanently discontinue
Hepatic dysfunction	• AST or ALT increases to 3-5 × ULN • Total bilirubin increases to 1.5-3 × ULN	Withhold until resolution to Grade ≤1
	• AST or ALT increases to >5× ULN • Total bilirubin increases to >3 × ULN	Permanently discontinue
Hypothyroidism Hyperthyroidism Thyroiditis	Grade 3 or 4	Withhold until resolution to Grade ≤1
Adrenal insufficiency	Grade ≥2	Withhold until resolution to Grade ≤1
Hypophysitis	Grade ≥2	Withhold until resolution to Grade ≤1
Type 1 diabetes mellitus	Grade ≥3	Withhold until resolution to Grade ≤1
Skin disorders	• Grade 2 lasting for ≥1 week • Grade 3 • Suspected SJS/TEN	Withhold until resolution to Grade ≤1
	• Grade 4 • Confirmed SJS/TEN	Permanently discontinue
Renal dysfunction	Serum creatinine increases to 1.5-3 × ULN or baseline	Withhold until resolution to Grade ≤1
	Serum creatinine increases to >3 × ULN or baseline	Permanently discontinue
Infusion reaction	Grade 1 or 2	Interrupt or slow the rate of infusion by 50%
	Grade ≥3	Permanently discontinue
Other adverse reactions	Grade 2 or 3	Withhold until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks of withholding cemiplimab.
	Grade 4 or recurrent Grade 3	Permanently discontinue

*: Grade is based on NCI-CTCAE v4.03.

7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:
The applicant is planning to conduct post-marketing surveillance in patients with advanced or recurrent cervical cancer previously treated with chemotherapy to evaluate the safety etc. of cemiplimab in clinical practice after marketing.

Given the incidence of adverse events in Study 1676, the applicant is planning to include the events that require particular attention following administration of cemiplimab, i.e., infusion reactions, enterocolitis/diarrhoea, gastritis, musculoskeletal and connective tissue disorders (including myositis, rhabdomyolysis, and myasthenia gravis), cardiac disorders (including myocarditis), renal disorders, endocrine dysfunction (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction), type 1 diabetes mellitus, pancreatitis (including pancreatic enzymes increased), eye disorders (including uveitis and keratitis), skin disorders, peripheral neuropathies (including Guillain-Barre syndrome), encephalitis/meningitis, blood disorders (including febrile neutropenia and immune thrombocytopenic purpura), hepatic dysfunction (including autoimmune hepatitis), ILD, and transplant-related adverse events in the safety specification for the surveillance.

A planned sample size of 100 and an observation period of 12 months were chosen, taking account of the incidences of the events that will be included in the above safety specification in Study 1676.

PMDA's discussion:
Since the safety information from cemiplimab-treated Japanese patients with advanced or recurrent cervical cancer that has progressed after chemotherapy is limited, it is necessary to conduct post-marketing surveillance to collect cemiplimab safety information in clinical practice.

Based on the considerations etc. in Section "7.R.3 Safety," the safety specification for the surveillance should include infusion reactions, colitis/severe diarrhea, myositis/rhabdomyolysis/myasthenia gravis, myocarditis/pericarditis, renal dysfunction (tubulointerstitial nephritis, etc.), endocrine dysfunction (thyroid dysfunction/adrenal dysfunction/pituitary dysfunction), type 1 diabetes mellitus, severe skin disorders, neuropathies (Guillain-Barre syndrome, etc.), encephalitis/meningitis, hepatic failure/hepatic dysfunction/hepatitis, ILD, use in organ transplant recipients (including hematopoietic stem cell transplant recipients), venous thromboembolism, febrile neutropenia, immune thrombocytopenic purpura, pancreatitis, and uveitis.

The planned sample size and observation period for the surveillance need to be reconsidered, taking account of the incidences of the above events that should be included in the safety specification for the surveillance.

7.3 Adverse events etc. observed in clinical studies

Among clinical study results submitted for safety evaluation, deaths are described in Section "7.1 Evaluation data" and Section "7.2 Reference data." The main adverse events other than deaths are described below.

7.3.1 Japanese phase I study (Study 1622, Part 1)

Adverse events occurred in (1) 6 of 6 subjects (100%) in the 250 mg group and (2) 6 of 7 subjects (85.7%) in the 350 mg group, and those for which a causal relationship to cemiplimab could not be ruled out occurred in (1) 5 of 6 subjects (83.3%) and (2) 6 of 7 subjects (85.7%). Adverse events reported by ≥20% of subjects in each group were (1) rash; pruritus; diarrhoea; hypophosphataemia; nasopharyngitis; and oropharyngeal pain (2 subjects each [33.3%]) and (2) contact dermatitis; and fatigue (2 subjects each [28.6%]).

Serious adverse events occurred in (1) 1 of 6 subjects (16.7%) and (2) 1 of 7 subjects (14.3%). The observed serious adverse events were (1) autoimmune colitis (1 subject [16.7%]) and (2) hyponatraemia (1 subject [14.3%]), and a causal relationship to cemiplimab could not be ruled out for (1) autoimmune colitis (1 subject).

An adverse event leading to cemiplimab discontinuation occurred in (2) 1 of 7 subjects (14.3%) [(1) None]. The observed adverse event leading to cemiplimab discontinuation was muscular weakness, and its causal relationship to cemiplimab could not be ruled out.

7.3.2 Global phase III study (Study 1676)

Adverse events occurred in 265 of 300 subjects (88.3%) in the cemiplimab group and 265 of 290 subjects (91.4%) in the IC group, and those for which a causal relationship to study drug could not be ruled out occurred in 170 of 300 subjects (56.7%) in the cemiplimab group and 236 of 290 subjects (81.4%) in the IC group. Table 57 shows adverse events reported by ≥10% of subjects in either group.

Table 57. Adverse events reported by ≥10% of subjects in either group

SOC PT (MedDRA ver.23.1)	n (%)			
	Cemiplimab N = 300		IC N = 290	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	265 (88.3)	135 (45.0)	265 (91.4)	155 (53.4)
Gastrointestinal disorders				
Nausea	55 (18.3)	1 (0.3)	97 (33.4)	6 (2.1)
Vomiting	48 (16.0)	2 (0.7)	68 (23.4)	7 (2.4)
Constipation	45 (15.0)	0	59 (20.3)	1 (0.3)
Diarrhoea	32 (10.7)	3 (1.0)	39 (13.4)	4 (1.4)
Abdominal pain	29 (9.7)	3 (1.0)	33 (11.4)	3 (1.0)
General disorders and administration site conditions				
Fatigue	50 (16.7)	4 (1.3)	45 (15.5)	4 (1.4)
Pyrexia	35 (11.7)	1 (0.3)	61 (21.0)	0
Asthenia	33 (11.0)	7 (2.3)	44 (15.2)	3 (1.0)
Infections and infestations				
Urinary tract infection	35 (11.7)	15 (5.0)	25 (8.6)	8 (2.8)
Metabolism and nutrition disorders				
Decreased appetite	45 (15.0)	1 (0.3)	46 (15.9)	2 (0.7)
Blood and lymphatic system disorders				
Anaemia	75 (25.0)	36 (12.0)	129 (44.5)	78 (26.9)
Neutropenia	6 (2.0)	3 (1.0)	44 (15.2)	26 (9.0)
Musculoskeletal and connective tissue disorders				
Back pain	33 (11.0)	4 (1.3)	25 (8.6)	2 (0.7)
Arthralgia	31 (10.3)	1 (0.3)	8 (2.8)	0

Serious adverse events occurred in 89 of 300 subjects (29.7%) in the cemiplimab group and 78 of 290 subjects (26.9%) in the IC group. Those reported by ≥3 subjects in each group were urinary tract infection (12 subjects [4.0%]); acute kidney injury (5 subjects [1.7%]); pneumonia; pyrexia; and autoimmune hepatitis (4 subjects each [1.3%]); and pyelonephritis; haematuria; hydronephrosis; immune-mediated hepatitis; pneumonitis; febrile neutropenia; and blood creatinine increased (3 subjects each [1.0%]) in the cemiplimab group and anaemia (14 subjects [4.8%]); urinary tract infection (10 subjects [3.4%]); pyrexia; and febrile neutropenia (5 subjects each [1.7%]); and pneumonia; pyelonephritis; vomiting; acute kidney injury; and thrombocytopenia (3 subjects each [1.0%]) in the IC group. A causal relationship to study drug could not be ruled out for autoimmune hepatitis (4 subjects); immune-mediated hepatitis; and pneumonitis (3 subjects each); febrile neutropenia; and acute kidney injury (2 subjects each); and pyrexia (1 subject) in the cemiplimab group and anaemia (12 subjects); febrile neutropenia (5 subjects); thrombocytopenia (3 subjects); pyrexia; vomiting; and acute kidney injury (2 subjects each); and pyelonephritis (1 subject) in the IC group.

Adverse events leading to study drug discontinuation occurred in 26 of 300 subjects (8.7%) in the cemiplimab group and 15 of 290 subjects (5.2%) in the IC group. Those reported by ≥2 subjects in each group were pneumonitis (5 subjects [1.7%]); autoimmune hepatitis; and immune-mediated hepatitis (3 subjects each [1.0%]); and hypothyroidism (2 subjects [0.7%]) in the cemiplimab group and infusion related reaction (2 subjects [0.7%]) in the IC group. A causal relationship to study drug could not be ruled out for pneumonitis (4 subjects); autoimmune hepatitis; and immune-mediated hepatitis (3 subjects each); and hypothyroidism (2 subjects) in the cemiplimab group and infusion related reaction (2 subjects) in the IC group.

7.3.3 Foreign phase I study (Study 1423)

Adverse events occurred in (1) 6 of 6 subjects (100%) in the 1 mg/kg Q2W group, (2) 96 of 98 subjects (98.0%) in the 3 mg/kg Q2W group, (3) 5 of 6 subjects (83.3%) in the 10 mg/kg Q2W group, and (4) 20 of 20 subjects (100%) in the 200 mg Q2W group for cemiplimab monotherapy, and those for which a causal relationship to cemiplimab could not be ruled out occurred in (1) 5 of 6 subjects (83.3%), (2) 67 of 98 subjects (68.4%), (3) 5 of 6 subjects (83.3%), and (4) 13 of 20 subjects (65.0%). Adverse events reported by ≥20% of subjects in each group were (1) fatigue (4 subjects [66.7%]); vomiting; and rash maculo-papular (3 subjects each [50.0%]); and constipation; nausea; dysphagia; cough; dizziness; and lymphopenia (2 subjects each [33.3%]), (2) fatigue (29 subjects [29.6%]); and diarrhoea (20 subjects [20.4%]), (3) decreased appetite (3 subjects [50.0%]); and nausea; fatigue; upper respiratory tract infection; arthralgia; anxiety; and depression (2 subjects each [33.3%]), and (4) asthenia; cough; dyspnoea; and arthralgia (4 subjects each [20.0%]).

Serious adverse events occurred in (1) 1 of 6 subjects (16.7%), (2) 20 of 98 subjects (20.4%), (3) 2 of 6 subjects (33.3%), and (4) 9 of 20 subjects (45.0%). Those reported by ≥2 subjects in each group were (2) autoimmune hepatitis (2 subjects [2.0%]) and (4) pneumonia; and pneumonitis (2 subjects each [10.0%]). A causal relationship to cemiplimab could not be ruled out for (2) autoimmune hepatitis (2 subjects) and (4) pneumonitis (2 subjects).

Adverse events leading to cemiplimab discontinuation occurred in (2) 7 of 98 subjects (7.1%), (3) 1 of 6 subjects (16.7%), and (4) 1 of 20 subjects (5.0%). Those reported by ≥2 subjects in each group were (2) autoimmune hepatitis (2 subjects [2.0%]), and a causal relationship to cemiplimab could not be ruled out for both cases.

7.3.4 Foreign phase II study (Study 1540)

Adverse events occurred in (1) 59 of 59 subjects (100%) in Group 1, (2) 78 of 78 subjects (100%) in Group 2, and (3) 54 of 56 subjects (96.4%) in Group 3, and those for which a causal relationship to cemiplimab could not be ruled out occurred in (1) 46 of 59 subjects (78.0%), (2) 62 of 78 subjects (79.5%), and (3) 36 of 56 subjects (64.3%). Adverse events reported by ≥15% of subjects in each Group were (1) diarrhoea (17 subjects [28.8%]); fatigue (15 subjects [25.4%]); nausea (14 subjects [23.7%]); headache (11 subjects [18.6%]); pruritus; rash; and constipation (10 subjects each [16.9%]); and arthralgia; and cough (9 subjects each [15.3%]), (2) fatigue (33 subjects [42.3%]); pruritus; and diarrhoea (21 subjects each [26.9%]); nausea (17 subjects [21.8%]); and cough (15 subjects [19.2%]), and (3) fatigue (16 subjects [28.6%]); diarrhoea; and nausea (10 subjects each [17.9%]); and rash (9 subjects [16.1%]).

Serious adverse events occurred in (1) 24 of 59 subjects (40.7%), (2) 23 of 78 subjects (29.5%), and (3) 22 of 56 subjects (39.3%). Those reported by ≥2 subjects in each Group were (1) cellulitis; and pneumonitis (4 subjects each [6.8%]), (2) pneumonia (4 subjects [5.1%]); pneumonitis (3 subjects [3.8%]); and cellulitis; sepsis; fall; pyrexia; muscular weakness; and breast cancer (2 subjects each [2.6%]), and (3) dehydration; and haematuria (2 subjects each [3.6%]). A causal relationship to cemiplimab could not be ruled out for (1) pneumonitis (4 subjects) and (2) pneumonitis (3 subjects); and pneumonia; and pyrexia (1 subject each).

Adverse events leading to cemiplimab discontinuation occurred in (1) 6 of 59 subjects (10.2%), (2) 6 of 78 subjects (7.7%), and (3) 3 of 56 subjects (5.4%). Those reported by ≥2 subjects in each Group were (1) pneumonitis (4 subjects [6.8%]) and (2) pneumonitis (2 subjects [2.6%]), and a causal relationship to cemiplimab could not be ruled out for all those events.

7.3.5 Foreign phase II study (Study 1620)

Adverse events occurred in 125 of 132 subjects (94.7%), and those for which a causal relationship to cemiplimab could not be ruled out occurred in 99 of 132 subjects (75.0%). Adverse events reported by ≥10% of subjects were fatigue (44 subjects [33.3%]); diarrhoea (33 subjects [25.0%]); pruritus (26 subjects [19.7%]); asthenia (21 subjects [15.9%]); decreased appetite (19 subjects [14.4%]); arthralgia; and anaemia (17 subjects each [12.9%]); urinary tract infection; nausea; and headache (16 subjects each [12.1%]); and constipation (14 subjects [10.6%]).

Serious adverse events occurred in 42 of 132 subjects (31.8%). Those reported by ≥2 subjects were urinary tract infection (5 subjects [3.8%]); colitis (4 subjects [3.0%]); and infected neoplasm; anaemia; adrenal insufficiency; acute kidney injury; and somnolence (2 subjects each [1.5%]). A causal relationship to

cemiplimab could not be ruled out for colitis (4 subjects); adrenal insufficiency (2 subjects); and acute kidney injury (1 subject).

Adverse events leading to cemiplimab discontinuation occurred in 17 of 132 subjects (12.9%). Those reported by ≥2 subjects were colitis; and general physical health deterioration (2 subjects each [1.5%]), and a causal relationship to cemiplimab could not be ruled out for colitis (2 subjects) and general physical health deterioration (1 subject).

7.3.6 Foreign phase III study (Study 1624)

Adverse events occurred in (1) 313 of 355 subjects (88.2%) in the cemiplimab group and (2) 322 of 342 subjects (94.2%) in the IC group, and those for which a causal relationship to study drug could not be ruled out occurred in (1) 204 of 355 subjects (57.5%) and (2) 303 of 342 subjects (88.6%). Adverse events reported by ≥10% of subjects in each group were (1) anaemia (52 subjects [14.6%]); decreased appetite (42 subjects [11.8%]); and fatigue (36 subjects [10.1%]) and (2) anaemia (171 subjects [50.0%]); nausea (97 subjects [28.4%]); alopecia (82 subjects [24.0%]); decreased appetite; and neutropenia (63 subjects each [18.4%]); fatigue (58 subjects [17.0%]); constipation; and thrombocytopenia (52 subjects each [15.2%]); vomiting (49 subjects [14.3%]); neutrophil count decreased (42 subjects [12.3%]); pneumonia; and peripheral neuropathy (37 subjects each [10.8%]); and platelet count decreased (36 subjects [10.5%]).

Serious adverse events occurred in (1) 100 of 355 subjects (28.2%) and (2) 94 of 342 subjects (27.5%). Those reported by ≥4 subjects in each group were (1) pneumonia (17 subjects [4.8%]); pneumonitis; and pulmonary embolism (6 subjects each [1.7%]); death (5 subjects [1.4%]); and septic shock; dyspnoea; pleural effusion; and respiratory failure (4 subjects each [1.1%]) and (2) pneumonia (17 subjects [5.0%]); anaemia (13 subjects [3.8%]); febrile neutropenia (8 subjects [2.3%]); thrombocytopenia (6 subjects [1.8%]); and dyspnoea; vomiting; and neutropenia (4 subjects each [1.2%]). A causal relationship to study drug could not be ruled out for (1) pneumonitis (6 subjects); pneumonia (4 subjects); dyspnoea (2 subjects); and pleural effusion; pulmonary embolism; respiratory failure; death; and septic shock (1 subject each) and (2) anaemia (12 subjects); febrile neutropenia (8 subjects); pneumonia; and thrombocytopenia (6 subjects each); vomiting (4 subjects); neutropenia (3 subjects); and dyspnoea (1 subject).

Adverse events leading to study drug discontinuation occurred in (1) 23 of 355 subjects (6.5%) and (2) 14 of 342 subjects (4.1%). Those reported by ≥2 subjects in each group were (1) pneumonitis (4 subjects [1.1%]); and ischaemic stroke; and aspartate aminotransferase increased (2 subjects each [0.6%]) and (2) thrombocytopenia (3 subjects [0.9%]); and anaemia (2 subjects [0.6%]), and a causal relationship to study drug could not be ruled out for (1) pneumonitis (4 subjects); and aspartate aminotransferase increased (2 subjects) and (2) thrombocytopenia (3 subjects); and anaemia (2 subjects).

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 new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that cemiplimab has efficacy in the treatment of advanced or recurrent cervical cancer that has progressed after chemotherapy, and that cemiplimab has acceptable safety in view of its benefits. Cemiplimab is a human IgG4 monoclonal antibody that targets human PD-1, and is classified as a drug with a new active ingredient. It binds to the extracellular domain of PD-1 (the PD-1 ligand binding site) and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. This results in enhancement of tumor antigen-specific T-cell activation and cytotoxic T cell activity against tumor cells, leading to inhibition of tumor growth. Cemiplimab is clinically meaningful because it offers a new treatment option for patients with advanced or recurrent cervical cancer that has progressed after chemotherapy. PMDA considers that the safety, clinical positioning, and indication of cemiplimab need to be further discussed.

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

Review Report (2)

November 14, 2022

Product Submitted for Approval

Brand Name	Libtayo I.V. Infusion 350 mg
Non-proprietary Name	Cemiplimab (Genetical Recombination)
Applicant	Sanofi K.K.
Date of Application	March 18, 2022

List of Abbreviations

See Appendix.

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

Based on the review presented in Section "7.R.2 Efficacy" in the Review Report (1), PMDA has concluded that cemiplimab was shown to have efficacy in patients with advanced or recurrent cervical cancer previously treated with chemotherapy, because a global phase III study (Study 1676) demonstrated the superiority of cemiplimab to IC in OS, the primary endpoint, in these patients.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2 Safety

PMDA’s conclusion based on the review presented in Section "7.R.3 Safety" in the Review Report (1):

Particular attention should be paid to the following adverse events following administration of cemiplimab:

Infusion reactions, colitis/diarrhoea, myositis, rhabdomyolysis/myasthenia gravis, myocarditis/pericarditis, renal disorders, endocrine dysfunction, type 1 diabetes mellitus, skin disorders, peripheral neuropathies (including Guillain-Barre syndrome), encephalitis/meningitis, hepatic dysfunction, ILD, transplant-related adverse events, venous thromboembolism, febrile neutropenia, immune thrombocytopenia, pancreatitis, and uveitis

Although attention should be paid to the possible occurrence of the above adverse events during the use of cemiplimab, cemiplimab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate actions, such as monitoring of adverse events, differential diagnosis and management in anticipation of adverse drug reactions due to excessive immune response, and interruption of cemiplimab.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.3 Clinical positioning and indication

Based on the review presented in Section "7.R.4 Clinical positioning and indication" in the Review Report (1), PMDA has concluded that the proposed indication should be modified to "advanced or recurrent cervical cancer that has progressed after chemotherapy," and that the following statements should be included in the PRECAUTIONS CONCERNING INDICATION section.

Precautions Concerning Indication

- The efficacy and safety of cemiplimab as first-line treatment have not been established.
- The efficacy and safety of cemiplimab as postoperative adjuvant therapy have not been established.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

Based on the above, PMDA instructed the applicant to amend the INDICATION and PRECAUTIONS CONCERNING INDICATION sections accordingly. The applicant agreed.

1.4 Dosage and administration

Based on the review presented in Section "7.R.5 Dosage and administration" in the Review Report (1), PMDA has concluded that the proposed dosage and administration statement (“The usual adult dosage is 350 mg of Cemiplimab (Genetical Recombination) administered as an intravenous infusion over 30 minutes every 3 weeks.”) is appropriate, and that the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

Precautions Concerning Dosage and Administration

- The efficacy and safety of cemiplimab in combination with other anti-neoplastic drugs have not been established.
- In the event of adverse reactions to cemiplimab, dosage modifications should be considered based on the table below.

Adverse reaction	Severity*	Dosage modifications
ILD	Grade 2	Withhold until resolution to Grade ≤1
	Grade ≥3 or recurrent Grade 2	Permanently discontinue
Colitis/Diarrhea	Grade 2 or 3	Withhold until resolution to Grade ≤1
	Grade 4 or recurrent Grade 3	Permanently discontinue
Hepatic dysfunction	• AST or ALT increases to 3-5 × ULN • Total bilirubin increases to 1.5-3 × ULN	Withhold until resolution to Grade ≤1
	• AST or ALT increases to >5× ULN • Total bilirubin increases to >3 × ULN	Permanently discontinue
Hypothyroidism Hyperthyroidism Thyroiditis	Grade 3 or 4	Withhold until resolution to Grade ≤1
Adrenal insufficiency	Grade ≥2	Withhold until resolution to Grade ≤1
Hypophysitis	Grade ≥2	Withhold until resolution to Grade ≤1
Type 1 diabetes mellitus	Grade ≥3	Withhold until resolution to Grade ≤1
Skin disorders	• Grade 2 lasting for ≥1 week • Grade 3 • Suspected SJS/TEN	Withhold until resolution to Grade ≤1
	• Grade 4 • Confirmed SJS/TEN	Permanently discontinue
Renal dysfunction	Serum creatinine increases to 1.5-3 × ULN or baseline	Withhold until resolution to Grade ≤1
	Serum creatinine increases to >3 × ULN or baseline	Permanently discontinue
Infusion reaction	Grade 1 or 2	Interrupt or slow the rate of infusion by 50%
	Grade ≥3	Permanently discontinue
Other adverse reactions	Grade 2 or 3	Withhold until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks of withholding cemiplimab.
	Grade 4 or recurrent Grade 3	Permanently discontinue

*: Grade is based on NCI-CTCAE v4.03.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

Based on the above, PMDA instructed the applicant to include the above statements in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections. The applicant agreed.

1.5 Risk management plan (draft)

The applicant is planning to conduct post-marketing surveillance with a planned sample size of 100 and an observation period of 12 months in cemiplimab-treated patients with advanced or recurrent cervical cancer that has progressed after chemotherapy to evaluate the safety etc. of cemiplimab in clinical practice after marketing.

PMDA's conclusion based on the considerations in Section "7.R.6 Post-marketing investigations" in the Review Report (1):

Post-marketing surveillance should be conducted to collect cemiplimab safety information in clinical practice. The surveillance plan should be as shown below.

- The safety specification should include infusion reactions, colitis/severe diarrhea, myositis/rhabdomyolysis/myasthenia gravis, myocarditis/pericarditis, renal dysfunction (tubulointerstitial nephritis, etc.), endocrine dysfunction (thyroid dysfunction/adrenal dysfunction/pituitary dysfunction),

type 1 diabetes mellitus, severe skin disorders, neuropathies (Guillain-Barre syndrome, etc.), encephalitis/meningitis, hepatic failure/hepatic dysfunction/hepatitis, ILD, use in organ transplant recipients (including hematopoietic stem cell transplant recipients), venous thromboembolism, febrile neutropenia, immune thrombocytopenic purpura, pancreatitis, and uveitis.

- The planned sample size and observation period should be reconsidered, taking account of the clinical study incidences of the events to be included in the safety specification for the surveillance.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

Based on the above considerations, PMDA instructed the applicant to reconsider the surveillance plan, and the applicant responded as follows:

- The safety specification will include infusion reactions, colitis/severe diarrhea, myositis/rhabdomyolysis/myasthenia gravis, myocarditis/pericarditis, renal dysfunction (tubulointerstitial nephritis, etc.), endocrine dysfunction (thyroid dysfunction/adrenal dysfunction/pituitary dysfunction), type 1 diabetes mellitus, severe skin disorders, neuropathies (Guillain-Barre syndrome, etc.), encephalitis/meningitis, hepatic failure/hepatic dysfunction/hepatitis, ILD, use in organ transplant recipients (including hematopoietic stem cell transplant recipients), venous thromboembolism, febrile neutropenia, immune thrombocytopenic purpura, pancreatitis, and uveitis.
- The planned sample size will be 120, taking account of the incidences, in Study 1676, of the events to be included in the safety specification.
- The observation period will be 12 months, taking account of the time to the first onset, in Study 1676, of the events to be included in the safety specification.

PMDA accepted the applicant's response.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for cemiplimab should include the safety specification presented in Table 58, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 59 and Table 60.

Table 58. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infusion reactions • Colitis/Severe diarrhea • Myositis/Rhabdomyolysis/Myasthenia gravis • Myocarditis/Pericarditis • Renal dysfunction (tubulointerstitial nephritis, etc.) • Endocrine dysfunction (thyroid dysfunction/adrenal dysfunction/pituitary dysfunction) • Type 1 diabetes mellitus • Severe skin disorders • Neuropathies (Guillain-Barre syndrome, etc.) • Encephalitis/Meningitis • Hepatic failure/Hepatic dysfunction/Hepatitis • ILD • Use in organ transplant recipients (including hematopoietic stem cell transplant recipients) • Venous thromboembolism	• Febrile neutropenia • Immune thrombocytopenic purpura • Pancreatitis • Uveitis • Embryo-fetal toxicity	None
Efficacy specification		
None		

Table 59. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • Use-results survey in patients with advanced or recurrent cervical cancer that has progressed after chemotherapy	None	• Disseminate data gathered during early post-marketing phase vigilance • Develop information materials to be distributed to healthcare professionals • Develop information materials to be distributed to patients

Table 60. Outline of use-results survey (draft)

Objective	To evaluate the safety etc. of cemiplimab in clinical practice.
Survey method	Central registry system
Population	Cemiplimab-treated patients with advanced or recurrent cervical cancer that has progressed after chemotherapy
Observation period	12 months
Planned sample size	120 patients
Main survey items	Safety specification: infusion reactions, colitis/severe diarrhea, myositis/rhabdomyolysis/myasthenia gravis, myocarditis/pericarditis, renal dysfunction (tubulointerstitial nephritis, etc.), endocrine dysfunction (thyroid dysfunction/adrenal dysfunction/pituitary dysfunction), type 1 diabetes mellitus, severe skin disorders, neuropathies (Guillain-Barre syndrome, etc.), encephalitis/meningitis, hepatic failure/hepatic dysfunction/hepatitis, ILD, use in organ transplant recipients (including hematopoietic stem cell transplant recipients), venous thromboembolism, febrile neutropenia, immune thrombocytopenic purpura, pancreatitis, and uveitis “” Other main survey items: patient characteristics (age, medical history, complications, prior therapies, etc.), the use of cemiplimab, etc.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration with the approval condition shown below, provided that necessary precautionary statements are included in the package insert and information on the proper use of the product is appropriately disseminated after the market launch, and provided that the proper use of the product is ensured under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Since the product is a drug with a new active

ingredient, the re-examination period is 8 years. The product is classified as a biological product, and the drug product and its drug substance are both classified as powerful drugs.

Indication

Advanced or recurrent cervical cancer that has progressed after chemotherapy

Dosage and Administration

The usual adult dosage is 350 mg of Cemiplimab (Genetical Recombination) administered as an intravenous infusion over 30 minutes every 3 weeks.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Warnings

1. Libtayo should be administered only to patients eligible for Libtayo therapy, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can provide adequate emergency medical care. Prior to initiation of treatment, patients or their families should be fully informed of its efficacy and risks, and their consent should be obtained.
2. Since cases of interstitial lung disease, including fatal cases, have been reported, patients should be closely monitored (e.g., chest X-ray, detection of initial symptoms such as shortness of breath, dyspnoea, and cough). If abnormalities are observed, discontinue Libtayo and take appropriate actions such as administration of corticosteroids.

Contraindication

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

Precautions Concerning Indication

1. The efficacy and safety of Libtayo as first-line treatment have not been established.
2. The efficacy and safety of Libtayo as postoperative adjuvant therapy have not been established.

Precautions Concerning Dosage and Administration

1. The efficacy and safety of Libtayo in combination with other anti-neoplastic drugs have not been established.
2. In the event of adverse reactions to Libtayo, dosage modifications should be considered based on the table below.

Adverse reaction	Severity*	Dosage modifications
Interstitial lung disease	Grade 2	Withhold until resolution to Grade ≤1
	Grade ≥3 or recurrent Grade 2	Permanently discontinue
Colitis/Diarrhea	Grade 2 or 3	Withhold until resolution to Grade ≤1
	Grade 4 or recurrent Grade 3	Permanently discontinue
Hepatic dysfunction	• AST or ALT increases to 3-5 × ULN • Total bilirubin increases to 1.5-3 × ULN	Withhold until resolution to Grade ≤1
	• AST or ALT increases to >5 × ULN • Total bilirubin increases to >3 × ULN	Permanently discontinue
Hypothyroidism Hyperthyroidism Thyroiditis	Grade ≥3	Withhold until resolution to Grade ≤1
Adrenal insufficiency	Grade ≥2	Withhold until resolution to Grade ≤1
Hypophysitis	Grade ≥2	Withhold until resolution to Grade ≤1
Type 1 diabetes mellitus	Grade ≥3	Withhold until resolution to Grade ≤1
Skin disorders	• Grade 2 lasting for ≥1 week • Grade 3 • Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until resolution to Grade ≤1
	• Grade 4 • Confirmed SJS or TEN	Permanently discontinue
Renal dysfunction	Serum creatinine increases to 1.5-3 × ULN or baseline	Withhold until resolution to Grade ≤1
	Serum creatinine increases to >3 × ULN or baseline	Permanently discontinue
Infusion reaction	Grade 1 or 2	Interrupt or slow the rate of infusion by 50%
	Grade ≥3	Permanently discontinue
Other adverse reactions	Grade 2 or 3	Withhold until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 12 weeks of withholding Libtayo.
	Grade 4 or recurrent Grade 3	Permanently discontinue

*: Grade is based on NCI-CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) v4.03.

List of Abbreviations

ADA	anti-drug antibody
ADCC	antibody dependent cell mediated cytotoxicity
ALP	alkaline phosphatase
ALT	alanine aminotransferase
application	marketing application
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
atezolizumab	Atezolizumab (Genetical Recombination)
avelumab	Avelumab (Genetical Recombination)
BALT	bronchus-associated lymphoid tissue
BCC	basal cell carcinoma
BV	Bevacizumab (Genetical Recombination)
CAL	cells at the limit of *in vitro* cell age
CBDCA	carboplatin
CD	cluster of differentiation
CD300a	inhibitory receptor protein
CDC	complement dependent cytotoxicity
cemiplimab	Cemiplimab (Genetical Recombination)
CE-SDS	capillary electrophoresis sodium dodecyl sulfate
CHO	Chinese hamster ovary cell
CI	confidence interval
cIEF	capillary Isoelectric Focusing
CPA	cyclophosphamide hydrate
CQA	critical quality attribute
CSCC	cutaneous squamous cell cancer
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DTX	docetaxel hydrate
durvalumab	Durvalumab (Genetical Recombination)
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme-linked immunosorbent assay
EMAX	maximum change in clearance with time
FAS	full analysis set
Fc	fragment, crystallizable
GALT	gut-associated lymphoid tissue
GBM	glioblastoma multiforme
GEM	gemcitabine hydrochloride
GGT	gamma-glutamyltransferase
GM-CSF	granulocyte macrophage colony-stimulating factor
HCP	host cell protein
HEK293 cell	human embryonic kidney 293 cell
HIV	human immunodeficiency virus
HLGT	high level group term
HLT	high level term
HRP	horseradish peroxidase
IC	investigator’s choice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICH Q5A (R1) guideline	Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin (PMSB/ELD Notification No. 329 dated February 22, 2000)
ICH Q5B guideline	Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (PMSB/ELD Notification No. 3 dated January 6, 1998)
ICH Q5D guideline	Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (PMSB/ELD Notification No. 873 dated July 14, 2000)
IDMC	independent data monitoring committee
IFN-γ	interferon-γ
Ig	immunoglobulin
IL	interleukin
ILD	interstitial lung disease
IRI	irinotecan hydrochloride
ITIM	immunoreceptor tyrosine-based inhibition motif
JP	Japanese Pharmacopoeia
K_D	dissociation constant
KLH	keyhole limpet hemocyanin
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MF	drug master file
MSI	microsatellite instability
MSI-High	microsatellite instability-high
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Cervical Cancer
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGT	nogitecan hydrochloride
nivolumab	Nivolumab (Genetical Recombination)
NSCLC	non-small cell lung cancer
NSQ	non-squamous
NSQ-NSCLC	non-squamous non-small cell lung cancer
OS	overall survival
[redacted]	[redacted]
PD-L1	programmed cell death-ligand-1
PD-L2	programmed cell death-ligand-2
PD-1	programmed cell death-1
PEM	pemetrexed sodium hydrate
pembrolizumab	Pembrolizumab (Genetical Recombination)
PFS	progression free survival
PK	pharmacokinetics
platinum agent	cisplatin or CBDCA
[redacted]	[redacted]
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PS	performance status
PT	preferred term
PTX	paclitaxel
QOL	quality of life
QW	quaque 1 week
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
SCC	squamous cell carcinoma
SEC	size exclusion liquid chromatography

SJS	Stevens-Johnson syndrome
SMQ	standardized MedDRA queries
SOC	system organ class
Study 1423	Study R2810-ONC-1423
Study 1540	Study R2810-ONC-1540
Study 1620	Study R2810-ONC-1620
Study 1622	Study R2810-ONC-1622
Study 1624	Study R2810-ONC-1624
Study 1676	Study R2810-ONC-1676
TC	tumor cell
TC <1%	<1% of tumor area occupied by PD-L1-expressing tumor cells
TC ≥1%	≥1% of tumor area occupied by PD-L1-expressing tumor cells
TCR	T cell receptor
TEN	toxic epidermal necrolysis
TNFα	tumor necrosis factor-α
T50	time to decline by 50% of the maximum change in clearance
VNR	vinorelbine ditartrate
V1	central volume of distribution
WCB	working cell bank