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.

Summary of Investigation Results

Anti-PD-1 antibody drugs

June 4, 2019

Non-proprietary name

a. Nivolumab (genetical recombination)

b. Pembrolizumab (genetical recombination)

Branded name (Marketing authorization holder)

a. Opdivo Intravenous Infusion 20 mg, 100 mg, 240 mg (Ono Pharmaceutical Co., Ltd.)

b. Keytruda Injection 20 mg, 100 mg (MSD K.K.)

Indications

a.

Malignant melanoma

Unresectable advanced or recurrent non-small cell lung cancer

Unresectable or metastatic renal cell carcinoma

Relapsed or refractory classical Hodgkin lymphoma

Relapsed or metastatic head and neck cancer

Unresectable, advanced or recurrent gastric cancer that has progressed after cancer chemotherapy

Unresectable, advanced or recurrent malignant pleural mesothelioma that has progressed after cancer chemotherapy

b.

Malignant melanoma

Unresectable advanced or recurrent non-small cell lung cancer

Relapsed or refractory classical Hodgkin lymphoma

Unresectable urothelial carcinoma exhibiting progression after chemotherapy

Advanced or recurrent, microsatellite instability-high (MSI-H) solid tumours exhibiting

3-3-2 Kasumigaseki, Chiyoda-ku, Tokyo 100-0013 Japan
E-mail: safety.info@pmda.go.jp

progression after chemotherapy (only when management cannot be achieved with standard therapies)

Summary of revisions

"Patients with tuberculosis infection or its history" should be added to the Careful Administration section, and "tuberculosis" should be added to the Clinically Significant Adverse Reactions section.

Investigation results and background of the revision

MHLW/PMDA concluded that revision of the package insert was necessary based on the following as a result of their investigation of the currently available evidence and in consultation with expert advisors:

- Cases of tuberculosis have been reported in patients treated with anti-PD-1 antibody drugs in Japan and overseas.
- Reduced survival in PD-1–deficient mice compared with wild-type mice has been reported in a non-clinical study (PNAS. 2010; 107:13402–7) when mice were infected with tubercle bacillus.
- The incidence of tuberculosis in patients administered Nivolumab (58.2 per 100 000 patients, based on the Specific Use-Results Survey in patients with unresectable advanced or recurrent non-small cell lung cancer in which 2 cases of tuberculosis were identified) is generally higher, approximately 4.4-fold the incidence of tuberculosis in the entire Japanese population (13.3 per 100 000 people, 2017 Annual Reports on Registered Tuberculosis Patients, Ministry of Health, Welfare and Labour).
- The reporting odds ratio (ROR) of events related to tuberculosis was 3.51 (95% CI [1.2, 10.4]) for anti-PD-1 antibody drugs, a value statistically significantly higher compared to that of epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs) for which tuberculosis is not a known adverse reaction, as calculated in a disproportionality analysis using reports of adverse reactions to anti-PD-1 antibody drugs and to EGFR-TKIs found in adverse drug reaction report databases.

Number of cases and patient mortalities reported in Japan during the previous 3 fiscal years

a.

A total of 10 cases involving tuberculosis have been reported to date (including 6 cases for which a causal relationship between the drug and event could not be ruled out). No patient mortalities have been reported to date.

b.

A total of 4 cases involving tuberculosis have been reported to date. (A causal relationship between the drug and event could not be established in any of these cases.) No patient mortalities have been reported to date.

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