Overview of Development Pipeline Progress Status
for the 2nd Quarter of the Fiscal Year Ending March 31, 2019

1. Development progress status of Opdivo (Update from May 2018)

- In Japan, Opdivo was approved for the adjuvant therapy of malignant melanoma, as well as the 1st line treatment of renal cell carcinoma (RCC) in combination with ipilimumab.

- In Europe, Opdivo was also approved for the adjuvant therapy of malignant melanoma. In the US, a supplemental application for Opdivo was submitted for the 1st line treatment of non-small cell lung cancer (NSCLC), based on the data in the patient population with high TMB in the CheckMate-227 study.

- In South Korea and Taiwan, Opdivo was approved for the 1st line treatment of RCC in combination with ipilimumab.

- As for the 3rd line treatment of small cell lung cancer (SCLC), it was granted under accelerated approval without making the result of Phase III clinical study available. In the Phase III for the 2nd line treatment of SCLC (CheckMate-331 study), it did not meet its primary endpoint of overall survival with Opdivo.

- Opdivo was first approved for the treatment of malignant pleural mesothelioma in Japan anywhere in the world.

- Phase III clinical study with Opdivo was initiated for the treatment of ovarian cancer in combination with a PARP inhibitor in Europe and the US.

- As for pancreatic cancer, because a potential efficacy of Opdivo was shown in combination therapy with anti-CSF-1R antibody, Phase II clinical study was started to confirm the efficacy in Europe, the US, Japan, South Korea and Taiwan.

2. Opdivo combination therapy with Immune-Oncology (I-O) compounds (Update from May 2018)

2.1 Opdivo combination therapy with ipilimumab

- Opdivo was approved for the 1st line treatment of malignant melanoma and RCC in combination therapy with ipilimumab in Japan, South Korea and Taiwan.

- A supplemental application for Opdivo was submitted in the US for the 1st treatment of NSCLC in combination therapy with ipilimumab, based on the result of CheckMate-227 study.

- Following Opdivo monotherapy, an application for Opdivo was approved for the treatment of patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) colorectal cancer in combination with ipilimumab in the US.

2.2 Opdivo combination therapy with I-O compounds other than ipilimumab

- Phase II clinical study with Opdivo was started for the treatment of pancreatic cancer in combination with anti-CSF-1R antibody in Europe, the US, Japan, South Korea and Taiwan.

- Phase II/III clinical study with Opdivo was started for the treatment of malignant melanoma in combination with anti-LAG-3 antibody (relatlimab).

- Phase I clinical study with Opdivo was started in Japan for solid tumor, in combination with ONO-7475, an Axl/Mer inhibitor discovered internally at Ono, to investigate the efficacy on solid tumor. In the US, clinical development with ONO-7475 monotherapy is ongoing for blood cancer.

3. Development pipeline in Japan (Other compounds than Opdivo in oncology area)

- Approvals for ONO-7702 (encorafenib), a BRAF inhibitor, and ONO-7703 (binimetinib), a MEK inhibitor are expected within this year for the treatment of malignant melanoma under application in combination therapy.

- An approval for ONO-5371 (metyrosine) is also expected for the treatment of pheochromocytoma within this year.

- An application for ONO-7643 (anamorelin), under the final clinical stage, is expected to be submitted within this year for the treatment of cancer cachexia, which will be the first indication in the world.

- The combination therapy of encorafenib and binimetinib is at the final clinical stage for the treatment of colorectal cancer (CRC). BRAF mutations are expected to occur in 10 - 15% of patients with CRC. As CRC is one of the most common type of cancer, the products are expected to be the promising ones.

- Phase II clinical study of an anti-CSF-1R antibody was started in patients with pancreatic cancer in combination with Opdivo.

- Phase II clinical study of ONO-4059, a Btk inhibitor, was started in patients with primary macroglobulinemia and lymphoplasmacytic lymphoma. In addition, Phase I/II clinical study is ongoing in patients with central nervous system lymphoma. As this disease is classified into the orphan diseases, we consider to file an application for this compound as in early stage as possible.

- As ONO-4578, a Prostaglandin receptor (EP_4) antagonist, has shown a synergetic effect on solid tumors in combination with Opdivo in the result from non-clinical studies, Phase I clinical study with ONO-4578 was started for solid tumors in Japan.

4. Development pipeline in Japan (Outside oncology area)

- A supplemental application for Onoact was filed for the treatment of ventricular arrhythmia. An application for Rivastach is under filing for the formulation containing a new ingredient and is expected to be approved within this fiscal year.

- Phase III clinical study of ONO-1162 (ivabradine) is favorably ongoing for the treatment of chronic heart failure. An application is expected to be filed within this year.

- An application for ONO-2370 (opicapone) is expected to be submitted for the treatment of Parkinson's disease within this fiscal year.

- Phase I clinical study of ONO-7269, a FXIa inhibitor discovered internally at Ono, was started to be developed targeting at the treatment of cerebral infarction.

5. Development pipeline outside Japan (Compounds other than Opdivo and including out-licensed compounds)

- Ono has a right to develop ONO-7702 (encorafenib), a BRAF inhibitor, and ONO-7703 (binimetinib), a MEK inhibitor in South Korea, and has been developing these products for the treatment of malignant melanoma and colorectal cancer in South Korea.

- Phase II clinical study with anti-CSF-1R antibody was also started in patients with pancreatic cancer in combination with Opdivo in South Korea and Taiwan.

- Phase I/II clinical study of ONO-4578, a Prostaglandin receptor (EP_4) antagonist, was started in Europe and the US in combination with Opdivo.

- ONO-5788 is a somatostatin analogue to be considered for the treatment of acromegaly, etc. The currently available somatostatin has been used subcutaneously and intramuscularly. As this compound is developed as an orally available one, Phase I clinical study was started with its expected convenience.