Development Pipeline Progress Status

■Development status of OPDIVO

○Second-line therapy and beyond for melanoma
In July 2014, OPDIVO was approved in Japan for the first time in the world and launched in September. It was launched in December 2014 in the US and approved in March 2015 in South Korea. In the EU and Taiwan, the application was filed and is currently under review.

○First-line monotherapy for melanoma
In the US, the application has already been accepted, and the projected action date for the completion of FDA review is August 27, 2015. The OPDIVO plus ipilimumab combination regimen is being evaluated in a Phase III study in the US/EU. In Japan, a Phase II study has been started.

○Second-line therapy and beyond for non-small cell lung cancer (NSCLC)
In March 2015, OPDIVO was approved in the US for the treatment of squamous NSCLC. In the EU, the application was filed and is currently under review. The application for the treatment of squamous NSCLC was submitted on April 22 in Japan and on April 24 in Taiwan. In South Korea, a Phase II study is ongoing to extrapolate the data from the Phase III study conducted overseas.

○ First-line therapy for NSCLC
A multi-national Phase III study is ongoing in Japan, South Korea and Taiwan, along with the US/EU.

○Renal cell carcinoma
A multi-national Phase III study of second-line therapy and beyond is ongoing in Japan and the US/EU. OPDIVO in combination with ipilimumab as first-line therapy is also being evaluated in a multi-national Phase III study including Japan.

○Head and neck carcinoma
A multi-national Phase III study is ongoing in Japan, South Korea and Taiwan, along with the US/EU.

○Gastric cancer
For the treatment of gastric cancer, which is relatively common in Asia, a Phase III study is ongoing in three countries (Japan, South Korea and Taiwan). A separate Phase I/II study is being conducted in the US/EU.

○Glioblastoma
For the treatment of glioblastoma, a form of brain tumor characterized by refractory nature, a Phase III study has been started in the US/EU. In Japan, a Phase III study is prepared to be conducted.

○Other (cancer types in relatively early stages of development)
In the treatment of Hodgkin lymphoma, OPDIVO is demonstrating very high efficacy, though in a limited number of patients. In 2014, the FDA granted Breakthrough Therapy Designation for this indication, so early approval is expected. A separate Phase II study has been started in patients with Hodgkin lymphoma in Japan.
For the treatment of two types of non-Hodgkin lymphoma (diffuse large B cell lymphoma and follicular lymphoma), Phase II studies are ongoing in the US/EU.
The esophageal cancer indication is being evaluated in a Phase II study in Japan, ahead of the US/EU.
For ovarian cancer, an investigator-initiated trial is taking place. Positive results are becoming available from this investigator-initiated Phase II trial, including those presented at the American Society of Clinical Oncology (ASCO) meeting in 2014, making OPDIVO the first PD-1 inhibitor to demonstrate efficacy in patients with ovarian cancer.
Based on the results of an exploratory study in the US/EU for the treatment of multiple types of cancer, only bladder cancer was selected for further evaluation, and a new Phase II study has been started.
Colon cancer is also being studied in a Phase I/II study in the US/EU.
In addition, an exploratory Phase I/II study is ongoing in the US/EU for the treatment of pancreatic cancer, gastric cancer, small-cell lung cancer, triple-negative breast cancer, etc. As with bladder cancer, we are planning to conduct separate, advanced-stage studies for tumor types in which OPDIVO is considered promising based on various factors such as dosage and potential combination with other drugs.
For hepatocellular carcinoma, a Phase I study has already been ongoing in the US/EU, and since hepatocellular carcinoma is relatively common in Asia, Japan has also participated in it.

●Combination of OPDIVO and other immuno-oncology compounds

In 2014, Ono Pharmaceutical Co., Ltd. entered into a new collaboration agreement with Bristol-Myers Squibb's (BMS) covering Japan, South Korea and Taiwan. Under this agreement, the two companies will jointly develop a total of 5 compounds, that is, OPDIVO, the anti-CT-LA4 antibody ipilimumab, anti-KIR antibody, anti-LAG-3 antibody, and CD137 receptor agonist. The development of combination regimens under this agreement is explained below.

As described above, OPDIVO in combination with ipilimumab is being studied for the treatment of melanoma (first-line therapy) and renal cell carcinoma (first-line therapy). The combination of OPDIVO with anti-KIR antibody, anti-LAG-3 antibody and CD137 receptor agonist is being evaluated in Phase I studies; based on tolerability and exploratory efficacy data, we will consider whether to advance them to the next step for further evaluation, including dosing regimens.
Apart from the collaboration agreement between Ono and BMS, a new collaboration agreement was concluded between Kyowa Hakko Kirin Co., Ltd. (KHK) and BMS/Ono at the end of 2014. Under this agreement, a study has been started in Japan to evaluate the combination of KHK's anti-CCR4 antibody mogamulizumab (approved in Japan for the treatment of blood cancer) with OPDIVO.

■Survival benefit of OPDIVO

A study comparing OPDIVO versus the standard of care dacarbazine in patients with melanoma marked the first time that a PD-1 inhibitor was proven to extend overall survival compared with the standard of care.
In patients with squamous NSCLC, a confirmatory study was conducted to compare OPDIVO versus the standard of care docetaxel. OPDIVO significantly improved overall survival, with a hazard ratio of 0.59, achieving very-high-impact results. Further details will be presented at the ASCO.
Docetaxel has been compared with various anticancer agents over the past 15 years. We think that this study is the first to provide such convincing evidence.
In non-squamous NSCLC as well, a confirmatory study was conducted with docetaxel as the comparator, which was stopped early because of OPDIVO's efficacy demonstrated by the results of the interim analysis. The results of this study will be presented at the ASCO. The fact that OPDIVO's overall survival benefit has been confirmed in three cancer types is extremely important.
Moreover, accumulating evidence indicates that patients with various types of cancer who are responsive to anti-PD-1 antibody experience durable responses, which reflects the extension of overall survival.

■Medical treatment flow for NSCLC

The medical treatment flow for NSCLC, which is a relatively common type of cancer, consists of first-line, second-line and third-line therapies. The second- and third-line therapies marked in red frame are the indications proposed in the Japanese application. If the ongoing Phase III study of OPDIVO monotherapy in previously untreated patients is successful, it will be possible to use OPDIVO as first-line therapy marked in green frame. The target population

of the first-line therapy study is limited to PD-L1 positive patients, and PD-L1-negative patients may benefit from OPDIVO if used in combination with various drugs.

■Comprehensive medical treatment for cancer patients

In addition to cancer therapy, we have worked on supportive care for cancer patients, such as improvement of Quality of Life (QOL) and prevention of adverse reactions to anticancer drugs, as a strategic area in the last 3 to 4 years. Currently, 11 compounds including OPDIVO are in our oncology pipeline. Having OPDIVO, which is showing promise in more and more cancer types, is equivalent to having multiple anticancer drugs. We will pursue its development more aggressively.

■Planned Presentation about nivolumab in American Society of Clinical Oncology (ASCO)

More than 20 presentations about nivolumab will be given at the ASCO meeting to be held from May 29 to June 2, 2015. This material shows 17 titles on the efficacy and safety of nivolumab. In terms of NSCLC, the results of Study CheckMate017, a Phase III study in patients with squamous NSCLC, and those of Study CheckMate057, a Phase III study in patients with non-squamous NSCLC, will be presented.
For renal cell carcinoma, preliminary results are available, but Phase III studies have not reached the interim analysis point, so the results of large-scale studies will not be presented.
For melanoma, the results of Study CheckMate067 will be presented, which compared nivolumab alone or combined with ipilimumab versus ipilimumab alone in treatment-naïve patients with melanoma.
In addition, efficacy data from small-scale, exploratory studies in hepatocellular carcinoma, small-cell lung cancer and glioblastoma will be presented.
From Japan, the data will be presented from two Phase II studies in patients with squamous and non-squamous NSCLC, which were conducted only in Japan. We believe that these studies have shown very positive results.
For ovarian cancer, follow-up data, a continuation of last year's presentation, will be presented.

■Global development projects

In projects other than OPDIVO, a Phase I study of ONO-4474 (Trk inhibitor), a kinase-related compound, one of the bioactive lipids in Ono's focus area, has been started for the treatment of pain associated with osteoarthrosis. A total of 10 in-house discovered compounds, including ONO-4474, are being developed globally.

■Development pipeline in Japan

The compounds being developed in Japan are shown in descending order of stage, most advanced first. The pediatric indication for Proemend being evaluated in a Phase III study, two additional indications for Orencia IV, carfilzomib showing great promise in the treatment of multiple myeloma, and ONO-5163 for the treatment of secondary hyperparathyroidsm, are being developed to make them available to patients as soon as possible.
For Onoact, a new study has been started for pediatric use in the treatment of tachyarrhythmia in low cardiac function, which was approved as an additional indication two years ago.
We will also pursue development of early-stage compounds. New Phase II studies of ONO-6950, an LT antagonist, and ONO-4053, an EP antagonist, have been started in Japan to evaluate their efficacy and differentiate them from currently available drugs.