Overview of Development Pipeline Progress Status in Second Quarter of Fiscal Year 2017

■ Main development status of Opdivo

○ In Japan, Opdivo was approved for the indication of gastric cancer ahead of the rest of the world on September 22.

○ In EU, Opdivo was approved for the indication of urothelial cancer (bladder cancer, etc.).

○ In the US, Opdivo was granted under accelerated approval for the indications of MSI-H or dMMR metastatic colorectal cancer and 2L hepatocellular carcinoma.

○ In South Korea, Opdivo was approved for the indications of renal cell cancer, Hodgkin lymphoma, head and neck cancer, and urothelial cancer.

○ In Taiwan, Opdivo was approved for the indications of renal cell cancer, head and neck cancer, non-squamous non-small cell lung cancer, Hodgkin lymphoma, and urothelial cancer. A supplemental application for gastric cancer has been filed.

○ In Japan, since Opdivo has been designated for the treatment of biliary tract cancer under the SAKIGAKE Designation System established by the Ministry of Health, Labour and Welfare (MHLW), we are committed to obtaining an early approval for this indication, for which it is now in Phase I in Japan, while the number of this patient population is very limited.

○ In the US, a clinical hold was placed on clinical studies in patients with multiple myeloma, in terms of safety issue which was raised from the overseas clinical studies with another immune checkpoint inhibitor. In association with this clinical hold, new patient entry has been suspended in the overseas clinical studies in this patient population with Opdivo. In Japan, Phase II clinical study has been started for this indication, but since no patients were recruited at that time, patient recruitment has been postponed. We will judge carefully by further reviewing the safety information from overseas clinical studies in the future.

■ Main clinical studies of Opdivo in combination with other I-O compounds

(Combination therapy of Opdivo with ipilimumab)

○ An application for Opdivo was filed for combination therapy with ipilimumab for malignant melanoma in Japan. In addition to the approvals in EU and the US, the combination therapy was approved in Korea and Taiwan.

○ In the CheckMate -214 study in patients with 1L renal cell cancer, data showing superior overall survival (OS) compared to the standard of care, sunitinib was obtained, and now the filing for approval has been under preparation in each country.

○ For non-small cell lung cancer, we are expecting the result of the ongoing CheckMate -227 study.

○ Phase III studies are underway for the treatment of small cell lung cancer, head and neck cancer, gastric cancer and malignant pleural mesothelioma.

(Combination therapy of Opdivo with I-O compounds other than ipilimumab)

○ Combination therapy of Opdivo each with lirilumab, relatlimab, urelumab, mogamulizumab, anti-TIGIT antibody, cabiralizumab and IDO1 inhibitor is currently under exploratory studies for solid tumors and blood cancers. Among them, we plan to select potential therapies particularly which may be highly effective against certain cancers and to proceed with a verification study.

■ **Domestic development pipeline (Oncology area other than Opdivo)**

○ Regarding Kyprolis for the treatment of multiple myeloma, following the approval for the dose and dosage of the combination therapy with other two products granted in 2016, it was approved for the dose and dosage of the combination therapy with the one product.

○ ONO-7702 (encorafenib), a BRAF inhibitor and ONO-7703 (binimetinib), a MEK inhibitor both licensed from Array in May are under clinical study for the treatment of malignant melanoma in Japan.

○ Clinical study with ONO-4059, a Btk inhibitor discovered internally at Ono, has been started for the treatment of central nervous system lymphoma independently in Japan.

■ **Domestic development pipeline (outside oncology area)**

○ A global Phase III study with Orencia subcutaneous injection has been started aiming to obtain additional approval for indications of polymyositis and dermatomyositis. It is estimated that there are about 17,000 patients in Japan.

○ ONO-5704, chemically bound with hyaluronic acid and NSAID, licensed from Seikagaku Corporation in September is in Phase III study for the treatment of osteoarthritis. Phase II study has newly started for the treatment of enthesopathy.

○ Phase I / II study with Opdivo has started for the treatment of sepsis.

■ **Overseas development pipeline (excluding Opdivo and including licensed-out compounds)**

○ We have obtained rights to develop and commercialize ONO-7702 (encorafenib), a BRAF inhibitor and ONO-7703 (binimetinib), a MEK inhibitor in Japan and South Korea, both licensed from Array in May. Phase III study is ongoing for the treatment of colorectal cancer and malignant melanoma in South Korea. Since the data has been already available for malignant melanoma, a filing for approval is under preparation.

■ **CheckMate -214 study: Combination therapy of Opdivo and ipilimumab for renal cell cancer**

○ In clinical study for combination therapy in patients with 1L renal cell cancer, data showing a superior overall survival (OS) of the combination therapy of Opdivo and ipilimumab compared to the standard of care, sunitinib was obtained with a hazard ratio of 0.63. A filing for approval in each country is under preparation.

○ A superior data has been obtained in patients with intermediate- and poor-risk patients (IMDC) having a poor outcome who were about 75% of the total patient population.

■ **CheckMate -238 study: Adjuvant therapy for Stage III/IV malignant melanoma patients**

○ In the result of Phase III study in adjuvant therapy in patients with malignant melanoma, which was presented at ESMO (European Society for Medical Oncology), Opdivo significantly improved recurrence-free survival, the primary endpoint, compared to ipilimumab, the standard of care. A filing for approval is under preparation with this result in each country including Japan where an application for approval will be filed shortly.

■ **ATTRACTION-4 study: 1L gastric cancer**

○ In the result from a Part of Phase II (conducted in the Part of Phase III and Phase II) in patients with 1L gastric cancer, which was presented at ESMO, Opdivo both in combination with SOX and CapeOX showed a control of disease progression.
(Blue line: treatment continued at cut-off point/ Red line: treatment interrupted at cut-off point)

○ We received comments from specialists that the data from the Part of Phase III could be also promising.

○ SOX therapy is a unique regimen in the Asian region and we believe that it is meaningful to bring the data on SOX therapy to Asian patient population.

■ **CheckMate -032 study: Combination study of Opdivo and ipilimumab for small cell lung cancer**

○ As for Tumor Mutation Burden (TMB/frequency of genetic mutation), which has recently been taken up as a new biomarker, the result of subgroup analysis of an exploratory Phase II study for small cell lung cancer was presented at the World Conference on Lung Cancer. The analysis result suggested that objective response rate was higher in the group with high TMB both in the Opdivo monotherapy and the Opdivo plus ipilimumab combination therapy.

○ Currently, Phase III studies are ongoing for small cell lung cancer in Opdivo alone and in combination therapy with Opdivo and ipilimumab. We are expecting the result from the studies.

■ **A Phase Ⅱ study of Opdivo in malignant pleural mesothelioma**

○ Data from Phase II study for malignant pleural mesothelioma was presented at the World Conference on Lung Cancer. Opdivo showed a high disease control rate of 67.6% and objective response rate of nearly 30% in the clinical study involving 34 patients in Japan.

○ Opdivo also showed a higher efficacy compared to the existing standard therapeutic drug in PFS (50%) and in OS (85%) at 6 months after treatment. While the data from the large scale clinical studies are very limited, the existing standard therapeutic drugs reveal about 3 months in PFS and about 8 to 9 months in the median OS.

○ We will collaborate and discuss with the PMDA based on this result to obtain an early approval for this patient population.

■ **Comprehensive drug therapy for cancer patients**

○ We are currently pursuing clinical development for 18 anti-cancer drugs including 2 XPO1 inhibitors licensed from Karyopharm in October and are engaged in identifying potential combination therapy as a "super regimen" for each cancer among them.

○ We are continuously promoting new collaboration activities and combination therapies, and committed to identifying the optimal combination therapies.

○ We are expecting further development of these 18 anti-cancer drugs including 5 in-house created products.

■ **Occurrence rate of body weight loss in each cancer**

○ We also expect ONO-7643, anamorelin, under development for cancer cachexia. While the occurrence rate may not always be in constant with the current situation because the data is rather old, it is known that there are many patients who lose weight in all cancers.

○ We are promoting development with ONO-7643 aimed at obtaining an approval for the indication of cancer cachexia in all cancers in Japan, ahead of the rest of the world.

■ **ONO-1162 / Ivabradine (Chronic heart failure)**

ONO-1162 is a selective If channel inhibitor for the treatment of chronic heart failure licensed from Selvier in France. It is characterized to decrease heart rate without affecting blood pressure. The estimated number of patients in Japan is about 1.5 million. We will introduce results of overseas Phase III and domestic Phase II studies.

■ **Main result of overseas Phase III studies**

○ In abroad, the results from Phase III studies are already available with a reliable high efficacy.

○ The product has the greatest feature to reduce only heart rate without affecting blood pressure at all. It is verified in the SHIFT study which is well known among doctors in the Cardiovascular Internal Medicine, that the product reduced the event-occurrence number in hospitalization due to cardiovascular death or deterioration of heart failure.

■ **Main result of domestic Phase II study**

○ The result of Phase II study is also available in Japan. The data to decrease heart rate was obtained, like those seen in overseas study. Currently, we are conducting clinical study at the final stage and are aiming at early launch in Japan.

■ **ONO-5704/SI-613**

○ ONO-5704, chemically bound with hyaluronic acid and NSAID licensed from Seikagaku Corporation, is already under Phase III study for osteoarthritis.

○ The domestic market size of the hyaluronic acid product is ¥40 to 50 billion. We are aiming at an early launch.