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**ONO PHARMACEUTICAL CO., LTD.**
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# Human Anti-human PD-1 Monoclonal Antibody OPDIVO® Intravenous Infusion 20 mg/100 mg launches in Japan for Treatment of Unresectable Melanoma

Ono Pharmaceutical Co., Ltd. (Osaka, Japan; President, Representative Director and CEO, Gyo Sagara; "ONO") announced that sales of OPDIVO® Intravenous Infusion 20 mg/100 mg, a human anti-human PD-1 monoclonal antibody for the treatment of unresectable melanoma, started today in Japan.

Melanoma is considered to be a form of skin cancer characterized by the malignant transformation of pigment-producing cells located in the skin. In Japan, there has been an unmet medical need for an effective treatment for patients with unresectable melanoma, who have an extremely poor prognosis that no treatment exists to significantly improve.

OPDIVO® is a human anti-human PD-1 monoclonal antibody. PD-1 (programmed death-1), a receptor expressed on the surface of lymphocytes, plays a role in a regulatory pathway that suppresses activated lymphocytes in the body (negative signal). Available evidence suggests that cancer cells exploit this pathway to escape from immune responses. OPDIVO® is thought to provide benefit by blocking PD-1-mediated negative regulation of lymphocytes (i.e., the interaction of PD-1 with its ligands PD-L1 and PD-L2), thereby enhancing the ability of the immune system to recognize cancer cells as foreign and eliminate them. OPDIVO® is the world's first approved drug targeting PD-1.

Accumulating further clinical data is important in ensuring that OPDIVO® will be used more safely and effectively. ONO is committed to taking actions necessary for the proper use of OPDIVO® by implementing a post-marketing use-results survey (all-case surveillance) and collecting clinical data on the safety and efficacy of OPDIVO® pursuant to the conditions for its approval.

[About close of the pre-NHI reimbursement drug access program]
The pre-NHI reimbursement drug access program has been offered based on ethical considerations after manufacturing and marketing approval until the product is listed on the national health insurance (NHI) price list and at some limited medical institutions where Phase II clinical trials of OPDIVO® were performed. The program was closed in accordance with listing of NHI price.

Outline of OPDIVO® Intravenous Infusion 20 mg/100 mg

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| Product name | OPDIVO® Intravenous Infusion 20 mg/100 mg |
| Generic name (JAN) | Nivolumab (recombinant) |
| Indication or usage | Unresectable melanoma |
| Dosage and Administration | The recommended dose for adults is 2 mg/kg (body weight) of nivolumab administered as an intravenous infusion every 3 weeks. |
| Feature | 1. OPDIVO® is the world's first approved human IgG4 monoclonal antibody targeting PD-1.<br>2. OPDIVO® provides benefit by blocking PD-1-mediated negative regulation of lymphocytes (i.e., the interaction of PD-1 with its ligands PD-L1 and PD-L2), thereby enhancing the ability of the immune system to recognize cancer cells as foreign and eliminate them.<br>3. In this Japanese phase II study in advanced melanoma patients with a history of chemotherapeutic regimens including dacarbazine, 22.9% of patients (8/35 : 90%CI［13.4,36.2］) who received the drug at 2mg/kg showed an objective response (OR) by RECIST 1.1. Durable and ongoing responses were observed with a median overall survival of 473 days(90%CI［276.0,－］.<br>4. Number of patients who had adverse reactions was 30 patients(85.7%) in the Japanese Phase II study (35patients), which include pruritus (11patients, 31.4%), tri-iodothyronine free decreased (8patients, 22.9%), blood TSH increased (7patients, 20.0%), leukoderma (6patients, 17.1%), white blood cell count decreased (6patients,17.1%), thyroxine free decreased (6patients,17.1%), hypothyreoidism (5patients,14.3%), fatigue (5 patients,14.3%), aspartate aminotransferase increased(5 patients,14.3%),blood alkaline phosphatase increased(5 patients,14.3%),blood creatine phosphokinase increased(5 patients,14.3%),blood lactate dehydrogenase increased(5 patients,14.3%),c-reactive protein increased(5 patients,14.3%),lymphocyte count decreased(5 patients,14.3%), Diarrhoea(4patients,11.4%),alanine aminotransferase increased(4patients,11.4%),gamma-glutamyltransferase increased(4patients,11.4%),eosinophil count increased(4patients,11.4%),surfactant protein increased(4patients,11.4%)<br>and skin hypopigmentation(4patients,11.4%).As cases of serious adverse reaction, interstitial pneumonia, liver disorder, hepatitis, Thyroid dysfunction, infusion reaction were reported. |
| Package | OPDIVO® Intravenous Infusion 20 mg　2ml：1vial<br>OPDIVO® Intravenous Infusion 100 mg　10ml：1vial |
| NHI Price | （100 mg）729,849 yen/vial　（20 mg）150,200 yen/vial |
| NHI Price listed date | September 2, 2014 |
| Launch date | September 2, 2014 |
| Conditions for approval | Because of the very limited number of patients treated with OPDIVO® in Japanese clinical trials, ONO is required to perform a post-marketing use-results survey covering all cases until data on a certain minimum number of patients have been accumulated. Through these activities, ONO should identify the characteristics of patients to be treated with OPDIVO® and collect safety and efficacy data as soon as possible, thereby taking actions necessary to ensure the proper use of OPDIVO®. |


About the agreement for OPDIVO®.

OPDIVO® is a human anti-human PD-1 monoclonal antibody generated under a research collaboration entered into in May 2005 between ONO and the US-based company Medarex, Inc. When Medarex, Inc. was acquired by Bristol-Myers Squibb Company (“BMS”) in 2009, it also granted BMS its rights to develop and commercialize the human anti-human PD-1 monoclonal antibody in North America. Through the collaboration agreement entered into in September 2011 between ONO and BMS, ONO granted BMS exclusive rights to develop and commercialize OPDIVO® in the rest of the world, except in Japan, Korea and Taiwan where ONO had retained all rights to develop and commercialize the compound. On July 24, 2014, ONO and BMS signed a new collaboration agreement in which the companies agreed to jointly develop and commercialize OPDIVO®, ipilimumab and three early-stage immunotherapies in Japan, South Korea and Taiwan.