

Summary of Investigation Results

Anti-PD-1 antibody drugs, anti-PD-L1 antibody drugs, and anti-CTLA-4 antibody drugs ^{*1}

Non-proprietary name Brand name	Non-proprietary name	Brand name (marketing authorization holder)
	a. Atezolizumab (genetical recombination) b. Avelumab (genetical recombination) c. Ipilimumab (genetical recombination) d. Cemiplimab (genetical recombination) e. Tislelizumab (genetical recombination) f. Durvalumab (genetical recombination) g. Tremelimumab (genetical recombination) h. Pembrolizumab (genetical recombination) i. Retifanlimab (genetical recombination)	a. Tecentriq for Intravenous Infusion 840 mg, 1200 mg (Chugai Pharmaceutical Co., Ltd.) b. Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd) c. Yervoy Injection 20 mg, 50 mg (Bristol-Myers Squibb K.K.) d. Libtayo I.V. Infusion 350 mg (Regeneron Japan KK) e. Tevimbra I.V. Infusion 100 mg (BeOne Medicines Japan) f. Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.) g Imjudo Injection 25 mg, 300 mg (AstraZeneca K.K.) h. Keytruda Injection 100 mg (MSD K.K.) i. Zynyz for Intravenous Infusion 500 mg (Incyte Biosciences Japan G.K.)
Japanese market launch	See Attachment.	
Indications	See Attachment.	
Summary of revisions	a, b, d-g, i “Severe gastritis and oesophagitis” should be added to the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS. c “Severe gastritis” should be added to the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS. h “Severe oesophagitis” should be added to the 11.1 Clinically Significant Adverse Reactions section in 11. ADVERSE REACTIONS.	
Investigation results	Cases involving Severe gastritis and oesophagitis were evaluated. Cases in	

and background of the revision	which a causal relationship between anti-PD-1 antibody drugs, anti-PD-L1 antibody drugs, and anti-CTLA-4 antibody drugs and Severe gastritis and oesophagitis was reasonably possible have been reported. As a result of consultation with expert advisors regarding the causality assessment of the cases and the necessity of revision of PRECAUTIONS, MHLW/PMDA concluded that revision of PRECAUTIONS was necessary.
Reference: Number of cases^{*2} involving gastritis and oesophagitis^{*3} reported in Japan	〈Cases involving gastritis〉 a. A total of 9^{*4} cases have been reported to date (including 1 case in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. b. A total of 0 cases have been reported to date. c. A total of 2^{*5} cases have been reported to date (including 0 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. d. A total of 2 cases have been reported to date (including 1 case in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. e. A total of 0 cases have been reported to date. f. A total of 8 cases have been reported to date (including 5 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. g. A total of 6^{*6} cases have been reported to date (including 5 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. h. —^{*7} i. A total of 0 cases have been reported to date. 〈Cases involving oesophagitis〉 a. A total of 2 cases have been reported to date (including 2 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. b. A total of 1 case has been reported to date (including 0 cases in which a causal relationship between the drug and the event was reasonably possible). No deaths have been reported to date. c. —^{*7}

	d. A total of 0 cases have been reported to date. e. A total of 0 cases have been reported to date. f. A total of 1 case has been reported to date (including 0 cases in which a causal relationship between the drug and the event was reasonably possible). A total of 1 death has been reported to date (including 0 cases in which a causal relationship between the drug and the death following the event was reasonably possible). g. A total of 0 cases have been reported to date. h. A total of 12 cases have been reported to date (including 4 cases in which a causal relationship between the drug and the event was reasonably possible). A total of 2 deaths have been reported to date (including 0 cases in which a causal relationship between the drug and the death following the event was reasonably possible). i. A total of 0 cases have been reported to date.
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*1: Anti-PD-1 antibody drugs, anti-PD-L1 antibody drugs, and anti-CTLA-4 antibody drugs, except for nivolumab (genetical recombination)

*2: Cases collected in PMDA's safety database for drugs.

*3: For gastritis, among cases that fell under MedDRA ver. 28.1 PTs "Gastritis erosive", "Immune-mediated gastritis", "Haemorrhagic erosive gastritis", "Gastritis haemorrhagic", "Necrotising gastritis", "Eosinophilic gastritis", "Chronic gastritis", "Ulcerative gastritis", "Gastritis hypertrophic", "Gastritis", "Collagenous gastritis", "Gastric ulcer haemorrhage", "Gastric ulcer perforation" and "Gastric ulcer" cases assessed as Grade 3 or higher according to CTCAE ver. 6.0 and for which results of tests such as endoscopy, biopsy, or similar findings are mentioned were retrieved. For oesophagitis, among cases that fell under MedDRA ver. 28.1 PTs "Oesophagitis", "Oesophageal disorder", "Immune-mediated oesophagitis", "Oesophageal ulcer", "Oesophagitis ulcerative", "Necrotising oesophagitis", "Erosive oesophagitis", "Eosinophilic oesophagitis", "Lymphocytic oesophagitis" and "Oesophagitis haemorrhagic" cases assessed as Grade 3 or higher according to CTCAE ver. 6.0 and for which results of tests such as endoscopy, biopsy, or similar findings are mentioned were retrieved.

*4: Cases that fell under the PT "Gastric ulcer haemorrhage", excluding cases for which bevacizumab (genetical recombination) was co-administered.

*5: Cases excluding those for which nivolumab (genetical recombination) was co-administered

*6: Durvalumab (genetical recombination) was co-administered in all the cases

*7: Excluded from evaluation because it is already described in the 11.1 Clinically Significant Adverse Reactions section of 11. ADVERSE REACTIONS.

The expert advisors present at the Expert Discussion regarding the current investigation were nominated based on their conflict of interest declarations concerning the relevant products, pursuant to the "Rules for Convening Expert Discussions, etc., by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 20-8, dated December 25, 2008).

Attachment

Brand name (marketing authorization holder)	Japanese market launch	Indications
e. Tecentriq for Intravenous Infusion 840 mg Tecentriq for Intravenous Infusion 1200 mg (Chugai Pharmaceutical Co., Ltd.)	November 2019 April 2018	< Common to both preparations > ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Adjuvant treatment for PD-L1 positive non-small cell lung cancer ○ Extensive stage small cell lung cancer ○ Unresectable alveolar soft part sarcoma ○ Recurrent or refractory extranodal NK/T-cell lymphoma/nasal type < Tecentriq for Intravenous Infusion 1200 mg > ○ Unresectable hepatocellular carcinoma ○ Unresectable thymic carcinoma < Tecentriq for Intravenous Infusion 840 mg > ○ PD-L1 positive, hormone receptor negative and HER2 negative inoperable or recurrent breast cancer
d. Bavencio intravenous infusion 200 mg (Merck Biopharma Co., Ltd)	November 2017	○ Radically unresectable Merkel cell carcinoma ○ Radically unresectable or metastatic renal cell carcinoma ○ Maintenance treatment of radically unresectable urothelial carcinoma following chemotherapy
h. Yervoy Injection 20 mg Yervoy Injection 50 mg (Bristol-Myers Squibb K.K.)	November 2021 August 2015	○ Radically unresectable malignant melanoma ○ Radically unresectable or metastatic renal cell carcinoma ○ Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Unresectable, advanced or recurrent malignant pleural mesothelioma ○ Radically unresectable, advanced or recurrent oesophageal carcinoma ○ Unresectable hepatocellular carcinoma
b. Libtayo I.V. Infusion 350 mg (Regeneron Japan KK)	March 2023	○ Advanced or recurrent cervical cancer that has progressed after cancer chemotherapy ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Radically unresectable, advanced or recurrent squamous cell carcinoma ○ Adjuvant treatment for squamous cell carcinoma at high risk of recurrence

This English version is intended to be a reference material for the convenience of users. In the event of inconsistency between the Japanese original and this English translation, the former shall prevail.

c. Tevimbra I.V. Infusion 100 mg (BeOne Medicines Japan)	July 2025	○ Radically unresectable, advanced or recurrent oesophageal carcinoma ○ Unresectable, advanced or recurrent gastric cancer ○ Recurrent or metastatic nasopharyngeal carcinoma
f. Imfinzi Injection 120 mg, 500 mg (AstraZeneca K.K.)	August 2018	○ Maintenance treatment of locally-advanced, unresectable non-small cell lung cancer following definitive chemoradiotherapy ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Neoadjuvant and adjuvant treatment for non-small cell lung cancer ○ Extensive stage small cell lung cancer ○ Maintenance treatment of limited-stage small cell lung cancer following definitive chemoradiation therapy ○ Unresectable hepatocellular carcinoma ○ Unresectable biliary tract cancer ○ Advanced or recurrent endometrial cancer ○ Neoadjuvant and adjuvant treatment for bladder cancer ○ High-risk non-muscle-invasive bladder cancer ○ Neoadjuvant and adjuvant treatment for gastric cancer
i. Imjudo Injection 25 mg, 300 mg (AstraZeneca K.K.)	March 2023	< Imjudo Injection 25 mg > ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Unresectable hepatocellular carcinoma < Imjudo Injection 300 mg > ○ Unresectable hepatocellular carcinoma
Keytruda Injection 100 mg (MSD K.K.)	February 2017	○ Malignant melanoma ○ Unresectable, advanced or recurrent non-small cell lung cancer ○ Neoadjuvant and adjuvant therapy for non-small cell lung cancer ○ Relapsed or refractory classical Hodgkin lymphoma ○ Radically unresectable urothelial carcinoma ○ Advanced or recurrent microsatellite instability-high (MSI-High) solid tumours that have progressed after cancer chemotherapy (limited to patients who are refractory or intolerant to standard treatments) ○ Radically unresectable or metastatic renal cell carcinoma ○ Adjuvant therapy for renal cell carcinoma ○ Recurrent or metastatic head and neck cancer

		○ Neoadjuvant and adjuvant therapy for locally advanced head and neck cancer ○ Radically unresectable advanced or recurrent oesophageal carcinoma ○ Unresectable, advanced or recurrent microsatellite instability-high (MSI-High) colorectal cancer ○ PD-L1-positive, hormone receptor-negative and HER2-negative inoperable or recurrent breast cancer ○ Neoadjuvant and adjuvant drug therapy for hormone receptor-negative and HER2-negative breast cancer at high risk of recurrence ○ Advanced or recurrent endometrial carcinoma ○ Advanced or recurrent, tumour mutational burden-high (TMB-High) solid tumours that have progressed after cancer chemotherapy (limited to patients who are refractory or intolerant to standard treatments) ○ Advanced or recurrent cervical cancer ○ Locally advanced cervical cancer ○ Recurrent or refractory primary mediastinal large B-cell lymphoma ○ Unresectable, advanced or recurrent gastric cancer ○ Unresectable biliary tract cancer ○ Unresectable, advanced or recurrent malignant pleural mesothelioma ○ Recurrent ovarian cancer resistant to platinum-based chemotherapy
g. Zynyz for Intravenous Infusion 500 mg (Incyte Biosciences Japan G.K.)	March 2026	Unresectable advanced or recurrent squamous cell carcinoma of the anal canal