Review Report

June 30, 2020
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	Imfinzi Injection 120 mg, Imfinzi Injection 500 mg
Non-proprietary Name	Durvalumab (Genetical Recombination) (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	November 13, 2019
Dosage Form/Strength	Injection: Each vial (2.4 or 10.0 mL) contains 120 or 500 mg of Durvalumab (Genetical Recombination).
Application Classification	Prescription drug, (4) Drug with a new indication, (6) Drug with a new dosage
Items Warranting Special Mention	None
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 extensive-stage small cell lung cancer, 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 indications and dosage and administration shown below, with the following approval condition. The incidence of febrile neutropenia needs to be further investigated via post-marketing surveillance.

Indications

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy
Extensive-stage small cell lung cancer

(Underline denotes additions.)

**Japanese Accepted Name (modified INN)*

Dosage and Administration

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy:

The usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks for a maximum of 12 months.

Extensive-stage small cell lung cancer:

The usual adult dosage is 1,500 mg of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent. Patients with a body weight of ≤30 kg receive 20 mg/kg (body weight) of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent. Durvalumab (Genetical Recombination) is administered as an intravenous infusion over ≥60 minutes.

(Underline denotes additions.)

Approval Condition

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

Attachment

Review Report (1)

May 22, 2020

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	Imfinzi Injection 120 mg, Imfinzi Injection 500 mg
Non-proprietary Name	Durvalumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	November 13, 2019
Dosage Form/Strength	Injection: Each vial (2.4 or 10.0 mL) contains 120 or 500 mg of Durvalumab (Genetical Recombination).

Proposed Indications

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy

Extensive-stage small cell lung cancer

(Underline denotes additions.)

Proposed Dosage and Administration

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy:

The usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks for a maximum of 12 months.

Extensive-stage small cell lung cancer:

The usual adult dosage is 1,500 mg of Durvalumab (Genetical Recombination) in combination with other anti-cancer agents every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent. Patients with a body weight of ≤30 kg receive 20 mg/kg (body weight) of Durvalumab (Genetical Recombination) in combination with other anti-cancer agents every 3 weeks for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent. Durvalumab (Genetical Recombination) is administered as an intravenous infusion over ≥60 minutes.

(Underline denotes additions.)

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

CD274 (programmed cell death ligand 1 [PD-L1]) is expressed on antigen presenting cells etc. in the body, and is considered to negatively regulate immune responses through binding to CD279 (programmed cell death 1 [PD-1]) and CD80 (B7-1) expressed on activated lymphocytes (T cells, B cells, natural killer T cells) etc. (*Annu Rev Immunol*. 2008; 26: 677-704, *Blood*. 2010; 116: 1291-8). Various tumor cells also express PD-L1 (*Nat Med*. 2002; 8: 793-800, *J immunol*. 2003; 170:1257-66), and the PD-L1/PD-1 pathway is considered a mechanism by which tumor cells evade antigen-specific T-cell attack, etc.

Durvalumab (Genetical Recombination) (durvalumab) is a human IgG1 monoclonal antibody against human PD-L1 discovered by AstraZeneca (the UK) and Abgenix (the US) (now Amgen). It binds to the extracellular domain of PD-L1, thereby blocking the binding of PD-L1 to PD-1, resulting in enhanced tumor antigen-specific cytotoxic T cell activity and inhibition of tumor growth.

In Japan, durvalumab was approved for the indication of "maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy" in July 2018.

1.2 Development history etc.

In the clinical development of durvalumab for extensive-stage small cell lung cancer (SCLC), the applicant initiated a global phase III study in chemotherapy-naïve patients with extensive-stage SCLC (CASPIAN study) in March 2017.

In the US and EU, applications for approval were filed based mainly on the results from the CASPIAN study in September and November 2019, respectively. In the US, durvalumab was approved for the following indication in March 2020: "IMFINZI, in combination with etoposide and either carboplatin or cisplatin, is indicated for the first-line treatment of adult patients with extensive-stage small cell lung cancer (ES-SCLC)." The EU application is currently under review.

As of March 2020, durvalumab has been approved for the indication of extensive-stage SCLC in 2 countries or regions.

In Japan, the CASPIAN study initiated patient enrollment in [redacted] 20[redacted].

The applicant has filed a partial change application for durvalumab in combination with a platinum agent and etoposide (ETP), for an additional indication of extensive-stage SCLC, based mainly on the results from the CASPIAN study.

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

Since the present application is intended for a new indication and a new dosage, no data relating to quality have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacology data were previously evaluated for the initial approval of durvalumab, and no new study data have been submitted.

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

Although the present application is intended for a new indication and a new dosage, the non-clinical pharmacokinetic data were previously evaluated for the initial approval of durvalumab, and no new study data have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

Since the present application is intended for a new indication and a new dosage, no toxicity data have been submitted.

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

Unless otherwise specified, the following are dosing regimens of anti-cancer agents other than durvalumab and tremelimumab[1)] in the clinical studies described in this section and Section "7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA" (Table 1).

Table 1. Listing of dosing regimens of anti-cancer agents used in clinical studies

	Dosing regimen
CBDCA	CASPIAN study: AUC 5-6 mg·min/mL intravenously on Day 1 of each 3-week cycle MYSTIC study: AUC 5 or 6 mg·min/mL intravenously on Day 1 of each 3-week cycle
CDDP	CASPIAN study: 75-80 mg/m^2 intravenously on Day 1 of each 3-week cycle MYSTIC study: 75 or 80 mg/m^2 for patients with SQ-NSCLC and 75 mg/m^2 for patients with NSQ-NSCLC intravenously on Day 1 of each 3-week cycle
DTX	60 mg/m^2 intravenously on Day 1 of each 4-week cycle
ETP	80-100 mg/m^2 intravenously on Days 1-3 of each 3-week cycle
GEM	ARCTIC study: 1,000 mg/m^2 intravenously on Days 1, 8, and 15 of each 4-week cycle MYSTIC study: 1,000 or 1,250 mg/m^2 intravenously on Days 1 and 8 of each 3-week cycle
PEM	500 mg/m^2 intravenously on Day 1 of each 3-week cycle
PTX	MYSTIC study: 200 mg/m^2 intravenously on Day 1 of each 3-week cycle EAGLE study: 100 mg/m^2 intravenously on Days 1, 8, 15, 22, 29, and 36 of each 8-week cycle
S-1	40, 50, or 60 mg* (selected according to body surface area) BID orally for 4 weeks followed by 2-week rest in each 6-week cycle
Erlotinib	150 mg QD orally
Cetuximab	400 mg/m^2 (the initial dose) and then 250 mg/m^2 (subsequent doses) QW intravenously
Vinorelbine	30 mg/m^2 intravenously on Days 1, 8, 15, and 22 of each 4-week cycle
Methotrexate	40 mg/m^2 QW intravenously

*: The dose was 40 mg for body surface area of <1.25 m^2, 50 mg for body surface area of ≥1.25 m^2 and <1.5 m^2, and 60 mg for body surface area of ≥1.5 m^2.

Although the present application is intended for a new indication and a new dosage, the data on biopharmaceutic studies and associated analytical methods were previously evaluated for the initial approval of durvalumab, and no new study data have been submitted.

[1)] Unapproved in Japan.

6.1 Clinical pharmacology

The pharmacokinetics (PK) of durvalumab in combination with a platinum agent and ETP were studied in patients with cancer.

6.1.1 Global phase III study (CTD 5.3.5.1.1, CASPIAN study [ongoing since March 2017 (data cutoff on March 11, 2019)])

An open-label, randomized controlled study was conducted to evaluate the efficacy and safety of durvalumab + platinum + ETP versus platinum + ETP in 805 chemotherapy-naïve patients with extensive-stage SCLC[2)] (268 in the durvalumab + a platinum agent [platinum] + ETP group [Group A], 268 in the durvalumab + tremelimumab + platinum + ETP group [Group B], 269 in the platinum + ETP group [Group C]) (276 subjects included in the PK analysis[3)]). The dosing regimens are shown below, and serum durvalumab concentrations etc. were determined.

Group A: Up to 4 cycles of platinum + ETP + durvalumab 1,500 mg every 3 weeks intravenously followed by durvalumab 1,500 mg Q4W intravenously
Group C: Up to 6 cycles of platinum + ETP every 3 weeks intravenously

The geometric mean C_{max} of durvalumab after the first dose (coefficient of variation [CV] %) was 503 μg/mL (30.5%). The geometric mean C_{min} of durvalumab before Dose 2 and Dose 5 (CV%) was 110 μg/mL (64.4%) and 241 μg/mL (49.7%), respectively.

Of 201 subjects who provided evaluable samples for anti-durvalumab antibody assay, no subjects tested positive for treatment-emergent anti-durvalumab antibodies.

6.1.2 PPK analyses

Population pharmacokinetic (PPK) analyses were performed using the model[4)] that was externally validated with durvalumab PK data from the CASPIAN study (647 evaluable durvalumab concentrations from 259 patients) and updated (software, NONMEM Version 7.3.0). The predicted durvalumab exposure was lower in patients weighing 30 kg who receive durvalumab 20 mg/kg Q3W or Q4W than in patients weighing >30 kg who receive durvalumab 1,500 mg/body Q3W or Q4W, but the predicted exposure ranges partially overlapped (Table 2).

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2) Patients were enrolled if they had a body weight of >30 kg and (1) American Joint Committee on Cancer (7th edition) Stage IV or (2) T3-4 due to multiple lung nodules that were too extensive or have tumor/nodal volume that was too large to be encompassed in a tolerable radiation plan.

3) The PK analysis included 263 subjects in Group A and 13 subjects in Group C.

4) The PPK model developed based on durvalumab PK data from Study 1108 and the ATLANTIC study was externally validated with durvalumab PK data from Study 1108 and the PACIFIC study (see "Review Report of Imfinzi Injection 120 mg and 500 mg, dated April 5, 2018"), and this updated model was externally validated again.

Table 2. PK parameters of durvalumab

Dosing regimen	Body weight (kg)	$C_{max, ss}$ (μg/mL)	AUC_{ss} (μg/mL)	$C_{min, ss}$ (μg/mL)
1,500 mg/body Q3W	31-128	688 (402, 1,470)	9,090 (3,780, 20,700)	221 (62.1, 511)
1,500 mg/body Q4W	31-128	686 (381, 1,440)	13,300 (5,140, 35,700)	186 (39, 725)
20 mg/kg Q3W	30	405 (240, 659)	5,550 (2,450, 13,200)	140 (35.5, 297)
20 mg/kg Q4W	30	428 (240, 765)	8,250 (3,410, 21,300)	139 (24.4, 479)

Median (Range)

6.1.3 Exposure-efficacy/safety relationship

The relationship between predicted durvalumab exposure from the PPK analysis [see Section 6.1.2] and efficacy/safety was evaluated based on the data from the CASPIAN study.

6.1.3.1 Exposure-efficacy relationship

The relationship between durvalumab exposure (AUC_{ss}, C_{min} after the first dose) and overall survival (OS) was explored using a Cox proportional hazards model. There was no clear relationship between durvalumab exposure and OS.

6.1.3.2 Exposure-safety relationship

The potential relationship between durvalumab exposure ($C_{max,ss}$, AUC_{ss}, $C_{min,ss}$, C_{min} after the first dose) and the occurrence of the following adverse events was assessed: Grade ≥3 adverse events for which a causal relationship to durvalumab could not be ruled out; Grade ≥3 adverse events of special interest[5)]; and adverse events leading to treatment discontinuation. There was no clear relationship between durvalumab exposure and the occurrence of the above adverse events.

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 of durvalumab was acceptable.

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 1 global phase III study presented in Table 3. The applicant also submitted reference data: the results from a total of 9 studies (1 global phase I study, 1 global phase II study, 4 global phase III studies, 1 foreign phase I/II study, 2 foreign phase II studies). The results from the global phase I study (Study 02), the global phase II study (ATLANTIC study), and the global phase III study (PACIFIC study) are omitted because these results were previously submitted and evaluated for the initial approval of durvalumab (see Review Report on Imfinzi Injection 120 mg and 500 mg, dated April 5, 2018).

5) Defined as endocrinopathies (adrenal insufficiency, hyperthyroidism, hypophysitis, hypothyroidism, type 1 diabetes mellitus), dermatitis, rash, diarrhea, colitis, Guillain-Barre syndrome, hepatic dysfunction-related events, infusion related reaction, hypersensitivity, intestinal perforation, myasthenia gravis, myocarditis, myositis, immune-mediated inflammatory response, pancreatic dysfunction-related events, pneumonitis, renal dysfunction-related events, and thyroiditis.

Table 3. Listing of efficacy and safety clinical studies

Data category	Geographical location	Study ID	Phase	Study population	No. of subjects enrolled	Dosing regimen[*1]	Main endpoints
Evaluation	Global	CASPIAN	III	Chemotherapy-naïve patients with extensive-stage SCLC	805 (a) 268 (b) 268 (c) 269	(a) Group A Up to 4 cycles of platinum + ETP + durvalumab 1,500 mg every 3 weeks intravenously followed by durvalumab 1,500 mg Q4W intravenously (b) Group B Up to 4 cycles of platinum + ETP + durvalumab 1,500 mg and tremelimumab 75 mg every 3 weeks intravenously followed by durvalumab 1,500 mg Q4W intravenously (c) Group C Up to 6 cycles of platinum + ETP every 3 weeks intravenously	Efficacy Safety
Reference	Global	ARCTIC	III	Patients with unresectable, advanced/recurrent NSCLC previously treated with platinum-containing chemotherapy	Sub-study A 126 (a) 62 (b) 64 Sub-study B 469 (a) 117 (b) 118 (c) 174 (d) 60	(a) Durvalumab 10 mg/kg Q2W intravenously (b) Investigator's choice of one of the following chemotherapy regimens ● GEM ● Vinorelbine ● Erlotinib (c) 4 cycles of durvalumab 20 mg/kg and tremelimumab 1 mg/kg every 4 weeks intravenously followed by durvalumab 10 mg/kg Q2W intravenously (d) Up to 6 cycles of tremelimumab 10 mg/kg every 4 weeks intravenously followed by tremelimumab 10 mg/kg Q12W intravenously	Efficacy Safety
		MYSTIC	III	Chemotherapy-naïve patients with unresectable, advanced/recurrent NSCLC	1,118 (a) 374 (b) 372 (c) 372	(a) Durvalumab 20 mg/kg Q4W intravenously (b) 4 cycles of durvalumab 20 mg/kg and tremelimumab 1 mg/kg every 4 weeks intravenously followed by durvalumab 20 mg/kg Q4W intravenously (c) Investigator's choice of one of the following chemotherapy regimens ● CBDCA + PTX ● Platinum/GEM ● Platinum/PEM	Efficacy Safety
		EAGLE	III	Patients with recurrent or metastatic head and neck squamous cell carcinoma previously treated with platinum-containing chemotherapy	736 (a) 240 (b) 247 (c) 249	(a) Durvalumab 10 mg/kg Q2W intravenously (b) 4 cycles of durvalumab 20 mg/kg and tremelimumab 1 mg/kg every 4 weeks intravenously followed by durvalumab 10 mg/kg Q2W intravenously (c) Investigator's choice of one of the following chemotherapy regimens ● Cetuximab ● DTX ● PTX ● Methotrexate ● S-1	Efficacy Safety
	Foreign	1108	I/II	Patients with advanced solid tumors[*2]	980	Durvalumab 10 mg/kg Q2W intravenously	Safety Tolerability PK
		HAWK	II	Patients with recurrent or metastatic head and neck squamous cell carcinoma previously treated with platinum-containing chemotherapy	158	Durvalumab 10 mg/kg Q2W intravenously	Efficacy Safety
		CONDOR	II	Patients with recurrent or metastatic head and neck squamous cell carcinoma previously treated with platinum-containing chemotherapy	267 (a) 67 (b)133 (c) 67	(a) Durvalumab 10 mg/kg Q2W intravenously (b) 4 cycles of durvalumab 20 mg/kg and tremelimumab 1 mg/kg every 4 weeks intravenously followed by durvalumab 10 mg/kg Q2W intravenously (c) Tremelimumab 10 mg/kg every 4 weeks for 7 doses intravenously followed by tremelimumab 10 mg/kg Q12W for 2 doses intravenously	Efficacy Safety

*1: Table 1 shows the dosing regimens of anti-cancer agents other than durvalumab and tremelimumab in clinical studies.

*2: Patients with 16 cancer types were enrolled: malignant melanoma, uveal melanoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, NSCLC, gastrooesophageal junction cancer, HR-negative and HER2-negative breast cancer, ovarian cancer, urothelial carcinoma, glioblastoma multiforme, pancreatic adenocarcinoma, soft tissue sarcoma, SCLC, MSI-High cancer, HPV-positive cancer, and nasopharyngeal carcinoma

The 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."

7.1 Evaluation data

7.1.1 Global study

7.1.1.1 Global phase III study (CTD 5.3.5.1.1, CASPIAN study [ongoing since March 2017 (data cutoff on March 11, 2019)])

An open-label, randomized controlled study was conducted to evaluate the efficacy and safety of Group A or B versus Group C in chemotherapy-naïve patients with extensive-stage SCLC[2)] (target sample size, 265 subjects per group) at 209 sites in 23 countries or regions including Japan.

The dosing regimens are shown below, and treatment was to be continued until disease progression or a discontinuation criterion was met.

Group A: Up to 4 cycles of platinum + ETP + durvalumab 1,500 mg every 3 weeks intravenously followed by durvalumab 1,500 mg Q4W intravenously

Group B: Up to 4 cycles of platinum + ETP + durvalumab 1,500 mg and tremelimumab 75 mg every 3 weeks intravenously followed by durvalumab 1,500 mg Q4W intravenously

Group C: Up to 6 cycles of platinum + ETP every 3 weeks intravenously

All of 537 subjects who were enrolled and randomized (268 in Group A, 269 in Group C) were included in the intention-to-treat (ITT) population, which was used for efficacy analyses (including 18 Japanese patients in Group A and 16 Japanese patients in Group C). Among the ITT population, 531 subjects (265 in Group A, 266 in Group C) were included in the safety population (including 18 Japanese patients in Group A and 16 Japanese patients in Group C). The remaining 6 subjects were excluded because they did not receive the study drug (3 in Group A, 3 in Group C).

At the time of initiating the study, the co-primary endpoints for the study were OS and progression-free survival (PFS) as assessed by blinded independent central review (BICR) per Response Evaluation Criteria in Solid Tumors (RECIST) ver1.1, and the primary analysis was a comparison between Group B and Group C. An interim analysis of OS was planned to evaluate efficacy. The primary analysis of PFS and the interim analysis of OS were to be performed after the occurrence of 372 PFS events in Groups B and C, and the final analysis of OS after the occurrence of 357 OS events in Groups B and C. However, because the results of the KEYNOTE-189 study[6)] etc. suggested the efficacy of a PD-1/PD-L1 inhibitor plus chemotherapy, a decision was made to give priority to efficacy evaluation of durvalumab in combination with chemotherapy, and the following amendments were made to the protocol (Protocol Version 3 [as of [redacted], 20[redacted]]).

- The primary analysis of OS in Group A versus Group C was added.
- The primary analysis of PFS in Group B versus Group C was eliminated, and the primary analysis of PFS in Group A versus Group C was added.

6) A global phase III study to evaluate the efficacy and safety of a platinum-based drug and PEM plus either pembrolizumab or placebo in chemotherapy-naïve patients with unresectable, advanced/recurrent NSQ-NSCLC.

- The primary analysis of PFS and the first interim analysis of OS were to be performed after the occurrence of 405 PFS events in Groups A and C.
- The second interim analysis of OS was to be performed after the occurrence of 330 OS events each in both (i) Groups A and C and (ii) and Groups B and C.
- The final analysis of OS was to be performed after the occurrence of 395 OS events each in both (i) Groups A and C and (ii) Groups B and C.

Furthermore, the results of the IMpower133 study[7)] suggested that (a) OS may be a more appropriate efficacy endpoint for immune checkpoint inhibitors, and (b) a longer follow-up was probably needed to appropriately evaluate the efficacy of durvalumab. Therefore, the following amendments were made to the protocol (Protocol Version 4 [as of [redacted], 20[redacted]]).

- PFS was reclassified from a co-primary endpoint to a secondary endpoint.
- Only one interim analysis of OS was to be performed after the occurrence of 318 OS events each in both (i) Groups A and C and (ii) Groups B and C.
- The final analysis of OS was to be performed after the occurrence of 425 OS events each in both (i) Groups A and C and (ii) Groups B and C.

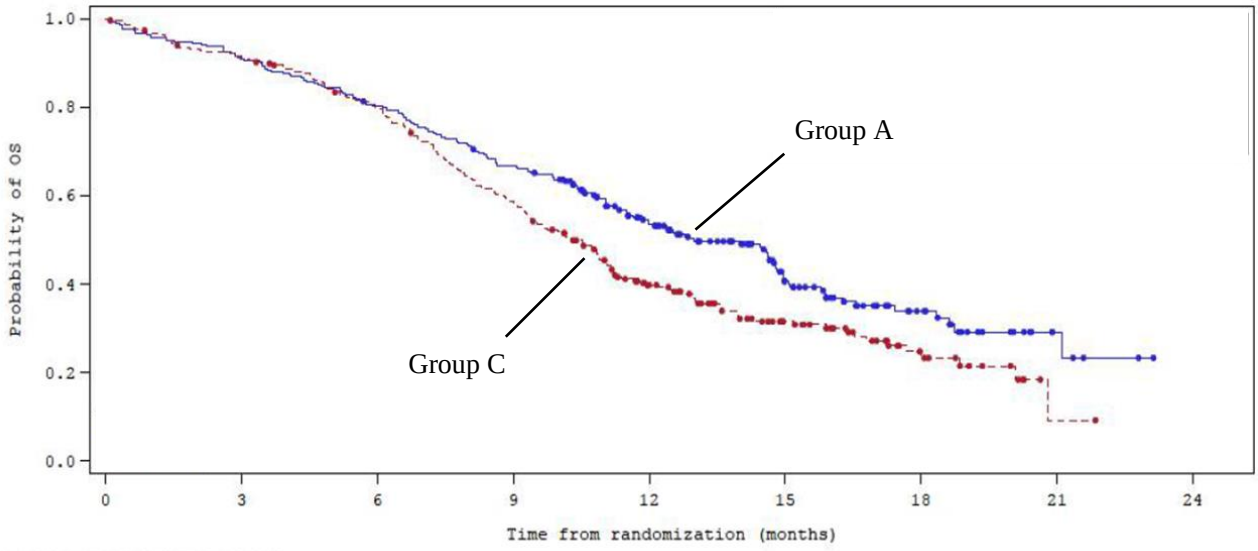
For multiplicity considerations due to multiple between-group comparisons of the primary endpoint for the study, a two-sided alpha of 1% was allocated to the comparison between Groups B and C, and a two-sided alpha of 4% was allocated to the comparison between Groups A and C. If one comparison was statistically significant, this alpha was to be recycled to the other comparison. The interim analysis was based on a Lan-DeMets alpha spending function with O'Brien Fleming type boundary to control the type I error rate. Table 4 shows the results of the interim analysis of OS (the primary endpoint) (data cutoff on March 11, 2019) with the Kaplan-Meier curves (Figure 1) in Group A versus Group C (the comparison between Groups A and C was one of the primary efficacy analyses). The superiority of Group A over Group C was demonstrated. Based on this analysis results, the data from Groups A and C only were submitted for the present partial change application. Thus, the following description regarding the CASPIAN study relates to only Groups A and C.

Table 4. Results of interim analysis of OS (ITT population, data cutoff on March 11, 2019)

	Group A		Group C
N	268		269
Number of events (%)	155 (57.8)		181 (67.3)
Median [95% CI] (months)	13.0 [11.5, 14.8]		10.3 [9.3, 11.2]
Hazard ratio [95% CI]*1		0.73 [0.59, 0.91]	
P-value (two-sided)*2		0.0047	

*1, Cox proportional hazards model stratified by planned platinum therapy (CBDCA or CDDP)
*2, Log-rank test stratified by planned platinum therapy (CBDCA or CDDP) with a significance level (two-sided) of 0.0178

7) A global phase I/III study to evaluate the efficacy and safety of CBDCA + ETP plus either atezolizumab or placebo in chemotherapy-naïve patients with extensive-stage SCLC.



Number of patients at risk

Group A	268	244	214	177	116	57	25	5	0
Group C	269	242	209	153	82	44	17	1	0

Figure 1. Kaplan-Meier curves of OS at interim analysis (ITT population, data cutoff on March 11, 2019)

As for safety, 75 of 265 subjects (28.3%) in Group A and 63 of 266 subjects (23.7%) in Group C died during the study treatment period or within 90 days of the last dose of study drug (including 3 Japanese patients in Group A and 1 Japanese patient in Group C). The causes of deaths other than disease progression (60 in Group A, 47 in Group C) were as follows:

Group A: sudden death and death (2 subjects each); and sepsis, septic shock, pancytopenia, dehydration, cardiac arrest, acute respiratory failure, aspiration, hypoxia, pulmonary artery thrombosis, pulmonary embolism, and hepatotoxicity (1 subject each)

Group C: pneumonitis and death (2 subjects each); and pneumonia, haematotoxicity, pancytopenia, thrombocytopenia/haemorrhage, cerebrovascular accident, cardiac arrest, acute cardiac failure, cardiopulmonary failure, acute respiratory failure, sudden cardiac death, sudden death, and unknown (1 subject each).

A causal relationship to study drug could not be ruled out for sepsis, pancytopenia, dehydration, cardiac arrest, and hepatotoxicity (1 subject each) in Group A and pancytopenia and thrombocytopenia/haemorrhage (1 subject each) in Group C. (The causes of deaths of Japanese patients were all disease progression.)

7.2 Reference data

7.2.1 Global studies

7.2.1.1 Global phase III study (CTD 5.3.5.1.3, ARCTIC study [January 2015 to February 2018])

An open-label, randomized controlled study was conducted at 260 sites in 26 countries or regions including Japan, to evaluate the efficacy and safety of durvalumab or durvalumab + tremelimumab versus standard of care (SOC) (gemcitabine hydrochloride [GEM], vinorelbine, or erlotinib) in patients with unresectable,

advanced or recurrent NSCLC[8] who had received at least 2 prior systemic treatment regimens including 1 platinum-based chemotherapy regimen. (The study comprised sub-studies A and B[9]; target sample size, 126 subjects in sub-study A, 480 subjects in sub-study B.)

The safety population included 585 subjects who were enrolled in the study and received study drug (125 in sub-study A [62 in the durvalumab group, 63 in the SOC group], 460 in sub-study B [117 in the durvalumab group, 110 in the SOC group, 173 in the durvalumab + tremelimumab group, 60 in the tremelimumab group]) (including 32 Japanese patients in sub-study A [16 in the durvalumab group, 16 in the SOC group] and 79 Japanese patients in sub-study B (20 in the durvalumab group, 23 in the SOC group, 28 in the durvalumab + tremelimumab group, 8 in the tremelimumab group]).

As for safety, the following number of subjects died during the study treatment period or within 90 days of the last dose of study drug:

Sub-study A: 20 of 62 subjects (32.3%) in the durvalumab group and 26 of 63 subjects (41.3%) in the SOC group (including 2 Japanese patients in the durvalumab group and 6 Japanese patients in the SOC group)

Sub-study B: 45 of 117 subjects (38.5%) in the durvalumab group, 41 of 110 subjects (37.3%) in the SOC group, 65 of 173 subjects (37.6%) in the durvalumab + tremelimumab group, and 24 of 60 subjects (40.0%) in the tremelimumab group (including 1 Japanese patient in the durvalumab group, 6 Japanese patients in the SOC group, 5 Japanese patients in the durvalumab + tremelimumab group, and 2 Japanese patients in the tremelimumab group).

The following number of subjects died of disease progression: 38 in sub-study A (15 in the durvalumab group, 23 in the SOC group) and 143 in sub-study B (37 in the durvalumab group, 35 in the SOC group, 51 in the durvalumab + tremelimumab group, 20 in the tremelimumab group).

The other causes of death were as follows:

Sub-study A: sepsis, pneumonia, cardiac failure, acute respiratory failure, and pulmonary embolism (1 subject each) in the durvalumab group; and pulmonary sepsis, cerebrovascular accident, and unknown (1 subject each) in the SOC group.

Sub-study B: sudden cardiac death (2 subjects), bacterial sepsis, acute respiratory failure, pulmonary embolism, respiratory failure, perforation, and unknown (1 subject each) in the durvalumab group; pneumonia (2 subjects), cardiac arrest, dyspnoea, respiratory failure, and sudden cardiac death (1 subject each) in the SOC group; cardiac failure, pulmonary embolism, and sudden cardiac death (2 subjects each), pneumonia, embolism, haemorrhagic shock, dyspnoea, haemoptysis, acute kidney injury, death, and unknown (1 subject each) in the durvalumab + tremelimumab group; and candida sepsis, infectious pleural effusion, respiratory failure, and colitis (1 subject each) in the tremelimumab group.

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[8] Patients with known *EGFR* activating mutations or *ALK* rearrangements were excluded.

[9] Patients with PD-L1-high tumors (TC ≥25%) were assigned to sub-study A and patients with PD-L1-low tumors (TC <25%) were assigned to sub-study B.

A causal relationship to study drug could not be ruled out for respiratory failure (1 subject) in the durvalumab group and colitis (1 subject) in the tremelimumab group in sub-study B. (The cause of death due to an adverse event in 1 Japanese patient [in the tremelimumab group of sub-study B] was colitis, and its causal relationship to study drug could not be ruled out.)

7.2.1.2 Global phase III study (CTD 5.3.5.1.4, MYSTIC study [August 2015 to October 2018])

An open-label, randomized controlled study was conducted at 203 sites in 17 countries or regions including Japan, to evaluate the efficacy and safety of durvalumab or durvalumab + tremelimumab versus SOC (carboplatin [CBDCA] + paclitaxel [PTX], platinum + GEM, or platinum + pemetrexed sodium hydrate [PEM]) in chemotherapy-naïve patients with unresectable, advanced or recurrent NSCLC[8)] (target sample size, 364 subjects in the durvalumab group, 364 subjects in the durvalumab + tremelimumab group, 364 subjects in the SOC group).

The safety population included 1,092 subjects who were enrolled in the study and received study drug (369 in the durvalumab group, 371 in the durvalumab + tremelimumab group, 352 in the SOC group) (including 25 Japanese patients in the durvalumab group, 24 Japanese patients in the durvalumab + tremelimumab group, and 23 Japanese patients in the SOC group).

As for safety, 119 of 369 subjects (32.2%) in the durvalumab group, 130 of 371 subjects (35.0%) in the durvalumab + tremelimumab group, and 19 of 352 subjects (5.4%) in the SOC group died during the study treatment period or within 90 days of the last dose of study drug[10)] (including 2 Japanese patients in the durvalumab group and 3 Japanese patients in the durvalumab + tremelimumab group).
The causes of deaths other than disease progression (106 in the durvalumab group, 96 in the durvalumab + tremelimumab group, 7 in the SOC group) were as follows:

The durvalumab group: pneumonia (3 subjects); septic shock (2 subjects); and cytomegaloviral pneumonia, completed suicide, cardiac tamponade, pneumonia aspiration, febrile neutropenia, pulmonary oedema, death, and sudden death (1 subject each)

The durvalumab + tremelimumab group: respiratory failure (3 subjects); pneumonitis, pneumonia, sepsis, pulmonary embolism, and sudden death (2 subjects each); and ILD, pneumocystis jirovecii pneumonia, septic shock/chronic obstructive pulmonary disease, anaphylactic shock, cerebral infarction, cerebral ischaemia, ischaemic stroke, acute myocardial infarction, cardiac failure, thrombosis, hypercapnia, pneumonia aspiration, pneumothorax, pulmonary oedema, intestinal ischaemia, acute pancreatitis, small intestinal obstruction, small intestinal perforation, acute hepatic failure, death, and euthanasia (1 subject each)

The SOC group: pneumonia, and pulmonary embolism (3 subjects each); and empyema, sepsis, thrombocytopenia, alveolitis/renal failure, peptic ulcer haemorrhage, and death (1

[10)] In the SOC group, adverse events occurring during the study treatment period or within 30 days of the last dose were collected.

subject each)

A causal relationship to study drug could not be ruled out for cytomegaloviral pneumonia (1 subject) in the durvalumab group; sudden death, ILD, acute pancreatitis, small intestinal obstruction, and acute hepatic failure (1 subject each) in the durvalumab + tremelimumab group; and empyema, thrombocytopenia, and alveolitis/renal failure[11] (1 subject each) in the SOC group. (The cause of death due to an adverse event in 1 Japanese patient in the durvalumab + tremelimumab group was ILD, and its causal relationship to study drug could not be ruled out.)

7.2.1.3 Global phase III study (CTD 5.3.5.1.5, EAGLE study [September 2015 to September 2018)

An open-label, randomized controlled study was conducted at 156 sites in 23 countries or regions including Japan, to evaluate the efficacy and safety of durvalumab or durvalumab + tremelimumab versus SOC (cetuximab, docetaxel hydrate [DTX], PTX, methotrexate, or S-1) in patients with recurrent or metastatic head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx previously treated with chemotherapy (target sample size, 240 subjects in the durvalumab group, 240 subjects in the durvalumab + tremelimumab group, 240 subjects in the SOC group).

The safety population included 723 subjects who were enrolled in the study and received study drug (237 in the durvalumab group, 246 in the durvalumab + tremelimumab group, 240 in the SOC group) (including 22 Japanese patients in the durvalumab group, 16 Japanese patients in the durvalumab + tremelimumab group, and 26 Japanese patients in the SOC group).

As for safety, 100 of 237 subjects (42.2%) in the durvalumab group, 121 of 246 subjects (49.2%) in the durvalumab + tremelimumab group, and 94 of 240 subjects (39.2%) in the SOC group died during the study treatment period or within 90 days of the last dose of study drug (including 12 Japanese patients in the durvalumab group, 3 Japanese patients in the durvalumab + tremelimumab group, and 7 Japanese patients in the SOC group).

The causes of deaths other than disease progression (81 in the durvalumab group, 95 in the durvalumab + tremelimumab group, 75 in the SOC group) were as follows:

The durvalumab group: asphyxia (3 subjects); death and general physical condition decreased (2 subjects each); and respiratory failure/lung disorder, respiratory failure, lung infection, tumour haemorrhage, inappropriate antidiuretic hormone secretion, disorientation, arterial haemorrhage, haemorrhage, haemorrhagic shock, acute respiratory failure, pneumonia aspiration, and apnoea (1 subject each)

The durvalumab + tremelimumab group: pulmonary embolism (3 subjects); cerebrovascular accident, acute coronary syndrome, asphyxia, and death (2 subjects each); and postoperative wound infection, pulmonary sepsis, respiratory tract infection, tumour haemorrhage, depressed level of consciousness, seizure, superior vena cava syndrome, acute

[11] A causal relationship to study drug was ruled out for renal failure.

respiratory failure, laryngeal oedema, pneumonia aspiration, pneumonitis, gastrointestinal haemorrhage, sudden cardiac death, thermal burn, and unknown (1 subject each)

The SOC group: pneumonia (4 subjects); asphyxia (3 subjects); respiratory failure and death (2 subjects each); and lung infection, haemorrhagic stroke, acute coronary syndrome, acute respiratory failure, pneumonia aspiration, large intestine perforation, asthenia/general physical condition decreased, and unknown (1 subject each)

A causal relationship to study drug could not be ruled out for death, inappropriate antidiuretic hormone secretion, disorientation, and haemorrhage (1 subject each) in the durvalumab group; and death and laryngeal oedema (1 subject each) in the durvalumab + tremelimumab group. (The causes of deaths of Japanese patients were all disease progression.)

7.2.2 Foreign studies

7.2.2.1 Foreign phase I/II study (CTD 5.3.5.2.1, Study 1108 [August 2012 to October 2017])

An open-label, uncontrolled study was conducted to evaluate the safety etc. of durvalumab in patients with advanced solid tumors (target sample size, 692-1,322 subjects) at 77 sites outside Japan.

The safety population included 980 subjects who were enrolled in the study and received durvalumab.

As for safety, 315 of 980 subjects (32.1%) died during the study treatment period or within 90 days of the last dose of study drug. The causes of deaths other than disease progression (241 subjects) were general physical condition decreased (15 subjects); respiratory failure (8 subjects); sepsis (6 subjects); death (4 subjects); acute respiratory failure and dyspnoea (3 subjects each); subileus, acute kidney injury, cardio-respiratory arrest, pneumonia, and pulmonary embolism (2 subjects each); and transaminases increased, transient ischaemic attack, hepatic failure, bronchial obstruction, ischaemic cardiomyopathy, respiratory distress, hyperbilirubinaemia, embolism, autoimmune hepatitis, paraneoplastic syndrome, tumour lysis syndrome, post procedural complication, small intestinal obstruction, cardiac arrest, haematemesis, urosepsis, cerebrovascular accident, disseminated intravascular coagulation, lung infection, pulmonary haemorrhage, pneumonitis, intra-abdominal haemorrhage, chronic hepatic failure, immune thrombocytopenic purpura, and unknown (1 subject each). A causal relationship to durvalumab could not be ruled out for pneumonia, autoimmune hepatitis, pneumonitis, and immune thrombocytopenic purpura (1 subject each).

7.2.2.2 Foreign phase II study (CTD 5.3.5.2.4, HAWK study [October 2014 to October 2018])

An open-label, uncontrolled study was conducted at 109 sites outside Japan, to evaluate the efficacy and safety of durvalumab in patients with PD-L1-positive,[12)] recurrent or metastatic head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx previously treated with chemotherapy (target sample size, 112 subjects).

[12)] Patients with PD-L1-high tumors (TC ≥25%) were enrolled.

The safety population included 112 subjects who were enrolled in the study and received durvalumab.

As for safety, 54 of 112 subjects (48.2%) died during the study treatment period or within 90 days of the last dose of study drug. The causes of deaths other than disease progression (39 subjects) were unknown (4 subjects); and pneumonia, pulmonary sepsis, septic shock/cardiac arrest, seizure, cardiopulmonary failure, dyspnoea/tachypnoea, pulmonary embolism, respiratory distress, respiratory failure, suicide attempt, and arterial haemorrhage (1 subject each). A causal relationship to study drug was ruled out for all those cases.

7.2.2.3 Foreign phase II study (CTD 5.3.5.2.5, CONDOR study [April 2015 to August 2018])

An open-label, randomized controlled study was conducted at 127 sites outside Japan, to evaluate the efficacy and safety of durvalumab, durvalumab + tremelimumab, and tremelimumab in patients with recurrent or metastatic head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx previously treated with chemotherapy (target sample size, 60 subjects in the durvalumab group, 120 subjects in the durvalumab + tremelimumab group, 60 subjects in the tremelimumab group).

The safety population included 263 subjects who were enrolled in the study and received study drug (65 in the durvalumab group, 133 in the durvalumab + tremelimumab group, 65 in the tremelimumab group).

As for safety, 28 of 65 subjects (43.1%) in the durvalumab group, 56 of 133 subjects (42.1%) in the durvalumab + tremelimumab group, and 28 of 65 subjects (43.1%) in the tremelimumab group died during the study treatment period or within 90 days of the last dose of study drug. The causes of deaths other than disease progression (26 in the durvalumab group, 42 in the durvalumab + tremelimumab group, 26 in the tremelimumab group) were as follows:

The durvalumab group: sepsis and unknown (1 subject each)

The durvalumab + tremelimumab group: abdominal infection, lung infection, pneumonia, depressed level of consciousness/pneumonia aspiration, ischaemic stroke, cardiac arrest, exsanguination, acute respiratory failure, dyspnoea, emphysema, pulmonary embolism, right heart failure, death, and unknown (1 subject each)

The tremelimumab group: cardiac failure and unknown (1 subject each)

A causal relationship to study drug could not be ruled out for acute respiratory failure (1 subject) in the durvalumab + tremelimumab group.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

PMDA decided to focus its efficacy review on the results from the overall population of the CASPIAN study, and evaluated the efficacy of durvalumab in Japanese patients in terms of the consistency of the results between the overall population and the Japanese subgroup, based on "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007), "Basic Principles on Global Clinical Trials

(Reference Cases)" (PFSB/ELD Administrative Notice dated September 5, 2012), "Guidelines on General Principles for Planning and Design of Multi-regional Clinical Trials" (PSEHB/PED Notification No. 0612-1 dated June 12, 2018), etc.

Based on the following considerations, PMDA concluded that the efficacy of durvalumab was demonstrated in chemotherapy-naïve patients with extensive-stage SCLC.

7.R.1.1 Control group

The applicant explained that platinum + ETP was selected as a control treatment in the CASPIAN study, for the following reasons:

- At the time of planning the CASPIAN study, platinum + ETP or platinum + irinotecan hydrochloride hydrate (CPT-11) were recommended for patients with extensive-stage SCLC by the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for Small Cell Lung Cancer (the NCCN guidelines) (v.2.2013), the Japanese clinical practice guidelines, etc.
- CDDP + CPT-11 did not significantly increase OS compared with CDDP + ETP, and the incidences of gastrointestinal toxicities were higher with CDDP + CPT-11 in several foreign clinical studies in patients with extensive-stage SCLC (*J Clin Oncol.* 2006; 24: 2038-43, etc.). Therefore, cisplatin (CDDP) + ETP was more strongly recommended than CDDP + CPT-11 by the ESMO guidelines (Small-cell lung cancer [SCLC]: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up) etc.

PMDA accepted the applicant's explanation.

7.R.1.2 Efficacy endpoint and evaluation results

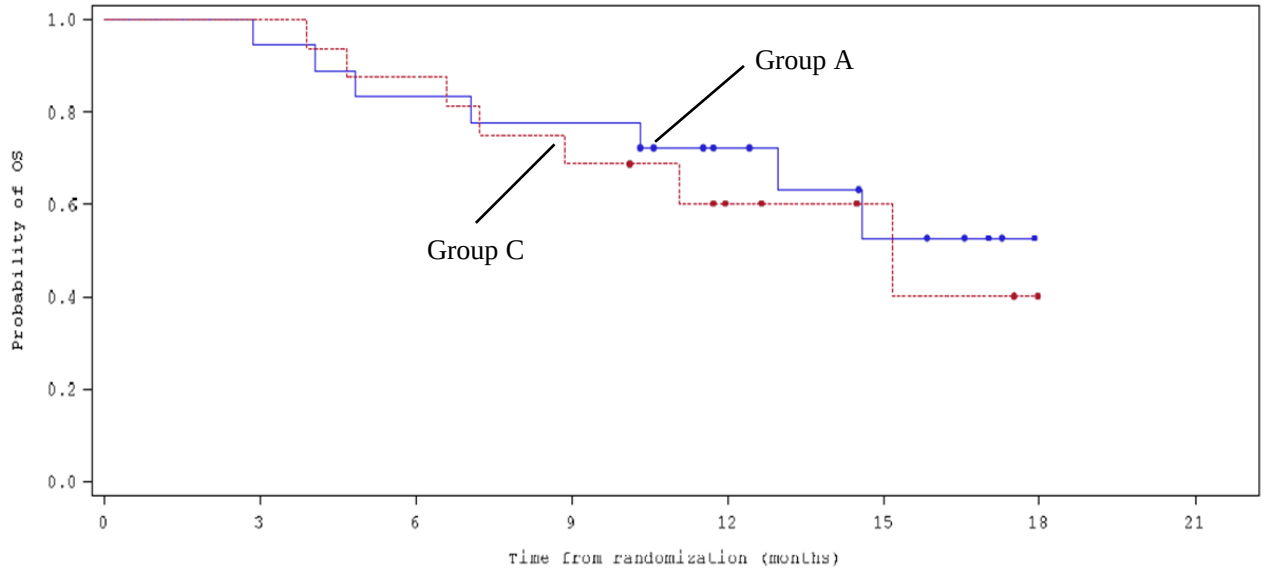
The CASPIAN study demonstrated the superiority of Group A over Group C in OS, the primary endpoint [see Section 7.1.1.1].

In the CASPIAN study, the results of the interim analysis of OS and the Kaplan-Meier curves of OS in Japanese patients are shown in Table 5 and Figure 2, respectively.

Table 5. Results of interim analysis of OS in Japanese patients (ITT population, data cutoff on March 11, 2019)

	Group A		Group C
N	18		16
Number of events (%)	7 (38.9)		7 (43.8)
Median [95% CI] (months)	−[10.3, −]		15.2 [7.2, −]
Hazard ratio [95% CI][*1]		0.77 [0.26, 2.26]	
P-value (two-sided)[*2]		0.6219	

−, Not estimable; *1, Unstratified Cox proportional hazards model; *2, Unstratified log-rank test



Number of patients at risk

Group A	18	17	15	14	9	5	0	0
Group C	16	16	14	11	5	3	0	0

Figure 2. Kaplan-Meier curves of OS in Japanese patients at interim analysis (data cutoff on March 11, 2019)

PMDA's discussion:

For the following reasons etc., PMDA concluded that the efficacy of durvalumab was demonstrated in chemotherapy-naïve patients with extensive-stage SCLC.

- The CASPIAN study demonstrated the superiority of Group A over Group C in the primary endpoint of OS.
- The number of Japanese patients and the number of events in Japanese patients in the CASPIAN study were limited, and there are limitations to evaluating the efficacy of durvalumab 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.2 Safety (for adverse events, see Section "7.3 Adverse events etc. observed in clinical studies")

PMDA's conclusion based on the discussion presented in the sections below:

Attention should be paid to the occurrence of the following adverse events during treatment with durvalumab + platinum + ETP in chemotherapy-naïve patients with extensive-stage SCLC: febrile neutropenia, myocarditis, myasthenia gravis, colitis/severe diarrhea, pituitary dysfunction, and type 1 diabetes mellitus, in addition to the events[13)] that were considered to require attention at the time of the initial approval of durvalumab for the NSCLC indication.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with durvalumab, durvalumab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, such as adverse event monitoring, differential diagnosis and

[13)] ILD, hepatic dysfunction, renal disorders, IRR, and endocrine dysfunction (thyroid dysfunction, adrenal dysfunction) (see "Review Report of Imfinzi Injection 120 mg and 500 mg, dated April 5, 2018").

management (taking account of adverse reactions due to excessive immune response), and dose delay etc. of durvalumab and the concomitant anti-cancer agents.

7.R.2.1 Safety profile

The applicant's explanation about the safety profile of durvalumab based on safety information from the CASPIAN study:

Safety data from the CASPIAN study are summarized in Table 6.

Table 6. Summary of safety data (CASPIAN study)

	n (%)	
	Group A N = 265	Group C N = 266
All adverse events	260 (98.1)	258 (97.0)
Grade ≥3 adverse events	169 (63.8)	172 (64.7)
Adverse events leading to death	13 (4.9)	15 (5.6)
Serious adverse events	82 (30.9)	96 (36.1)
Adverse events leading to treatment discontinuation		
Durvalumab	18 (6.8)	—
Platinum agent	17 (6.4)	23 (8.6)
ETP	12 (4.5)	19 (7.1)
Adverse events leading to dose delay		
Durvalumab	107 (40.4)	—
Platinum agent	82 (30.9)	93 (35.0)
ETP	87 (32.8)	99 (37.2)
Adverse events leading to dose reduction		
Durvalumab	—	—
Platinum agent	25 (9.4)	33 (12.4)
ETP	23 (8.7)	35 (13.2)

In the CASPIAN study, adverse events of any grade reported at a ≥5% higher incidence in Group A than in Group C were cough (33 subjects [12.5%] in Group A, 18 subjects [6.8%] in Group C), hyponatraemia (26 subjects [9.8%], 12 subjects [4.5%]), hyperthyroidism (26 subjects [9.8%], 1 subject [0.4%]), and hypothyroidism (25 subjects [9.4%], 4 subjects [1.5%]). Grade ≥3 adverse events reported at a ≥2% higher incidence in Group A than in Group C were hypertension (8 subjects [3.0%], 1 subject [0.4%]). There were no adverse events leading to death, serious adverse events, or adverse events leading to discontinuation or dose delay/reduction of study drug reported at a ≥2% higher incidence in Group A than in Group C.

The applicant provided the following explanation about differences in the safety profile between the CASPIAN study and the PACIFIC study,[14)] which used durvalumab monotherapy at the currently approved dosage.

Table 7 shows the results of comparison of the incidence of adverse events between Group A of the CASPIAN study and the durvalumab group of the PACIFIC study.

[14)] A global phase III study to evaluate the efficacy and safety of durvalumab versus placebo in patients with locally-advanced, unresectable NSCLC that has not progressed following definitive, platinum-based chemoradiotherapy.

Table 7. Summary of safety data (CASPIAN study and PACIFIC study)

	n (%)	
	CASPIAN Group A N = 265	PACIFIC Durvalumab group N = 475
All adverse events	260 (98.1)	460 (96.8)
Grade ≥3 adverse events	169 (63.8)	166 (34.9)
Adverse events leading to death	13 (4.9)	21 (4.4)
Serious adverse events	82 (30.9)	138 (29.1)
Adverse events leading to study drug discontinuation	18 (6.8)	73 (15.4)
Adverse events leading to dose delay of study drug	107 (40.4)	204 (42.9)

Adverse events of any grade reported at a ≥10% higher incidence in Group A of the CASPIAN study than in the durvalumab group of the PACIFIC study were neutropenia (111 subjects [41.9%] in the CASPIAN study, 4 subjects [0.8%] in the PACIFIC study), anaemia (102 subjects [38.5%], 36 subjects [7.6%]), nausea (89 subjects [33.6%], 68 subjects [14.3%]), alopecia (83 subjects [31.3%], 6 subjects [1.3%]), thrombocytopenia (41 subjects [15.5%], 4 subjects [0.8%]), and leukopenia (40 subjects [15.1%], 3 subjects [0.6%]). Grade ≥3 adverse events reported at a ≥5% higher incidence in Group A of the CASPIAN study than in the durvalumab group of the PACIFIC study were neutropenia (64 subjects [24.2%], 0 subjects), anaemia (24 subjects [9.1%], 14 subjects [2.9%]), leukopenia (17 subjects [6.4%], 0 subjects), neutrophil count decreased (17 subjects [6.4%], 0 subjects), thrombocytopenia (15 subjects [5.7%], 2 subjects [0.4%]), and febrile neutropenia (14 subjects [5.3%], 1 subject [0.2%]). Adverse events leading to dose delay of durvalumab reported at a ≥5% higher incidence in Group A of the CASPIAN study than in the durvalumab group of the PACIFIC study were neutropenia (51 subjects [19.2%], 1 subject [0.2%]). There were no adverse events leading to death, serious adverse events, or adverse events leading to durvalumab discontinuation reported at a ≥5% higher incidence in Group A of the CASPIAN study than in the durvalumab group of the PACIFIC study.

PMDA's discussion:
The incidences of some adverse events were higher in Group A of the CASPIAN study than in Group C of the CASPIAN study or the durvalumab group of the PACIFIC study. However, all of these events were known adverse events of durvalumab or the concomitant chemotherapy, and there was no trend towards a higher incidence of serious adverse events. Given these findings, durvalumab + platinum + ETP is tolerable in patients with extensive-stage SCLC, as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, such as. adverse event monitoring, differential diagnosis and management (taking account of adverse drug reactions due to excessive immune response), and dose delay etc. of durvalumab.

7.R.2.2 Differences in safety between Japanese and non-Japanese populations

The applicant provided the following explanation about differences in the safety of durvalumab + platinum + ETP between Japanese and non-Japanese populations, based on safety information from the CASPIAN study.

Safety data from Japanese and non-Japanese patients in Group A of the CASPIAN study are summarized in Table 8.

Table 8. Summary of safety data (CASPIAN study)

	n (%)	
	Japanese patients N = 18	Non-Japanese patients N = 247
All adverse events	18 (100)	242 (98.0)
Grade ≥3 adverse events	14 (77.8)	155 (62.8)
Adverse events leading to death	0	13 (5.3)
Serious adverse events	8 (44.4)	74 (30.0)
Adverse events leading to treatment discontinuation		
Durvalumab	0	18 (7.3)
Platinum agent	0	17 (6.9)
ETP	0	12 (4.9)
Adverse events leading to dose delay		
Durvalumab	10 (55.6)	97 (39.3)
Platinum agent	8 (44.4)	74 (30.0)
ETP	9 (50.0)	78 (31.6)
Adverse events leading to dose reduction		
Durvalumab	—	—
Platinum agent	7 (38.9)	18 (7.3)
ETP	7 (38.9)	16 (6.5)

Adverse events of any grade reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were constipation (13 subjects [72.2%] in the Japanese subgroup, 31 subjects [12.6%] in the non-Japanese subgroup), nausea (8 subjects [44.4%], 81 subjects [32.8%]), decreased appetite (6 subjects [33.3%], 42 subjects [17.0%]), febrile neutropenia (6 subjects [33.3%], 11 subjects [4.5%]), neutrophil count decreased (5 subjects [27.8%], 21 subjects [8.5%]), hiccups (5 subjects [27.8%], 5 subjects [2.0%]), insomnia (4 subjects [22.2%], 19 subjects [7.7%]), pyrexia (4 subjects [22.2%], 18 subjects [7.3%]), malaise (4 subjects [22.2%], 3 subjects [1.2%]), dry skin (3 subjects [16.7%], 8 subjects [3.2%]), spinal compression fracture (2 subjects [11.1%], 0 subjects), bacterial infection (2 subjects [11.1%], 1 subject [0.4%]), and conjunctivitis (2 subjects [11.1%], 1 subject [0.4%]). Grade ≥3 adverse events reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup were febrile neutropenia (6 subjects [33.3%], 8 subjects[15)] [3.2%]), neutrophil count decreased (4 subjects [22.2%], 13 subjects [5.3%]), and decreased appetite (2 subjects [11.1%], 0 subjects). There were no adverse events leading to death, serious adverse events, or adverse events leading to discontinuation or dose delay of durvalumab reported at a ≥10% higher incidence in the Japanese subgroup than in the non-Japanese subgroup.

PMDA's discussion:

The number of Japanese patients included in the CASPIAN study was limited, and there are limitations to assessing differences in the safety of durvalumab between Japanese and non-Japanese populations. However, PMDA concludes that durvalumab + platinum + ETP is tolerable also in Japanese patients, as long as appropriate actions (e.g., dose delay of durvalumab, a platinum agent, and ETP) are taken, for the following reasons: (a) there was no trend towards a higher incidence of adverse events leading to death in Japanese patients than in non-Japanese patients; (b) adverse events other than febrile neutropenia and neutrophil count decreased were largely of Grade ≤2; and (c) the analysis results presented in Section 7.R.2.3.

15) Although NCI-CTCAE v4.03 does not provide the definition of Grade 1 or Grade 2 of febrile neutropenia, Grade 1 febrile neutropenia was reported in 1 subject and Grade 2 febrile neutropenia in 2 subjects.

In the following sections, PMDA focused its safety review on (a) febrile neutropenia (which showed a higher incidence of Grade ≥3 adverse events in the Japanese subgroup than in the non-Japanese subgroup in the CASPIAN study), and (b) myocarditis, myasthenia gravis, colitis/severe diarrhea, pituitary dysfunction, and type 1 diabetes mellitus, which were reported as events for which a causal relationship to durvalumab could not be ruled out in clinical studies and post-marketing experience of durvalumab.

7.R.2.3 Febrile neutropenia

The applicant's explanation about febrile neutropenia associated with durvalumab + platinum + ETP:
Adverse events coded as MedDRA PTs "febrile neutropenia," "neutropenic infection," and "neutropenic sepsis" were counted as febrile neutropenia.

The incidence of febrile neutropenia in the CASPIAN study is shown in Table 9.

Table 9. Incidence of febrile neutropenia (CASPIAN study)

PT (MedDRA ver.21.1)	n (%)			
	Group A N = 265		Group C N = 266	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Febrile neutropenia	17 (6.4)	14 (5.3)	17 (6.4)	17 (6.4)
Febrile neutropenia	17 (6.4)	14 (5.3)	17 (6.4)	17 (6.4)

In the CASPIAN study, serious febrile neutropenia occurred in 12 of 265 subjects (4.5%) in Group A (febrile neutropenia [12 subjects]) and 12 of 266 subjects (4.5%) in Group C (febrile neutropenia [12 subjects]), and a causal relationship to study drug could not be ruled out for those reported by 10 subjects in Group A (febrile neutropenia [10 subjects]) and 12 subjects in Group C (febrile neutropenia [12 subjects]). There was no febrile neutropenia leading to death or dose delay of durvalumab, and febrile neutropenia leading to dose delay of study drug other than durvalumab occurred in 2 of 266 subjects (0.8%) in Group C. No febrile neutropenia led to study drug discontinuation.

In the CASPIAN study, the median time (range) to the first onset of febrile neutropenia was 15 days (8-91 days) in Group A and 15 days (4-92 days) in Group C.

Table 10 shows the details of patients with serious febrile neutropenia (related to durvalumab) associated with durvalumab + platinum + ETP in the CASPIAN study.

Table 10. Listing of patients with serious febrile neutropenia (related to durvalumab) (CASPIAN study)

Age	Sex	Race	PT (MedDRA ver.21.1)	Grade	Time to onset (days)	Duration (days)	Treatment with durvalumab	Outcome
6[redacted]	M	Non-Japanese	Febrile neutropenia	3	62	7	Continued	Resolved
7[redacted]	M	Non-Japanese	Febrile neutropenia	3	9	8	Continued	Resolved

The incidence of febrile neutropenia in the Japanese subgroup of the CASPIAN study is shown in Table 11.

Table 11. Incidence of febrile neutropenia in Japanese subgroup (CASPIAN study)

PT (MedDRA ver.21.1)	n (%)			
	Group A N = 18		Group C N = 16	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Febrile neutropenia	6 (33.3)	6 (33.3)	3 (18.8)	3 (18.8)
Febrile neutropenia	6 (33.3)	6 (33.3)	3 (18.8)	3 (18.8)

PMDA's discussion:

Since there were no clear differences in the incidence of febrile neutropenia between Groups A and C in the overall population of the CASPIAN study, it is difficult to draw a definitive conclusion on the risk of febrile neutropenia associated with durvalumab. Nonetheless, given the following point etc., attention should be paid to the possible occurrence of febrile neutropenia following administration of durvalumab + platinum + ETP in Japanese patients.

- Though the number of Japanese patients treated was limited, the incidence of febrile neutropenia following administration of durvalumab + platinum + ETP was higher in the Japanese subgroup than in the non-Japanese subgroup.

Thus, using the package insert etc., the applicant should appropriately inform healthcare professionals about the incidence of febrile neutropenia in the clinical study, including the higher incidence in Japanese patients than in non-Japanese patients. The applicant should also pay attention to the occurrence of febrile neutropenia after marketing, etc., and appropriately provide any new information to healthcare professionals.

7.R.2.4 Myocarditis

The applicant's explanation about myocarditis associated with durvalumab:

Adverse events coded as MedDRA PTs "autoimmune myocarditis," "eosinophilic myocarditis," "hypersensitivity myocarditis," and "myocarditis" were counted as myocarditis.

Table 12 shows the details of patients with serious myocarditis for which a causal relationship to durvalumab could not be ruled out in clinical studies of durvalumab.

Table 12. Listing of patients with serious myocarditis for which a causal relationship to durvalumab could not be ruled out

Age	Sex	Race	Tumor type	Durvalumab dose	Concomitant drugs	PT (MedDRA ver.22.1)	Grade	Time to onset (days)	Duration (days)	Treatment with durvalumab	Outcome
CASPIAN											
6[redacted]	F	Non-Japanese	ES-SCLC	1,500 mg Q4W	tremelimumab, CBDCA, ETP	Myocarditis	5	38	Unknown	Discontinued	Death
7[redacted]	F	Non-Japanese	ES-SCLC	1,500 mg Q4W	tremelimumab, CBDCA, ETP	Myocarditis	3	25	Unknown	Continued	Unresolved
D419NC00001[*2]											
3[redacted]	F	Non-Japanese	Cervical cancer	1,500 mg Q4W	IPH2201	Myocarditis	3	15	57	Discontinued	Resolved
4[redacted]	M	Non-Japanese	Advanced solid tumors	1,500 mg Q4W	monalizumab,[*1] cetuximab	Myocarditis	2	74	31	Continued	Resolved
D4190C00006[*3]											
7[redacted]	M	Non-Japanese	NSCLC	20 mg/kg Q4W	tremelimumab	Myocarditis	3	57	11	Continued	Resolved
D4190C00007[*4]											
7[redacted]	F	Non-Japanese	MDS	1,500 mg Q4W	tremelimumab	Myocarditis	3	4	36	Discontinued	Resolved
				1,500 mg Q4W	tremelimumab	Myocarditis	4	40	3	Not applicable	Resolved
				1,500 mg Q4W	tremelimumab	Myocarditis	5	43	1	Not applicable	Death
7[redacted]	M	Non-Japanese	MDS	1,500 mg Q4W	tremelimumab, azacytidine	Myocarditis	3	32	9	Discontinued	Resolved
D4190C00010[*5]											
5[redacted]	F	Non-Japanese	Advanced solid tumors	20 mg/kg Q4W	tremelimumab	Myocarditis	4	236	13	Discontinued	Resolved
D5660C00004[*6]											
5[redacted]	M	Non-Japanese	Head and neck squamous cell carcinoma	1,500 mg Q4W	AZD9150	Myocarditis	5	10	35	Discontinued	Death
D6060C00002[*7]											
5[redacted]	F	Non-Japanese	Renal cell carcinoma	1,500 mg Q4W	MEDI0562	Autoimmune myocarditis	4	47	46	Discontinued	Resolved
D6070C00005[*8]											
7[redacted]	M	Non-Japanese	Pancreatic carcinoma	1,500 mg Q4W	oleclumab,[*1] GEM, nab-PTX	Myocarditis	3	16	5	Discontinued	Resolved
D8860C00005[*9]											
7[redacted]	M	Non-Japanese	Head and neck squamous cell carcinoma	1,500 mg Q4W	MEDI0457	Myocarditis	3	43	3	Dose delay	Resolved
DANUBE[*10]											
7[redacted]	M	Non-Japanese	Bladder cancer	1,500 mg Q4W	None	Myocarditis	4	31	Unknown	Discontinued	Unresolved
6[redacted]	F	Non-Japanese	Bladder cancer	1,500 mg Q4W	None	Myocarditis	4	310	Unknown	Discontinued	Unresolved
HIMALAYA[*11]											
7[redacted]	M	Non-Japanese	HCC	1,500 mg Q4W	tremelimumab	Myocarditis	5	17	Unknown	Discontinued	Death
7[redacted]	M	Non-Japanese	HCC	1,500 mg Q4W	None	Myocarditis	3	40	Unknown	Discontinued	Unresolved
HUDSON[*12]											
5[redacted]	F	Non-Japanese	NSCLC	1,500 mg Q4W	AZD9150	Myocarditis	3	322	Unknown	Unknown	Unknown
[redacted][*13]											
6[redacted]	F	Non-Japanese	NSCLC	1,500 mg Q4W	CBDCA, PTX	Myocarditis	3	55	29	Discontinued	Resolved
5[redacted]	M	Non-Japanese	NSCLC	1,500 mg Q4W	CBDCA, PTX	Myocarditis	2	74	Unknown	Discontinued	Unresolved

PEARL[*14]											
5[redacted]	M	Non-Japanese	NSCLC	20 mg/kg Q4W	None	Autoimmune myocarditis	4	11	Unknown	Not applicable	Unresolved
7[redacted]	M	Non-Japanese	NSCLC	20 mg/kg Q4W	None	Myocarditis	5	64	Unknown	Not applicable	Death
POSEIDON[*15]											
6[redacted]	M	Non-Japanese	NSCLC	1,500 mg Q4W	tremelimumab	Autoimmune myocarditis	5	23	Unknown	Discontinued	Death
POTOMAC[*16]											
8[redacted]	M	Japanese	Bladder cancer	1,500 mg Q4W	BCG	Myocarditis	3	26	Unknown	Discontinued	Unresolved

*1, Unapproved in Japan; *2, A foreign phase I study in patients with advanced solid tumors; *3, A foreign phase Ib study in patients with unresectable, advanced NSCLC; *4, A foreign phase I study in patients with MDS previously treated with hypomethylating agents; *5, A foreign phase I study in patients with advanced solid tumors; *6, A foreign phase Ib/II study in patients with advanced solid tumors; *7, A foreign phase I study in patients with advanced solid tumors; *8, A foreign phase Ib/II study in patients with unresectable pancreatic carcinoma; *9, A foreign phase Ib/IIa study in patients with HPV-positive, recurrent or metastatic head and neck squamous cell carcinoma; *10, A global phase III study in patients with unresectable urothelial carcinoma; *11, A global phase III study in patients with unresectable hepatocellular carcinoma; *12, A foreign phase II study in patients with unresectable, advanced/recurrent NSCLC previously treated with immune checkpoint inhibitors; *13, A global phase III study in patients with [redacted]; *14, A foreign phase III study in chemotherapy-naïve patients with unresectable, advanced/recurrent NSCLC; *15, A global phase III study in chemotherapy-naïve patients with unresectable, advanced/recurrent NSCLC; *16, A global phase III study in patients with non-muscle invasive bladder cancer

PMDA's discussion:

Since multiple cases of fatal or serious myocarditis for which a causal relationship to durvalumab could not be ruled out were reported in clinical studies of durvalumab, attention should be paid to the possible occurrence of myocarditis following administration of durvalumab. Thus, using the package insert etc., the applicant should appropriately inform healthcare professionals about the incidence of myocarditis in clinical studies.

7.R.2.5 Myasthenia gravis

The applicant's explanation about myasthenia gravis associated with durvalumab:

Adverse events coded as MedDRA PTs "myasthenia gravis," "myasthenia gravis crisis," "myasthenic syndrome," and "ocular myasthenia" were counted as myasthenia gravis.

Table 13 shows the details of patients with serious myasthenia gravis for which a causal relationship to durvalumab could not be ruled out in clinical studies of durvalumab.

Table 13. Listing of patients with serious myasthenia gravis for which a causal relationship to durvalumab could not be ruled out

Age	Sex	Race	Tumor type	Durvalumab dose	Concomitant drugs	PT (MedDRA ver.22.1)	Grade	Time to onset (days)	Duration (days)	Treatment with durvalumab	Outcome
CASPIAN											
7[redacted]	F	Non-Japanese	ES-SCLC	1,500 mg Q4W	tremelimumab, CBDCA, ETP	Myasthenia gravis	3	25	Unknown	Continued	Unresolved
BALTIC[*1]											
4[redacted]	M	Non-Japanese	ES-SCLC	1,500 mg Q4W	tremelimumab, ETP	Myasthenic syndrome	3	68	Unknown	Not applicable	Unresolved
[redacted][*2]											
7[redacted]	F	Non-Japanese	Bladder cancer	1,500 mg Q4W	None	Myasthenia gravis	2	38	21	Not applicable	Resolved
DANUBE											
5[redacted]	M	Non-Japanese	Bladder cancer	1,500 mg Q4W	tremelimumab	Myasthenic syndrome	3	49	Unknown	Discontinued	Resolved
6[redacted]	M	Non-Japanese	Bladder cancer	1,500 mg Q4W	None	Myasthenia gravis	4	126	Unknown	Discontinued	Unresolved
D4190C00006											
6[redacted]	F	Non-Japanese	NSCLC	10 mg/kg Q4W	tremelimumab	Myasthenia gravis	4	39	Unknown	Unknown	Unresolved
D4190C00022[*3]											
7[redacted]	M	Non-Japanese	HCC	1,500 mg Q4W	None	Myasthenia gravis	2	72	Unknown	Continued	Unresolved
D4880C00010[*4]											
5[redacted]	F	Japanese	Thymoma	10 mg/kg Q4W	tremelimumab	Myasthenia gravis	4	12	Unknown	Discontinued	Unresolved
HIMALAYA											
7[redacted]	M	Non-Japanese	HCC	1,500 mg Q4W	None	Myasthenia gravis	3	54	Unknown	Not applicable	Unresolved
7[redacted]	M	Non-Japanese	HCC	1,500 mg Q4W	tremelimumab	Myasthenia gravis	4	47	Unknown	Discontinued	Unresolved
POTOMAC											
7[redacted]	M	Non-Japanese	Bladder cancer	1,500 mg Q4W	BCG	Myasthenia gravis	4	29	Unknown	Discontinued	Unresolved

*1, A foreign phase II study in patients with extensive-stage SCLC previously treated with platinum-containing chemotherapy
*2, A foreign phase [redacted] study in patients with [redacted]
*3, A global phase II study in patients with unresectable hepatocellular carcinoma
*4, A Japanese phase I study in patients with advanced solid tumors

PMDA's discussion:

Multiple cases of serious myasthenia gravis for which a causal relationship to durvalumab could not be ruled out were reported in clinical studies of durvalumab, etc. Therefore, attention should be paid to the possible occurrence of myasthenia gravis following administration of durvalumab. Thus, using the package insert etc., the applicant should appropriately inform healthcare professionals about the incidence of myasthenia gravis in clinical studies.

7.R.2.6 Colitis/severe diarrhea

The applicant's explanation about colitis/severe diarrhea associated with durvalumab:

Adverse events coded as any of the following MedDRA PTs (MedDRA ver.22.1) were counted as adverse events related to colitis/severe diarrhea[16)]: "acute haemorrhagic ulcerative colitis," "autoimmune colitis," "colitis," "erosive colitis," "microscopic colitis," "enteritis," "enterocolitis," "haemorrhagic enterocolitis," "autoimmune enteropathy," "proctitis," "haemorrhagic proctitis," "necrotising colitis," "ulcerative colitis," "diarrhoea," "haemorrhagic diarrhoea," "frequent bowel movements," and "gastroenteritis."

16) Grade ≥3 events of "diarrhoea," "haemorrhagic diarrhoea," "frequent bowel movements," and "gastroenteritis" were counted.

In the CASPIAN study, colitis/severe diarrhea occurred in 5 subjects (1.9%) in Group A (diarrhoea [3 subjects]; colitis and proctitis [1 subject each]) and 4 subjects (1.5%) in Group C (diarrhoea [3 subjects]; enterocolitis [1 subject]). Serious colitis/severe diarrhea occurred in 1 subject (0.4%) in Group A (diarrhoea [1 subject]) and 3 subjects (1.3%) in Group C (diarrhoea [3 subjects]), and a causal relationship to study drug could not be ruled out for all of these events. There was no colitis/severe diarrhea leading to death.

In clinical studies of durvalumab monotherapy, serious colitis/severe diarrhea occurred in 42 subjects (diarrhoea [21 subjects]; colitis [15 subjects]; enterocolitis [3 subjects]; enteritis [2 subjects]; and autoimmune colitis, haemorrhagic diarrhoea, and proctitis [1 subject each] [some subjects had more than 1 event]), and a causal relationship to durvalumab could not be ruled out for those reported by 25 subjects (colitis [12 subjects]; diarrhoea [7 subjects]; enterocolitis [3 subjects]; and autoimmune colitis, enteritis, and proctitis [1 subject each]). There was no colitis/severe diarrhea leading to death.

PMDA's discussion:
There were no clear differences in the incidence of colitis/severe diarrhea between Groups A and C in the CASPIAN study, but serious colitis/severe diarrhea for which a causal relationship to durvalumab could not be ruled out was reported in Japanese and foreign clinical studies, etc. Therefore, using the package insert etc., the applicant should inform healthcare professionals about the incidence of colitis/severe diarrhea in Japanese and foreign clinical studies.

7.R.2.7 Pituitary dysfunction

The applicant's explanation about pituitary dysfunction associated with durvalumab:
Adverse events coded as any of the following MedDRA PTs (MedDRA ver.22.1) were counted as adverse events related to pituitary dysfunction: "diabetes insipidus," "hypopituitarism," "hypothalamo-pituitary disorder," "hypophysitis," "lymphocytic hypophysitis," "adrenocorticotropic hormone deficiency," and "hypothalamic pituitary adrenal axis suppression."

No pituitary dysfunction was reported in the CASPIAN study.

In clinical studies of durvalumab, serious pituitary dysfunction occurred in 30 subjects (hypopituitarism [17 subjects]; hypophysitis [10 subjects]; diabetes insipidus and adrenocorticotropic hormone deficiency [2 subjects each]; and lymphocytic hypophysitis [1 subject] [some patients had more than 1 event]). A causal relationship to durvalumab could not be ruled out for those reported by 29 subjects (hypopituitarism [17 subjects]; hypophysitis [10 subjects]; adrenocorticotropic hormone deficiency [2 subjects]; and diabetes insipidus and lymphocytic hypophysitis [1 subject each] [some patients had more than 1 event]). There was no pituitary dysfunction leading to death.

PMDA's discussion:
No pituitary dysfunction was reported in the CASPIAN study, but serious pituitary dysfunction for which a causal relationship to durvalumab could not be ruled out was reported in Japanese and foreign clinical studies, etc. Therefore, using the package insert etc., the applicant should appropriately inform healthcare professionals about the incidence of pituitary dysfunction in Japanese and foreign clinical studies.

7.R.2.8 Type 1 diabetes mellitus

The applicant's explanation about type 1 diabetes mellitus associated with durvalumab:
Adverse events coded as MedDRA PTs (MedDRA ver.22.1) "type 1 diabetes mellitus," "fulminant type 1 diabetes mellitus," and "latent autoimmune diabetes in adults" were counted as adverse events related to type 1 diabetes mellitus.

In the CASPIAN study, type 1 diabetes mellitus occurred in 2 subjects (0.8%) in Group A (type 1 diabetes mellitus [2 subjects]). Both cases were serious, and their causal relationship to durvalumab could not be ruled out. There was no type 1 diabetes mellitus leading to death.

In clinical studies of durvalumab, serious type 1 diabetes mellitus occurred in 16 subjects (type 1 diabetes mellitus [14 subjects]; fulminant type 1 diabetes mellitus [2 subjects]), and a causal relationship to durvalumab could not be ruled out for all of these events. There was no type 1 diabetes mellitus leading to death.

PMDA's discussion:
Serious type 1 diabetes mellitus for which a causal relationship to durvalumab could not be ruled out occurred in the CASPIAN study. Further, serious type 1 diabetes mellitus for which a causal relationship to durvalumab could not be ruled out was reported also in Japanese and foreign clinical studies. Therefore, using the package insert etc., the applicant should appropriately inform healthcare professionals about the incidence of type 1 diabetes mellitus in Japanese and foreign clinical studies.

7.R.3 Clinical positioning and indication

The proposed indication for durvalumab was "extensive-stage small cell lung cancer." The following statement was included in the PRECAUTIONS CONCERNING INDICATIONS section of the proposed package insert.

- Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of durvalumab, and of the information presented in the CLINICAL STUDIES section, including the definition of extensive-stage disease for patients enrolled in the clinical study.

Based on Sections "7.R.1 Efficacy" and "7.R.2 Safety," and the discussion presented in the following sections, PMDA concluded that the proposed indication and the proposed statement in the PRECAUTIONS CONCERNING INDICATIONS section were appropriate.

7.R.3.1 Clinical positioning of durvalumab and target population

Durvalumab for chemotherapy-naïve patients with extensive-stage SCLC is described as follows in the

Japanese and foreign clinical practice guidelines and the major textbook of clinical oncology.
Clinical practice guidelines
● NCCN guidelines (ver. 3. 2020):
Durvalumab/platinum + ETP is an initial treatment option for patients with extensive-stage SCLC.

PMDA asked the applicant to explain the target population and the clinical positioning of durvalumab + platinum + ETP for patients with extensive-stage SCLC.

The applicant's response:
The CASPIAN study in chemotherapy-naïve patients with extensive-stage SCLC demonstrated the clinical usefulness of durvalumab + platinum + ETP. Therefore, durvalumab + platinum + ETP is positioned as a treatment option for chemotherapy-naïve patients with extensive-stage SCLC.

Moreover, the definition of extensive-stage SCLC for patients enrolled in the CASPIAN study, is important information for selecting eligible patients. Therefore, the definition should be included in the CLINICAL STUDIES section of the package insert and a relevant precautionary statement in the PRECAUTIONS CONCERNING INDICATIONS section.

Based on the above, the applicant has proposed the indication of "extensive-stage small cell lung cancer" with the following statement included in the PRECAUTIONS CONCERNING INDICATIONS section.
● Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of durvalumab, and of the information presented in the CLINICAL STUDIES section, including the definition of extensive-stage disease for patients enrolled in the clinical study.

The applicant's explanation about when to use durvalumab + platinum + ETP and when to use atezolizumab + CBDCA + ETP or CDDP + CPT-11 in patients with extensive-stage SCLC:
At present, when to use which treatment is unknown, because there are no clinical study data comparing the efficacy and safety of durvalumab + platinum + ETP versus atezolizumab + CBDCA + ETP or CDDP + CPT-11. In clinical practice, the optimal therapy will be selected according to the clinical condition of individual patients.

PMDA accepted the applicant's explanation.

7.R.3.2 Efficacy and safety of durvalumab by PD-L1 expression status and target population
Since durvalumab is an antibody drug directed against human PD-L1, PMDA asked the applicant to explain the efficacy and safety of durvalumab by PD-L1 expression status, and the target population for durvalumab.

The applicant's response:
The submission of a tumor tissue sample was not mandatory in the CASPIAN study for the following reason:
● Fine-needle aspiration biopsy etc. are commonly used for diagnosing of SCLC, but adequate tumor tissues

for PD-L1 testing cannot be obtained by these techniques.

Therefore, VENTANA PD-L1 (SP263) IHC Assay, developed by Ventana Medical Systems, was used to analyze available tumor tissue samples for their PD-L1 expression on immune cells (IC) and tumor cells (TC), and (a) the efficacy and (b) safety of durvalumab were analyzed by PD-L1 expression status on IC or TC (cutoff value, 1%).

The results of (a) efficacy and (b) safety of durvalumab by PD-L1 expression status are shown below.

(a) Efficacy

Table 14 and Figures 3 to 6 show the results of the interim analysis of OS and the Kaplan-Meier curves of OS by PD-L1 expression status in the ITT population of the CASPIAN study (data cutoff on March 11, 2019).

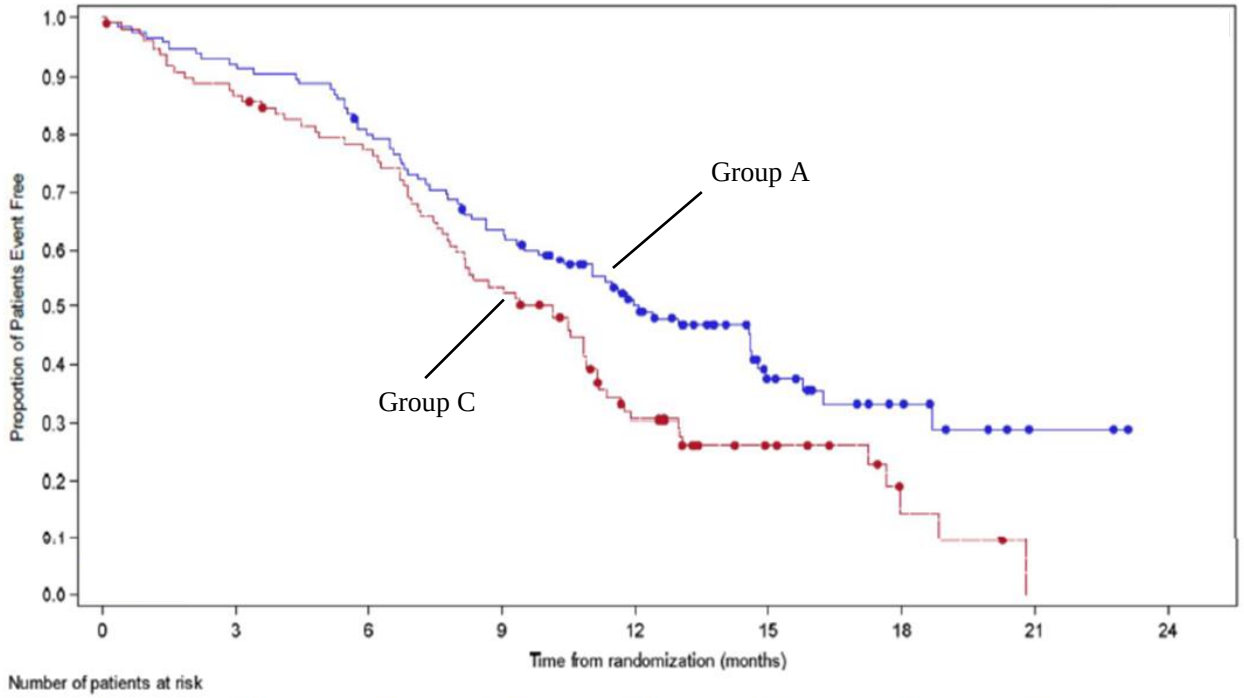
Only a part of patients in the ITT population were evaluable for PD-L1 expression, and there are limitations to evaluating the efficacy of durvalumab + platinum + ETP by PD-L1 expression status. However, Group A was superior to Group C in all of the IC <1%, IC ≥1%, TC <1%, and TC ≥1% subgroups. Therefore, PD-L1 expression status cannot be conclusively identified as a predictive factor for response (in terms of OS) to durvalumab, and durvalumab is expected to have efficacy irrespective of PD-L1 expression level.

Table 14. Results of interim analysis of OS by PD-L1 expression status in tumor tissue samples (data cutoff on March 11, 2019)

PD-L1 expression	Treatment group	N	Median [95% CI] (months)	Hazard ratio*[95% CI]	*P*-value for interaction
IC <1%	A	116	12.1 [9.9, 14.8]	0.64 [0.46, 0.90]	0.83
	C	99	10.2 [8.0, 10.9]		
IC ≥1%	A	35	14.9 [11.3, 21.1]	0.69 [0.37, 1.29]	
	C	27	12.5 [6.3, 15.9]		
TC <1%	A	145	14.5 [11.3, 14.9]	0.66 [0.49, 0.90]	0.49
	C	118	10.2 [8.2, 11.2]		
TC ≥1%	A	6	11.3 [2.9, －]	0.46 [0.10, 1.67]	
	C	8	8.7 [0.4, 12.5]		

－, Not estimable

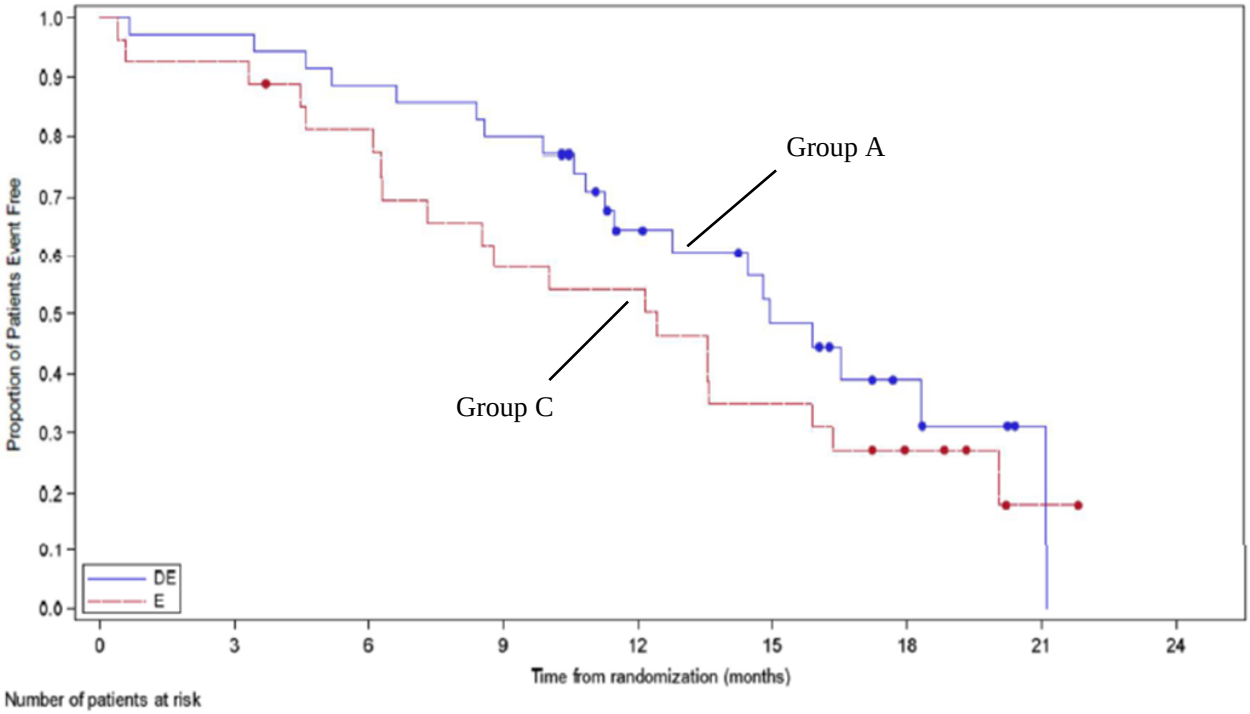
*Unstratified Cox proportional hazards model



Number of patients at risk

Group A	116	107	92	72	47	21	10	2	0
Group C	99	85	74	51	24	12	4	0	0

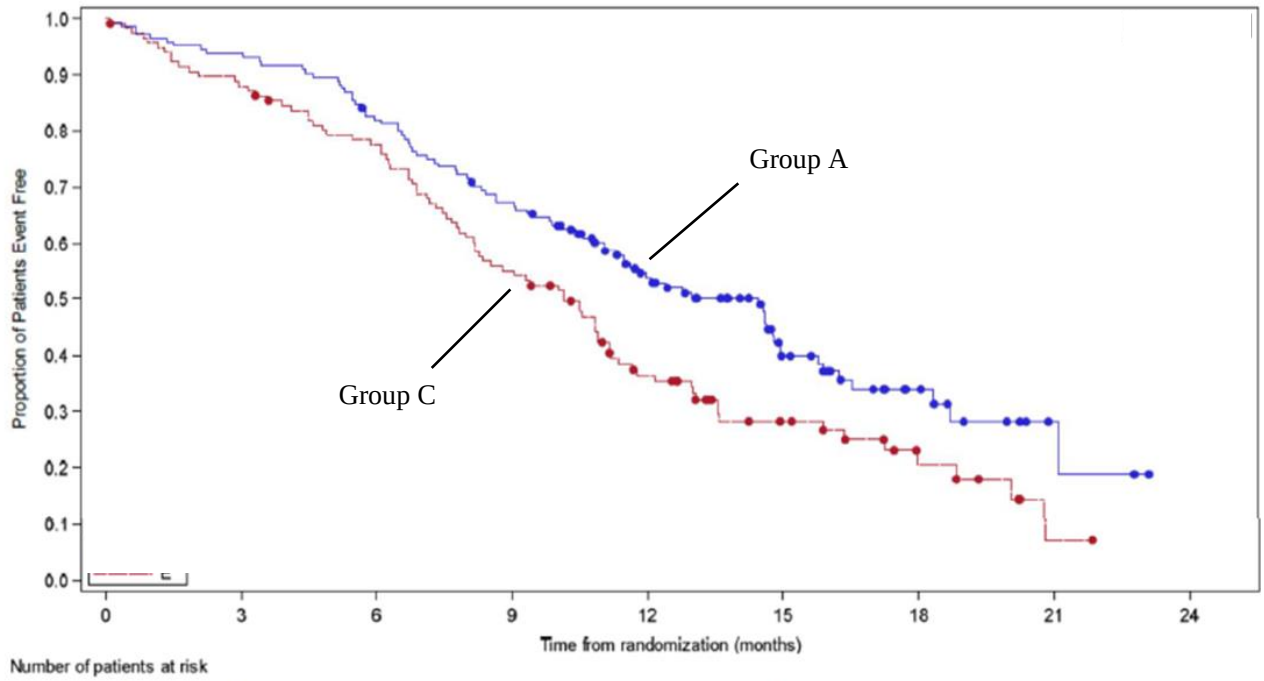
Figure 3. Kaplan-Meier curves of OS by PD-L1 expression status at interim analysis (IC <1% subgroup, data cutoff on March 11, 2019)



Number of patients at risk

Group A	35	34	31	28	18	12	5	1	0
Group C	27	25	21	15	14	9	5	1	0

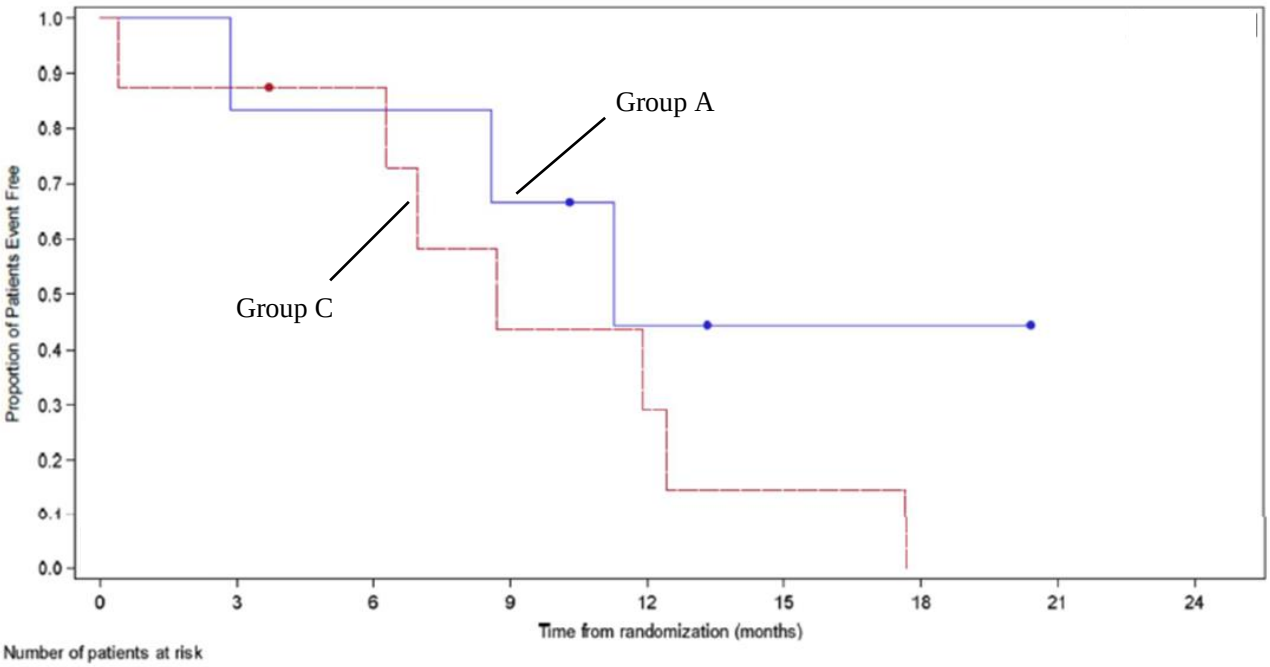
Figure 4. Kaplan-Meier curves of OS by PD-L1 expression status at interim analysis (IC ≥1% subgroup, data cutoff on March 11, 2019)



Number of patients at risk

Group A	145	136	118	96	63	32	14	3	0
Group C	118	103	89	63	36	20	9	1	0

Figure 5. Kaplan-Meier curves of OS by PD-L1 expression status at interim analysis (TC <1% subgroup, data cutoff on March 11, 2019)



Number of patients at risk

Group A	6	5	5	4	2	1	1	0	0
Group C	8	7	6	3	2	1	0	0	0

Figure 6. Kaplan-Meier curves of OS by PD-L1 expression status at interim analysis (TC ≥1% subgroup, data cutoff on March 11, 2019)

(b) Safety

In Group A of the CASPIAN study, the incidences of adverse events of any grade in the IC <1% and IC ≥1% subgroups were 99.1% and 97.1%, respectively, the incidences of Grade ≥3 adverse events were 63.8% and 57.1%, respectively, and the incidences of serious adverse events were 32.8% and 28.6%, respectively. The incidences of adverse events of any grade in the TC <1% and TC ≥1% subgroups were 98.6% and 100%, respectively, the incidences of Grade ≥3 adverse events were 62.1% and 66.7%, respectively, and the incidences of serious adverse events were 31.7% and 33.3%, respectively. There was no clear difference in the safety of durvalumab according to PD-L1 expression status in tumor specimens.

Based on the above (a) and (b), the use of durvalumab is recommended for the patient population of the CASPIAN study, irrespective of PD-L1 expression level.

PMDA's discussion:

PMDA largely accepted the above explanation by the applicant. However, the applicant should continue to collect information on the predictive factors for response to durvalumab, including factors other than PD-L1, and appropriately provide any new information to healthcare professionals.

7.R.4 Dosage and administration

The proposed dosage and administration was as follows:

> The usual adult dosage is 1,500 mg of Durvalumab (Genetical Recombination) in combination with other anti-cancer agents every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent. Patients with a body weight of ≤30 kg receive 20 mg/kg (body weight) of Durvalumab (Genetical Recombination) in combination with other anti-cancer agents every 3 weeks for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent. Durvalumab (Genetical Recombination) is administered as an intravenous infusion over ≥60 minutes.

The following statements were included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section of the proposed package insert.

- Other anti-cancer agents for combination with durvalumab should be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section.
- Recommended treatment modifications for adverse reactions

PMDA's conclusion:

Based on Sections "7.R.1 Efficacy" and "7.R.2 Safety," and the discussion presented in the following sections, the following information should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

- Recommended treatment modifications for adverse reactions

The dosage and administration for extensive-stage SCLC should be as follows:

The usual adult dosage is 1,500 mg of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent. Patients with a body weight of ≤30 kg receive 20 mg/kg (body weight) of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent. Durvalumab (Genetical Recombination) is administered as an intravenous infusion over ≥60 minutes.

7.R.4.1 Dosage and administration for durvalumab

The applicant's rationale for the proposed dosage and administration:

The dosing regimen for the CASPIAN study was selected as shown below, and the study demonstrated the clinical usefulness of durvalumab in patients with extensive-stage SCLC. Taking account of the control limit established for durvalumab,[17] patients weighing ≤30 kg were not to be enrolled in the CASPIAN study so that [redacted] in durvalumab conformed to [redacted][18] specified in the U.S. Pharmacopoeia.

(1) 1,500 mg Q4W was selected as the dosing regimen of durvalumab monotherapy, because 1,500 mg/body Q4W was predicted to result in similar exposure as 20 mg/kg Q4W that had been demonstrated to be tolerable (see "Review Report of Imfinzi Injection 120 mg and 500 mg, dated April 5, 2018") etc.

(2) 1,500 mg Q3W was selected as the dosing regimen of durvalumab in combination with a platinum agent and ETP, for the following reasons:
   (i) The predicted durvalumab exposure at 1,500 mg Q3W was higher than that at the approved dosage of 10 mg/kg Q2W, but the incidence of adverse events did not tend to increase with increasing doses of durvalumab (see "Review Report of Imfinzi Injection 120 mg and 500 mg, dated April 5, 2018").
   (ii) A platinum agent and ETP, used in combination with durvalumab, are administered Q3W.

(3) Patients whose weight fell to ≤30 kg after the start of the study were required to receive the weight-based dose of 20 mg/kg, taking account of the above (1) and the following point.
   - In the MYSTIC study in patients with NSCLC in which durvalumab was administered at 20 mg/kg Q4W, OS tended to be longer in the durvalumab group than in the SOC group, and the safety profile of durvalumab was manageable.

As there were no patients whose weight fell to ≤30 kg after the start of the CASPIAN study, there are no clinical study data from patients weighing ≤30 kg treated with durvalumab 20 mg/kg. However, a weight-based dose of 20 mg/kg can be chosen for patients weighing ≤30 kg, because the PPK analyses [see Section 6.1.2] showed no clear relationship between durvalumab exposure and efficacy/safety [see Section 6.1.3].

There are no clinical study data from patients (the patient population of the CASPIAN study) treated with durvalumab in combination with anti-cancer agents other than platinum + ETP at present. Therefore,

17) [redacted].
18) [redacted] is recommended.

information on other anti-cancer agents for combination with durvalumab should be provided in the CLINICAL STUDIES section of the package insert.

Based on the above, the applicant included the following statement in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and proposed the dosage and administration shown below.

- Other anti-cancer agents for combination with durvalumab should be selected by physicians with a full understanding of the information presented in the CLINICAL STUDIES section.

The proposed dosage and administration:

The usual adult dosage is 1,500 mg of Durvalumab (Genetical Recombination) in combination with other anti-cancer agents every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent. Patients with a body weight of ≤30 kg receive 20 mg/kg (body weight) of Durvalumab (Genetical Recombination) in combination with other anti-cancer agents every 3 weeks for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent. Durvalumab (Genetical Recombination) is administered as an intravenous infusion over ≥60 minutes.

PMDA's discussion:

PMDA largely accepted the above explanation by the applicant. However, since there are no clinical study data from patients with extensive-stage SCLC treated with durvalumab in combination with anti-cancer agents other than platinum + ETP, anti-cancer agents for combination with durvalumab should be specified in the DOSAGE AND ADMINISTRATION section.

Based on the above, the dosage and administration should be modified as follows:

The usual adult dosage is 1,500 mg of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent. Patients with a body weight of ≤30 kg receive 20 mg/kg (body weight) of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent. Durvalumab (Genetical Recombination) is administered as an intravenous infusion over ≥60 minutes.

7.R.4.2 Recommended treatment modifications for durvalumab

The applicant's explanation about the recommended treatment modifications for durvalumab:

The protocol of CASPIAN study included the treatment modification guidelines for durvalumab for adverse reactions and treatments guidelines for management of adverse reactions, based on the toxicity management guidelines. The study demonstrated the clinical usefulness of durvalumab administered in accordance with these guidelines. Thus, the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section will include a revised version of the currently approved guidelines.

The following changes are made to the currently approved guidelines:

- Deleted: The guidelines for dose delay/discontinuation of durvalumab for type 1 diabetes mellitus.

Added: Management recommendations in the event of type 1 diabetes mellitus.

- Added: The guidelines for dose delay/discontinuation of durvalumab for myositis, myasthenia gravis, and myocarditis.
- Added: Management recommendations in the event of hypothyroidism.

PMDA's discussion:

PMDA largely accepted the above explanation by the applicant, and concluded that the following recommended treatment modification guidelines should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section. (Underline denotes additions to the currently approved guidelines and strikethrough denotes deletions.) Using information materials etc., the applicant should provide information on how type 1 diabetes mellitus and hypothyroidism were managed in the CASPIAN study.

Table 15. Recommended treatment modifications for adverse reactions

Adverse reaction	Severity	Imfinzi treatment modification
ILD	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hepatic dysfunction	● AST or ALT 3-5 × ULN or total bilirubin 1.5-3 × ULN ● AST or ALT ≤8 × ULN or total bilirubin ≤5 × ULN	Withhold dose until resolution to Grade ≤1
	● AST or ALT >8 × ULN or total bilirubin >5 × ULN ● Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN with no other cause	Permanently discontinue
Colitis or diarrhea	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hyperthyroidism, Adrenal insufficiency, Hypopituitarism	Grade 2-4	Withhold dose until clinically stable
~~Type 1 diabetes mellitus~~	~~Grade 2-4~~	~~Withhold dose until clinically stable~~
Renal dysfunction	Serum creatinine 1.5-3 × ULN or baseline	Withhold dose until resolution to Grade ≤1
	Serum creatinine >3 × ULN or baseline	Permanently discontinue
Myositis	Grade 2 or 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 30 days or if there are signs of respiratory insufficiency.
	Grade 4	Permanently discontinue
Skin disorder	● Grade 2 for ≥1 week ● Grade 3	Withhold dose until resolution to Grade ≤1
	Grade 4	Permanently discontinue
Myocarditis	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if myocardial biopsy suggests myocarditis.
	Grade 3 or 4	Permanently discontinue
Myasthenia gravis	Grade 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur or if there are signs of respiratory insufficiency or autonomic nervous system imbalance.
	Grade 4	Permanently discontinue
IRR	Grade 1 or 2	Interrupt or decrease the rate of infusion by 50%
	Grade 3 or 4	Permanently discontinue
Other adverse reactions (excluding hypothyroidism and type 1 diabetes mellitus)	Grade 2 or 3	Withhold dose until resolution to Grade ≤1
	Grade 4	Permanently discontinue

Severity grade based on NCI-CTCAE v4.03

7.R.5 Post-marketing investigations

The applicant's explanation about post-marketing surveillance plan:

The applicant plans to conduct post-marketing surveillance in patients with extensive-stage SCLC treated with durvalumab + platinum + ETP to assess the safety of durvalumab in combination with platinum + ETP in clinical practice after marketing.

No new safety concern has been identified from data including the incidence of adverse events in the CASPIAN study. However, since there is limited safety information from Japanese patients with extensive-stage SCLC treated with durvalumab + platinum + ETP, etc., the applicant plans to do the following:

(a) The safety specification for the post-marketing surveillance will include myocarditis and myasthenia gravis as events requiring attention during treatment with durvalumab, in addition to events[19)] included in important identified risks and important potential risks (except for "embryo-fetal toxicity" and "use in organ transplant recipients [including hematopoietic stem cell transplant recipients]") in the risk management plan proposed for the present partial change application.

(b) The post-marketing surveillance will be conducted to investigate the occurrence of the above events in patients receiving durvalumab + platinum + ETP in clinical practice after marketing.

The planned sample size and observation period:

- A planned sample size of 102 patients was selected, taking account of the incidences of the above events, etc., in the CASPIAN study.
- An observation period of 12 months was selected because in the CASPIAN study most of the above events occurred within 52 weeks after the start of treatment with durvalumab.

PMDA's discussion:

For the reasons listed below, the applicant should include febrile neutropenia in the safety specification of post-marketing surveillance in patients with extensive-stage SCLC, investigate the occurrence of febrile neutropenia through the surveillance, and provide safety information collected to healthcare professionals.

- While the approved dosage is for durvalumab monotherapy, the dosage proposed in the present partial change application is for durvalumab in combination with other anti-cancer agents.
- There is limited safety information from Japanese patients treated with durvalumab in combination with platinum + ETP.
- In the CASPIAN study, the incidence of febrile neutropenia with durvalumab + platinum + ETP was higher in Japanese patients with extensive-stage SCLC than in non-Japanese patients [see Section 7.R.2.3]. Therefore, the occurrence of febrile neutropenia (including severity, actions taken, and outcome) in clinical practice should be investigated.

Thus, the planned sample size and observation period for the surveillance should be reconsidered, taking account of the incidence of febrile neutropenia, etc.

19) ILD, hepatic dysfunction, endocrine dysfunction (thyroid dysfunction, adrenal dysfunction), renal disorders (interstitial nephritis, etc.), myositis, infusion reaction, colitis/severe diarrhoea, type 1 diabetes mellitus, rhabdomyolysis, pituitary dysfunction, meningitis, immune thrombocytopenic purpura

There are no clear differences in safety profile between patients with extensive-stage SCLC and patients receiving durvalumab for the approved indication [see Section 7.R.2.1] in terms of the events included in the safety specification by the applicant, and there seem to be no new safety issues related to the events. Therefore, there is little need to include the events in the safety specification for the surveillance, provided that information is collected appropriately through routine pharmacovigilance activities.

7.3 Adverse events etc. observed in clinical studies

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

7.3.1 Global phase III study (CASPIAN study)

Adverse events occurred in 260 of 265 subjects (98.1%) in Group A and 258 of 266 subjects (97.0%) in Group C, and those for which a causal relationship to study drug could not be ruled out occurred in 237 of 265 subjects (89.4%) in Group A and 240 of 266 subjects (90.2%) in Group C. Adverse events reported by ≥10% of subjects in either group are shown in Table 16.

Table 16. Adverse events reported by ≥10% of subjects in either group

SOC PT (MedDRA ver.21.1)	n (%)			
	Group A N = 265		Group C N = 266	
	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	260 (98.1)	169 (63.8)	258 (97.0)	172 (64.7)
Blood and lymphatic system disorders				
Anaemia	102 (38.5)	24 (9.1)	125 (47.0)	48 (18.0)
Leukopenia	40 (15.1)	17 (6.4)	32 (12.0)	14 (5.3)
Neutropenia	111 (41.9)	64 (24.2)	124 (46.6)	88 (33.1)
Thrombocytopenia	41 (15.5)	15 (5.7)	53 (19.9)	26 (9.8)
Metabolism and nutrition disorders				
Decreased appetite	48 (18.1)	2 (0.8)	46 (17.3)	2 (0.8)
Respiratory, thoracic and mediastinal disorders				
Cough	33 (12.5)	2 (0.8)	18 (6.8)	0
Dyspnoea	31 (11.7)	5 (1.9)	28 (10.5)	3 (1.1)
Gastrointestinal disorders				
Constipation	44 (16.6)	2 (0.8)	51 (19.2)	0
Diarrhoea	26 (9.8)	3 (1.1)	30 (11.3)	3 (1.1)
Nausea	89 (33.6)	1 (0.4)	89 (33.5)	5 (1.9)
Vomiting	39 (14.7)	0	44 (16.5)	3 (1.1)
Skin and subcutaneous tissue disorders				
Alopecia	83 (31.3)	3 (1.1)	91 (34.2)	2 (0.8)
General disorders and administration site conditions				
Asthenia	40 (15.1)	5 (1.9)	40 (15.0)	3 (1.1)
Fatigue	48 (18.1)	4 (1.5)	45 (16.9)	3 (1.1)
Investigations				
Neutrophil count decreased	26 (9.8)	17 (6.4)	31 (11.7)	17 (6.4)

Serious adverse events occurred in 82 of 265 subjects (30.9%) in Group A and 96 of 266 subjects (36.1%) in Group C. Those reported by ≥6 subjects in Group A were febrile neutropenia (12 subjects [4.5%]) and pneumonia (6 subjects [2.3%]). Those reported by ≥6 subjects in Group C were febrile neutropenia and anaemia (12 subjects each [4.5%]), pneumonia and thrombocytopenia (9 subjects each [3.4%]), and neutropenia (7

subjects [2.6%]). A causal relationship to study drug could not be ruled out for febrile neutropenia (10 subjects) and pneumonia (1 subject) in Group A; and febrile neutropenia and anaemia (12 subjects each), thrombocytopenia (8 subjects), neutropenia (7 subjects), and pneumonia (1 subject) in Group C.

Adverse events leading to study drug discontinuation occurred in 25 of 265 subjects (9.4%) in Group A and 25 of 266 subjects (9.4%) in Group C. Those reported by ≥3 subjects in Group A were acute kidney injury (3 subjects [1.1%]). Those reported by ≥3 subjects in Group C were acute kidney injury (4 subjects [1.5%]), and thrombocytopenia (3 subjects [1.1%]). A causal relationship to study drug could not be ruled out for all of these events.

7.3.2 Global phase III study (ARCTIC study)

Adverse events occurred in the following subjects:

Sub-study A: (1) 60 of 62 subjects (96.8%) in the durvalumab group
(2) 63 of 63 subjects (100%) in the SOC group
Sub-study B: (3) 109 of 117 subjects (93.2%) in the durvalumab group
(4) 105 of 110 subjects (95.5%) in the SOC group
(5) 160 of 173 subjects (92.5%) in the durvalumab + tremelimumab group
(6) 51 of 60 subjects (85.0%) in the tremelimumab group

Adverse events for which a causal relationship to study drug could not be ruled out occurred in (1) 35 of 62 subjects (56.5%), (2) 55 of 63 subjects (87.3%), (3) 73 of 117 subjects (62.4%), (4) 89 of 110 subjects (80.9%), (5) 108 of 173 subjects (62.4%), and (6) 38 of 60 subjects (63.3%). Adverse events reported by ≥20% of subjects in any group were (1) decreased appetite (16 subjects [25.8%]) and constipation (13 subjects [21.0%]), (2) decreased appetite (20 subjects [31.7%]), anaemia (19 subjects [30.2%]), and constipation and nausea (15 subjects each [23.8%]), (3) decreased appetite (27 subjects [23.1%]) and diarrhoea (25 subjects [21.4%]), (4) anaemia (27 subjects [24.5%]), fatigue (25 subjects [22.7%]), decreased appetite (24 subjects [21.8%]), pyrexia (23 subjects [20.9%]), and nausea (22 subjects [20.0%]), (5) diarrhoea (38 subjects [22.0%]) and decreased appetite (35 subjects [20.2%]), (6) diarrhoea (21 subjects [35.0%]), pruritus (14 subjects [23.3%]), and decreased appetite (12 subjects [20.0%]).

Serious adverse events occurred in (1) 23 of 62 subjects (37.1%), (2) 16 of 63 subjects (25.4%), (3) 36 of 117 subjects (30.8%), (4) 28 of 110 subjects (25.5%), (5) 65 of 173 subjects (37.6%), (6) 23 of 60 subjects (38.3%). Those reported by ≥4 subjects in any group were (1) pneumonia (4 subjects [6.5%]), (2) febrile neutropenia (5 subjects [7.9%]), (5) dyspnoea and pneumonia (7 subjects each [4.0%]), pneumonitis and pulmonary embolism (5 subjects each [2.9%]), (6) diarrhoea (7 subjects [11.7%]) and colitis (5 subjects [8.3%]). A causal relationship to study drug could not be ruled out for (1) pneumonia (1 subject), (2) febrile neutropenia (5 subjects), (5) pneumonitis (5 subjects), dyspnoea (2 subjects), and pneumonia (1 subject), and (6) diarrhoea (7 subjects) and colitis (5 subjects).

Adverse events leading to study drug discontinuation occurred in (1) 8 of 62 subjects (12.9%), (2) 12 of 63 subjects (19.0%), (3) 7 of 117 subjects (6.0%), (4) 19 of 110 subjects (17.3%), (5) 32 of 173 subjects (18.5%), and (6) 17 of 60 subjects (28.3%). Those reported by ≥4 subjects in any group were (5) pneumonitis (5 subjects [2.9%]) and (6) diarrhoea (8 subjects [13.3%]) and colitis (4 subjects [6.7%]), and a causal relationship to study drug could not be ruled out for all of these events.

7.3.3 Global phase III study (MYSTIC study)

Adverse events occurred in (1) 343 of 369 subjects (93.0%) in the durvalumab group, (2) 341 of 371 subjects (91.9%) in the durvalumab + tremelimumab group, and (3) 337 of 352 subjects (95.7%) in the SOC group. Those for which a causal relationship to study drug could not be ruled out occurred in (1) 200 of 369 subjects (54.2%), (2) 223 of 371 subjects (60.1%), and (3) 292 of 352 subjects (83.0%). Adverse events reported by ≥20% of subjects in any group are shown in Table 17.

Table 17. Adverse events reported by ≥20% of subjects in any group

SOC PT (MedDRA ver.21.0)	n (%)					
	(1) N = 369		(2) N = 371		(3) N = 352	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	343 (93.0)	153 (41.5)	341 (91.9)	194 (52.3)	337 (95.7)	166 (47.2)
Blood and lymphatic system disorders						
Anaemia	37 (10.0)	8 (2.2)	37 (10.0)	6 (1.6)	145 (41.2)	43 (12.2)
Metabolism and nutrition disorders						
Decreased appetite	74 (20.1)	6 (1.6)	89 (24.0)	6 (1.6)	78 (22.2)	4 (1.1)
Gastrointestinal disorders						
Constipation	64 (17.3)	1 (0.3)	61 (16.4)	2 (0.5)	83 (23.6)	1 (0.3)
Diarrhoea	53 (14.4)	2 (0.5)	82 (22.1)	11 (3.0)	46 (13.1)	5 (1.4)
Nausea	46 (12.5)	1 (0.3)	79 (21.3)	4 (1.1)	145 (41.2)	6 (1.7)
Vomiting	32 (8.7)	4 (1.1)	31 (8.4)	1 (0.3)	75 (21.3)	7 (2.0)
General disorders and administration site conditions						
Fatigue	65 (17.6)	10 (2.7)	86 (23.2)	11 (3.0)	80 (22.7)	8 (2.3)

Serious adverse events occurred in (1) 131 of 369 subjects (35.5%), (2) 178 of 371 subjects (48.0%), and (3) 112 of 352 subjects (31.8%). Those reported by ≥8 subjects in any group were (1) pneumonia (20 subjects [5.4%]), (2) pneumonia (21 subjects [5.7%]), diarrhoea (12 subjects [3.2%]), and pneumonitis (9 subjects [2.4%]), (3) pneumonia (19 subjects [5.4%]), anaemia (14 subjects [4.0%]), and pulmonary embolism (8 subjects [2.3%]). A causal relationship to study drug could not be ruled out for (1) pneumonia (3 subjects), (2) diarrhoea (11 subjects), pneumonitis (8 subjects), and pneumonia (3 subjects), (3) anaemia (11 subjects), pneumonia and pulmonary embolism (1 subject each).

Adverse events leading to study drug discontinuation occurred in (1) 42 of 369 subjects (11.4%), (2) 75 of 371 subjects (20.2%), and (3) 53 of 352 subjects (15.1%). Those reported by ≥4 subjects in any group were (1) pneumonia (4 subjects [1.1%]), (2) pneumonitis (7 subjects [1.9%]), diarrhoea, colitis, and ILD (5 subjects each [1.3%]), asthenia and drug-induced liver injury (4 subjects each [1.1%]), (3) anaemia (7 subjects [2.0%]), blood creatinine increased (5 subjects [1.4%]), neutropenia, thrombocytopenia, pneumonia, and fatigue (4 subjects each [1.1%]). A causal relationship to study drug could not be ruled out for (1) pneumonia (1 subject), (2) pneumonitis (7 subjects), colitis and ILD (5 subjects each), diarrhoea and drug-induced liver injury (4

subjects each), (3) neutropenia and blood creatinine increased (4 subjects each), anaemia, thrombocytopenia, and fatigue (3 subjects each).

7.3.4 Global phase III study (EAGLE study)

Adverse events occurred in (1) 214 of 237 subjects (90.3%) in the durvalumab group, (2) 232 of 246 subjects (94.3%) in the durvalumab + tremelimumab group, and (3) 229 of 240 subjects (95.4%) in the SOC group. Those for which a causal relationship to study drug could not be ruled out occurred in (1) 136 of 237 subjects (57.4%), (2) 150 of 246 subjects (61.0%), and (3) 197 of 240 subjects (82.1%). Adverse events reported by ≥15% of subjects in any group are shown in Table 18.

Table 18. Adverse events reported by ≥15% of subjects in any group

SOC PT (MedDRA ver.21.0)	n (%)					
	(1) N = 237		(2) N = 246		(3) N = 240	
	All Grades	Grade ≥3	All Grades	Grade ≥3	All Grades	Grade ≥3
Any adverse event	214 (90.3)	104 (43.9)	232 (94.3)	137 (55.7)	229 (95.4)	113 (47.1)
Blood and lymphatic system disorders						
Anaemia	47 (19.8)	12 (5.1)	59 (24.0)	14 (5.7)	57 (23.8)	14 (5.8)
Metabolism and nutrition disorders						
Decreased appetite	30 (12.7)	1 (0.4)	45 (18.3)	9 (3.7)	49 (20.4)	6 (2.5)
Gastrointestinal disorders						
Diarrhoea	25 (10.5)	1 (0.4)	40 (16.3)	2 (0.8)	33 (13.8)	5 (2.1)
Nausea	27 (11.4)	1 (0.4)	30 (12.2)	3 (1.2)	41 (17.1)	0
Skin and subcutaneous tissue disorders						
Rash	19 (8.0)	0	18 (7.3)	0	36 (15.0)	0
General disorders and administration site conditions						
Asthenia	43 (18.1)	4 (1.7)	52 (21.1)	14 (5.7)	57 (23.8)	4 (1.7)
Fatigue	31 (13.1)	4 (1.7)	40 (16.3)	8 (3.3)	35 (14.6)	2 (0.8)

Serious adverse events occurred in (1) 69 of 237 subjects (29.1%), (2) 79 of 246 subjects (32.1%), and (3) 61 of 240 subjects (25.4%). Those reported by ≥5 subjects in any group were (1) pneumonia (8 subjects [3.4%]) and pneumonia aspiration (5 subjects [2.1%]), (2) pneumonia (9 subjects [3.7%]), tumour haemorrhage (7 subjects [2.8%]), anaemia (5 subjects [2.0%]), (3) pneumonia (9 subjects [3.8%]). A causal relationship to study drug could not be ruled out for (1) pneumonia aspiration (1 subject), (2) anaemia (3 subjects) and pneumonia (2 subjects), (3) pneumonia (2 subjects).

Adverse events leading to study drug discontinuation occurred in (1) 23 of 237 subjects (9.7%), (2) 36 of 246 subjects (14.6%), and (3) 24 of 240 subjects (10.0%). Those reported by ≥3 subjects in any group were (1) asphyxia (3 subjects [1.3%]), (2) pulmonary embolism and pneumonitis (4 subjects each [1.6%]), and (3) pneumonia (3 subjects [1.3%]). A causal relationship to study drug could not be ruled out for (2) pneumonitis (3 subjects) and (3) pneumonia (1 subject).

7.3.5 Foreign phase I/II study (Study 1108)

Adverse events occurred in 960 of 980 subjects (98.0%), and those for which a causal relationship to durvalumab could not be ruled out occurred in 568 of 980 subjects (58.0%). Adverse events reported by ≥20%

of subjects were fatigue (378 subjects [38.6%]), nausea (245 subjects [25.0%]), decreased appetite (244 subjects [24.9%]), dyspnoea (222 subjects [22.7%]), and constipation (210 subjects [21.4%]).

Serious adverse events occurred in 459 of 980 subjects (46.8%). Those reported by ≥2% of subjects were dyspnoea (44 subjects [4.5%]), pneumonia (27 subjects [2.8%]), abdominal pain (26 subjects [2.7%]), sepsis (24 subjects [2.4%]), pyrexia (21 subjects [2.1%]), and general physical condition decreased (20 subjects [2.0%]). A causal relationship to durvalumab could not be ruled out for dyspnoea, abdominal pain, and pneumonia (1 subject each).

Adverse events leading to durvalumab discontinuation occurred in 78 of 980 subjects (8.0%). Those reported by ≥3 subjects were general physical condition decreased (9 subjects [0.9%]), dyspnoea, pneumonia, and colitis (3 subjects each [0.3%]). A causal relationship to durvalumab could not be ruled out for colitis (3 subjects).

7.3.6 Foreign phase II study (HAWK study)

Adverse events occurred in 107 of 112 subjects (95.5%). Those for which a causal relationship to durvalumab could not be ruled out occurred in 64 of 112 subjects (57.1%). Adverse events reported by ≥20% of subjects were fatigue (29 subjects [25.9%]), constipation (24 subjects [21.4%]), and nausea (23 subjects [20.5%]).

Serious adverse events occurred in 45 of 112 subjects (40.2%). Those reported by ≥3 subjects were pneumonia (4 subjects [3.6%]) and fatigue (3 subjects [2.7%]), and a causal relationship to durvalumab was ruled out for all of these events.

Adverse events leading to durvalumab discontinuation occurred in 10 of 112 subjects (8.9%). There were no adverse events leading to durvalumab discontinuation reported by ≥2 subjects.

7.3.7 Foreign phase II study (CONDOR study)

Adverse events occurred in (1) 60 of 65 subjects (92.3%) in the durvalumab group, (2) 126 of 133 subjects (94.7%) in the durvalumab + tremelimumab group, and (3) 61 of 65 subjects (93.8%) in the tremelimumab group. Those for which a causal relationship to study drug could not be ruled out occurred in (1) 41 of 65 subjects (63.1%), (2) 77 of 133 subjects (57.9%), and (3) 36 of 65 subjects (55.4%). Adverse events reported by ≥20% of subjects in any group were (1) fatigue (19 subjects [29.2%]) and diarrhoea (13 subjects [20.0%]), (2) diarrhoea (31 subjects [23.3%]) and decreased appetite (28 subjects [21.1%]), (3) nausea (18 subjects [27.7%]), diarrhoea (17 subjects [26.2%]), dyspnoea, and fatigue (13 subjects each [20.0%]).

Serious adverse events occurred in (1) 18 of 65 subjects (27.7%), (2) 60 of 133 subjects (45.1%), and (3) 25 of 65 subjects (38.5%). Those reported by ≥4 subjects in any group were (2) pneumonia (9 subjects [6.8%]), diarrhoea (5 subjects [3.8%]), dyspnoea, hypercalcaemia, dehydration, and lung infection (4 subjects each [3.0%]), (3) diarrhoea (5 subjects [7.7%]). A causal relationship to study drug could not be ruled out for (2) diarrhoea (4 subjects) and dehydration (2 subjects), and (3) diarrhoea (3 subjects).

Adverse events leading to study drug discontinuation occurred in (1) 3 of 65 subjects (4.6%), (2) 18 of 133 subjects (13.5%), and (3) 8 of 65 subjects (12.3%). Those reported by ≥2 subjects in any group were (2) diarrhoea (3 subjects [2.3%]) and (3) diarrhoea (4 subjects [6.2%]). A causal relationship to study drug could not be ruled out for (2) diarrhoea (3 subjects) and (3) diarrhoea (3 subjects).

8. Results of Compliance Assessment Concerning the 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 inspection and assessment are currently ongoing, and their results and PMDA's conclusion will be reported in the Review Report (2).

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

The inspection is currently ongoing, and its results and PMDA's conclusion will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that durvalumab + platinum + ETP has efficacy in the treatment of extensive-stage SCLC and acceptable safety in view of its benefits. Durvalumab is clinically meaningful because it offers a new treatment option for patients with extensive-stage SCLC. PMDA considers that the indication, dosage and administration, post-marketing investigations, etc., need to be further discussed.

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

Review Report (2)

June 29, 2020

Product Submitted for Approval

Brand Name	Imfinzi Injection 120 mg, Imfinzi Injection 500 mg
Non-proprietary Name	Durvalumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	November 13, 2019

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 discussion presented in Section "7.R.1 Efficacy" in the Review Report (1), PMDA concluded that durvalumab was shown to have efficacy in these patients, because a global phase III study in chemotherapy-naïve patients with extensive-stage SCLC (CASPIAN study) demonstrated the superiority of durvalumab + platinum + ETP (Group A) over platinum + ETP (Group C) in OS, the primary endpoint.

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

1.2 Safety

PMDA's conclusion based on the discussion presented in Section "7.R.2 Safety" in the Review Report (1): Attention should be paid to the following adverse events in patients with extensive-stage SCLC who receive durvalumab + platinum + ETP:

> Febrile neutropenia, myocarditis, myasthenia gravis, colitis/severe diarrhea, pituitary dysfunction, and type 1 diabetes mellitus, in addition to the events that were considered to require attention at the time of the initial approval of durvalumab for the NSCLC indication (ILD, hepatic dysfunction, renal disorders, IRR, endocrine dysfunction [thyroid dysfunction, adrenal dysfunction]).

Attention should be paid to the possible occurrence of these adverse events during treatment with durvalumab.

Although attention should be paid to the possible occurrence of the above adverse events during treatment with durvalumab, durvalumab is tolerable as long as physicians with adequate knowledge of and experience in cancer chemotherapy take appropriate measures, such as adverse event monitoring; differential diagnosis and management, taking account of adverse drug reactions due to excessive immune response; and dose delay etc. of durvalumab and the concomitant anti-cancer agents.

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

1.3 Clinical positioning and indication

Based on the discussion presented in Section "7.R.3 Clinical positioning and indication" in the Review Report (1), PMDA concluded that the proposed indication and the proposed statement in the PRECAUTIONS CONCERNING INDICATIONS section were appropriate.

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

1.4 Dosage and administration

PMDA's conclusion based on the discussion presented in Section "7.R.4 Dosage and administration" in the Review Report (1):

The following recommended treatment modification guidelines should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section.

Precautions Concerning Dosage and Administration

- Recommended treatment modification guidelines for adverse reactions [for differences from the currently approved guidelines, see Section 7.R.4.2].

The dosage and administration for extensive-stage SCLC should be as follows:

The usual adult dosage is 1,500 mg of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent. Patients with a body weight of ≤30 kg receive 20 mg/kg (body weight) of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent. Durvalumab (Genetical Recombination) is administered as an intravenous infusion over ≥60 minutes.

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

Based on the above, PMDA instructed the applicant to use the above wording for DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections. The applicant agreed.

1.5 Risk management plan (draft)

The applicant plans to conduct post-marketing surveillance in patients with extensive-stage SCLC treated with durvalumab + platinum + ETP to assess the safety of durvalumab + platinum + ETP in clinical practice after marketing. The planned sample size is 102 patients, and the observation period is 12 months.

PMDA's conclusion based on the discussion presented in Section "7.R.5 Post-marketing investigations" in the Review Report (1):
The applicant should include febrile neutropenia in the safety specification of post-marketing surveillance in patients with extensive-stage SCLC, investigate the occurrence of febrile neutropenia through the surveillance, and provide safety information collected to healthcare professionals. Thus, the planned sample size and observation period for the surveillance should be reconsidered, taking account of the incidence of febrile neutropenia, etc.

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

Based on the above etc., PMDA instructed the applicant to reconsider the surveillance plan.

The applicant responded that they would:
- Include febrile neutropenia in the safety specification.
- Change the planned sample size to 212 patients and the observation period to 16 weeks, taking account of the incidence of febrile neutropenia, time to onset, etc., in the CASPIAN study.

PMDA accepted the applicant's response.

In view of the discussion above etc., PMDA has concluded that the risk management plan (draft) for durvalumab should include the safety specification presented in Table 19, and that the applicant should conduct additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities presented in Tables 20 and 21.

Table 19. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
● ILD ● Colitis/severe diarrhoea ● Hepatic dysfunction ● Endocrine dysfunction (thyroid dysfunction, adrenal dysfunction, pituitary dysfunction) ● Type 1 diabetes mellitus ● Renal disorders (interstitial nephritis, etc.) ● Myositis ● Myocarditis ● Myasthenia gravis ● Infusion reaction	● ~~Colitis/severe diarrhoea~~ ● ~~Type 1 diabetes mellitus~~ ● Rhabdomyolysis ● ~~Pituitary dysfunction~~ ● Meningitis ● Immune thrombocytopenic purpura ● Embryo-fetal toxicity ● Use in organ transplant recipients (including hematopoietic stem cell transplant recipients) ● Febrile neutropenia in patients receiving durvalumab + chemotherapy	None
Efficacy specification		
None		

Underline and strikethrough denote changes related to the new indication and dosage and administration proposed in the present application.

Table 20. 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
● Specified use-results survey of durvalumab as maintenance therapy after definitive chemoradiotherapy in patients with locally-advanced, unresectable NSCLC ● Use-results survey in patients with extensive-stage SCLC	● Post-marketing clinical study (an extension to the PACIFIC study)	● Develop information materials to be distributed to healthcare professionals. ● Develop information materials to be distributed to patients.

Underline denotes planned activities for the additional indication and dosage regimen in the present application.

Table 21. Outline of use-results survey (draft)

Objective	To investigate the occurrence of febrile neutropenia in patients receiving durvalumab + platinum + ETP in clinical practice after marketing.
Survey method	Central registry system
Population	Patients with extensive-stage SCLC treated with durvalumab + platinum + ETP
Observation period	16 weeks
Planned sample size	212 patients
Main survey items	Safety specification: Febrile neutropenia Other main survey items: patient characteristics (sex, age, disease stage, complications, prior therapies, etc.), the use of durvalumab, concomitant medications, etc.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of 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.

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

The new drug application data (CTD 5.3.5.1.1) 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.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indications and dosage and administration shown below, with the following approval condition, 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 product is used properly under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can adequately respond to emergencies. The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until July 1, 2026).

Indications (Underline denotes additions.)

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy

Extensive-stage small cell lung cancer

Dosage and Administration (Underline denotes additions.)

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy:

The usual adult dosage is 10 mg/kg (body weight) of Durvalumab (Genetical Recombination) administered as an intravenous infusion over ≥60 minutes every 2 weeks for a maximum of 12 months.

Extensive-stage small cell lung cancer:

The usual adult dosage is 1,500 mg of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 1,500 mg every 4 weeks as a single agent. Patients with a body weight of ≤30 kg receive 20 mg/kg (body weight) of Durvalumab (Genetical Recombination) in combination with a platinum agent and etoposide every 3 weeks for 4 cycles, followed by 20 mg/kg every 4 weeks as a single agent. Durvalumab (Genetical Recombination) is administered as an intravenous infusion over ≥60 minutes.

Approval Condition

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

Warnings

1. Imfinzi should be used only in patients considered eligible to receive Imfinzi, under the supervision of physicians with adequate knowledge of and experience in cancer chemotherapy at medical institutions that can adequately respond to emergencies. Prior to initiation of treatment, patients or their families must provide consent after being fully informed of the efficacy of treatment and associated risks.
2. Since cases of interstitial lung disease (including radiation pneumonitis), 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, cough, and pyrexia). If abnormalities are observed, discontinue Imfinzi and take appropriate measures such as administration of corticosteroids.

Contraindication

Patients with a history of hypersensitivity to any of the components of Imfinzi

Precautions Concerning Indications (Underline denotes additions.)

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy:

The efficacy and safety of Imfinzi in adjuvant chemotherapy have not been established.

Extensive-stage small cell lung cancer:

Eligible patients must be selected by physicians with a full understanding of the efficacy and safety of durvalumab, and of the information presented in the CLINICAL STUDIES section, including the definition of extensive-stage disease for patients enrolled in the clinical study.

Precautions Concerning Dosage and Administration (Underline denotes additions.)

Both indications:

In the event of adverse reactions to Imfinzi, Imfinzi treatment modification should be considered based on the table below.

Recommended treatment modifications for adverse reactions

Adverse reaction	Severity	Imfinzi treatment modification
Interstitial lung disease	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hepatic dysfunction	● AST or ALT 3-5 × ULN or total bilirubin 1.5-3 × ULN ● AST or ALT ≤8 × ULN or total bilirubin ≤5 × ULN	Withhold dose until resolution to Grade ≤1
	● AST or ALT >8 × ULN or total bilirubin >5 × ULN ● Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN with no other cause	Permanently discontinue
Colitis or diarrhea	Grade 2	Withhold dose until resolution to Grade ≤1
	Grade 3 or 4	Permanently discontinue
Hyperthyroidism, Adrenal insufficiency, Hypopituitarism	Grade 2-4	Withhold dose until clinically stable
Renal dysfunction	Serum creatinine 1.5-3 × ULN or baseline	Withhold dose until resolution to Grade ≤1
	Serum creatinine >3 × ULN or baseline	Permanently discontinue
Myositis	Grade 2 or 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur within 30 days or if there are signs of respiratory insufficiency.
	Grade 4	Permanently discontinue
Skin disorder	● Grade 2 for ≥1 week ● Grade 3	Withhold dose until resolution to Grade ≤1
	Grade 4	Permanently discontinue
Myocarditis	Grade 2	Withhold dose until resolution to Grade ≤1. Permanently discontinue if myocardial biopsy suggests myocarditis.
	Grade 3 or 4	Permanently discontinue
Myasthenia gravis	Grade 3	Withhold dose until resolution to Grade ≤1. Permanently discontinue if resolution to Grade ≤1 does not occur or if there are signs of respiratory insufficiency or autonomic nervous system imbalance.
	Grade 4	Permanently discontinue
Infusion reaction	Grade 1 or 2	Interrupt or decrease the rate of infusion by 50%
	Grade 3 or 4	Permanently discontinue
Other adverse reactions (excluding hypothyroidism and type 1 diabetes mellitus)	Grade 2 or 3	Withhold dose until resolution to Grade ≤1
	Grade 4	Permanently discontinue

Severity grade based on NCI-CTCAE (Common Terminology Criteria for Adverse Events) v4.03

Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy:

The efficacy and safety of Imfinzi in combination with other anti-cancer agents have not been established.

Appendix

List of Abbreviations

ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
partial change application	application for partial change of marketing approval
AST	aspartate aminotransferase
atezolizumab	Atezolizumab (Genetical Recombination)
atezolizumab + CBDCA + ETP	combination of atezolizumab, CBDCA, and ETP
AUC_{ss}	area under the serum concentration-time curve at steady state
BCG	Bacillus Calmette-Guérin
BICR	blinded independent central review
BID	bis in die
CBDCA	carboplatin
CBDCA + ETP	combination of CBDCA and ETP
CBDCA + PTX	combination of CBDCA and PTX
CDDP	cisplatin
CDDP + PEM	combination of CDDP and PEM
cetuximab	Cetuximab (Genetical Recombination)
CI	confidence interval
$C_{max, ss}$	maximum serum concentration at steady state
$C_{min,ss}$	minimum serum concentration at steady state
CPT-11	irinotecan hydrochloride hydrate
DTX	docetaxel hydrate
durvalumab	Durvalumab (Genetical Recombination)
durvalumab + platinum + ETP	combination of durvalumab, a platinum agent, and ETP
durvalumab + tremelimumab	combination of durvalumab and tremelimumab
durvalumab + tremelimumab + platinum + ETP	combination of durvalumab, tremelimumab, a platinum agent, and ETP
EGFR	epidermal growth factor receptor
erlotinib	Erlotinib Hydrochloride
ESMO guidelines	Small-cell lung cancer (SCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up
ETP	etoposide
EU	Endotoxin Unit
GEM	gemcitabine hydrochloride
HER2	human epidermal growth factor receptor 2
HPV	human papillomavirus
HR	hormone receptor (estrogen receptor or progesterone receptor)
IC	immune cell
IC <1%	<1% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
IC ≥1%	≥1% of tumor area occupied by PD-L1-expressing tumor-infiltrating immune cells
ILD	interstitial lung disease
IRR	infusion related reaction
ITT	intention-to-treat
Japanese clinical practice guidelines	EBM-based clinical practice guidelines for lung cancer 2016, The Japan Lung Cancer Society ed.
MDS	myelodysplastic syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MSI-High	microsatellite instability-high
nab-PTX	paclitaxel (albumin-bound)

NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Small Cell Lung Cancer
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
NSQ	non-squamous
NSQ-NSCLC	non-squamous non-small cell lung cancer
OS	overall survival
PD-L	programmed cell death-ligand
PD-1	programmed cell death-1
PEM	pemetrexed sodium hydrate
PFS	progression free survival
PK	pharmacokinetics
platinum +CPT-11	combination of a platinum agent and CPT-11
platinum + ETP	combination of a platinum agent and ETP
platinum + GEM	combination of a platinum agent and GEM
platinum + PEM	combination of a platinum agent and PEM
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PT	preferred term
PTX	paclitaxel
QD	quaque die
QW	quaque 1 week
Q12W	quaque 12 weeks
Q2W	quaque 2 weeks
Q3W	quaque 3 weeks
Q4W	quaque 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SCLC	small cell lung cancer
SOC	standard of care
SQ	squamous
SQ-NSCLC	squamous non-small cell lung cancer
S-1	a combination formulation of tegafur, gimeracil, and oteracil potassium
Study 02	Study D4190C00002
Study 1108	Study CD-ON-MEDI4736-1108
TC	tumor cell
TC <1%	<1% of tumor area occupied by PD-L1-expressing tumor cells
TC <25%	<25% of tumor area occupied by PD-L1-expressing tumor cells
TC ≥1%	≥1% of tumor area occupied by PD-L1-expressing tumor cells
TC ≥25%	≥25% of tumor area occupied by PD-L1-expressing tumor cells
ARCTIC study	Study D4191C00004
ATLANTIC study	Study D4191C00003
BALTIC study	Study D419QC00002
[redacted] study	Study [redacted]
CASPIAN study	Study D419QC00001
CONDOR study	Study D4193C00003
DANUBE study	Study D419BC00001
EAGLE study	Study D4193C00002
HAWK study	Study D4193C00001
HIMALAYA study	Study D419CC00002
HUDSON study	Study D6185C00001
MYSTIC study	Study D419AC00001

PACIFIC study	Study D4191C00001
[redacted] study	Study [redacted]
PEARL study	Study D419AC00002
POSEIDON study	Study D419MC00004
POTOMAC study	Study D419JC00001
tremelimumab	Tremelimumab (Genetical Recombination)
vinorelbine	Vinorelbine Ditartrate