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ONO PHARMACEUTICAL CO., LTD.
Corporate Communications
Phone: +81-6-6263-5670

Fully Human Anti-PD-1 Antibody "ONO-4538/BMS-936558" Results from Phase 1 Study in Patients with Melanoma Presented at Annual Meeting of the American Society of Clinical Oncology (ASCO)

Bristol-Myers Squibb Company ("BMY") announced the follow up results from Phase 1 combination study with Yervoy® (ipilimumab) in patients with melanoma was presented at 50th annual meeting of the American Society of Clinical Oncology (ASCO), on June 2 (US time).

ONO-4538/BMS-936558, a fully human anti-PD-1 antibody, is an investigational cancer immunotherapy generated under a research collaboration entered into in May 2005 between Ono Pharmaceutical Co., Ltd. ("Ono") and Medarex, Inc. When Medarex, Inc. was acquired by BMY in 2009, it also granted BMY its rights to develop and commercialize the anti-PD-1 antibody in North America. Through the collaboration agreement entered into in September 2011 between Ono and BMY, Ono granted BMY exclusive rights to develop and commercialize ONO-4538/BMS-936558 in the rest of the world, except in Japan, Korea and Taiwan where Ono has retained all rights to develop and commercialize the compound.

BMY is conducting studies in NSCLC, RCC, melanoma, head and neck carcinoma, hematologic malignancies, glioblastoma, colon cancer, pancreatic cancer and gastric cancer and so on in the overseas countries where BMY has the rights to develop and commercialize the compound.
On the other hand, in Japan, Ono filed an application to obtain a manufacturing and marketing approval for treatment of melanoma in Dec 2013. Also Ono is conducting Phase 2 studies in NSCLC and esophageal cancer, and a global Phase 3 study in RCC.

Attached from the following page is the press release made by BMY for your information.

One- & Two-Year Survival Rates of 94% and 88% Announced from Phase 1b Trial of Investigational PD-1 Checkpoint Inhibitor Nivolumab and *Yervoy*® (ipilimumab) in Advanced Melanoma; Ongoing Phase 2/3 Trials to Confirm Results

(PRINCETON, NJ, June 2, 2014) – Bristol-Myers Squibb Company (NYSE: BMY) today announced follow up results from Study -004, a multi-arm Phase 1b dose-ranging trial evaluating the safety and activity of the combination regimen of nivolumab, an investigational PD-1 immune checkpoint inhibitor, and *Yervoy*® (ipilimumab) given either concurrently or sequentially in patients with advanced melanoma (n=127). After an additional year of follow up of the cohort that received the concurrent combination regimen of nivolumab 1 mg/kg plus *Yervoy* 3mg/kg (n=17), the one-year overall survival (OS) rate was 94% and the two-year OS rate was 88%. These are the doses used in the ongoing Phase 2 and Phase 3 trials, CheckMate -069 and -067. No new safety signals were reported in the concurrent combination cohorts with additional follow up (n=53) and grade 3-4 treatment-related adverse events (AEs) occurred in 62% of patients. The most common were asymptomatic increases in lipase (15%), ALT (12%) and AST (11%). These data will be presented today at the 50th Annual Meeting of the American Society of Clinical Oncology (ASCO) and featured during an ASCO press briefing at 8 a.m. CDT (Abstract # LBA9003).

"The treatment of advanced melanoma has changed dramatically in the last few years, but there continues to be a need to increase the number of patients who experience a long-term survival benefit," said Dr. Mario Sznol, Yale University School of Medicine and Yale Cancer Center, presenter of the results. "While these are Phase 1b data, the duration of response and one- and two-year survival rates observed with the combination regimen of nivolumab and *Yervoy* are very encouraging and support the rationale for the ongoing, late stage trials of this combination regimen."

"The science of immuno-oncology – harnessing the patient's immune system to treat cancer – is rapidly evolving," said Michael Giordano, senior vice president, Head of Development, Oncology & Immunology at Bristol-Myers Squibb. "These results are the most advanced data set to date evaluating the potential of combining immunotherapies. As leaders in the field, they reinforce our aspiration that combining immunotherapies may be foundational and may have the potential to change the standard of care by transforming survival expectations."

Results from Phase 1b Combination Regimen (Study -004)

Study 004 is a dose-ranging Phase 1 study (n=127) evaluating the safety, antitumor activity and pharmacokinetics of the combination regimen of nivolumab and *Yervoy* given concurrently or

sequentially in patients with advanced melanoma. Prior to enrollment, patients could have received up to three systemic therapies.

In the concurrent regimen cohort (n=53), eligible patients received nivolumab and *Yervoy* every three weeks for four doses, followed by nivolumab alone every three weeks for four doses. This concurrent combination regimen treatment was subsequently continued every 12 weeks for up to eight doses. Cohorts of a maximum of seventeen patients per dose level were enrolled (nivolumab 0.3 mg/kg + *Yervoy* 3 mg/kg [n=14]; nivolumab 1 mg/kg + *Yervoy* 3 mg/kg [n=17]; nivolumab 3 mg/kg + *Yervoy* at an investigational dose of 1 mg/kg [n=16]; nivolumab 3 mg/kg + *Yervoy* 3 mg/kg [n=6]). In an expansion cohort (n=41), eligible patients received the concurrent combination regimen of nivolumab 1 mg/kg and *Yervoy* 3 mg/kg every three weeks for four doses, followed by nivolumab alone at 3 mg/kg every two weeks until progression, which is the same schedule utilized in the ongoing Phase 2 and Phase 3 trials. In the sequenced regimen cohort (n=33), patients previously treated with *Yervoy* received nivolumab alone at 1 mg/kg or 3 mg/kg every two weeks.

Results from this trial were first published in the *New England Journal of Medicine* and presented at ASCO in 2013. The updated data, including those shown below, are based on a median follow up of 22 months and reflect an additional year of follow up from patients initially enrolled in the trial.

Efficacy Summary: Concurrent and Sequenced Cohorts

Nivolumab (mg/kg) + Yervoy (mg/kg) [n]	ORR, %	CR, %	1-Year OS, %	2-Year OS, %
Concurrent Cohorts [53]	42	17	85	79
0.3 + 3 [14]	21	14	57	50
1 + 3 [17]	53	18	94	88
3 + 1 [16]	44	25	94	NC
3 + 3 [6]	50	0	100	NC
Expansion 1 + 3 [41]	43	10**	NC	NC
Sequenced Cohort [33]	31	3	70 [23]	NC

NC: Not calculated/insufficient follow up; ORR: objective response rate; CR: complete response

***Two unconfirmed responses*

Responses were observed regardless of BRAF mutational status or PD-L1 expression.

No new safety signals were reported with additional follow up. Grade 3-4 treatment-related AEs occurred in 62% of patients in the concurrent cohorts, managed with standard algorithms. The most common were asymptomatic increases in lipase (15%), ALT (12%) and AST (11%). Twenty-two

patients (23%) discontinued treatment due to related AEs. There was one drug-related death due to fatal multi-organ failure following an initial event of colitis.

About Advanced Melanoma

Melanoma is a form of skin cancer characterized by the uncontrolled growth of pigment-producing cells (melanocytes) located in the skin. Metastatic melanoma is the deadliest form of the disease, and occurs when cancer spreads beyond the surface of the skin to other organs, such as the lymph nodes, lungs, brain or other areas of the body. The incidence of melanoma has been increasing for at least 30 years. In 2012, an estimated 232,130 melanoma cases were diagnosed globally. Melanoma is mostly curable when treated in its early stages. However, in its late stages, the average survival rate has historically been just six months with a one-year mortality rate of 75%, making it one of the most aggressive forms of cancer.

About Bristol-Myers Squibb Immuno-Oncology Trials in Melanoma

Bristol-Myers Squibb is committed to the research and development of immuno-oncology as an innovative approach to treating melanoma and has a broad development program evaluating its approved and investigational immunotherapies – either as single agents or as part of a regimen - across lines of therapy, stages of disease and biomarker expression. Among these are five Phase 3 trials. There are two ongoing Phase 3 trials evaluating nivolumab as a single agent at the 3 mg/kg dose in treatment-naïve patients (CheckMate -066) as well as in patients who have been previously treated (CheckMate -037). A Phase 3 trial evaluating *Yervoy* 3 mg/kg vs. *Yervoy* 10 mg/mg in patients with previously treated or treatment-naïve metastatic melanoma is ongoing (Study -169) and the first results of a Phase 3 trial evaluating the investigational use of *Yervoy* 10 mg/kg in patients with Stage 3 melanoma who are at high risk of recurrence following complete surgical resection (Study -029) will be featured today during an ASCO press briefing at 8 a.m. CDT and presented in an oral session at 3 p.m. CDT (Abstract #LBA9008). Additionally, a Phase 3 trial evaluating the combination regimen of nivolumab and *Yervoy* in treatment-naïve patients is ongoing (CheckMate -067).

About Nivolumab and *Yervoy*

Cancer cells may exploit “regulatory” pathways, such as checkpoint pathways, to hide from the immune system and shield the tumor from immune attack. Nivolumab and *Yervoy* are both monoclonal antibodies and immune checkpoint inhibitors, but target different receptors for distinct T-cell checkpoint pathways.

Nivolumab is an investigational, fully-human PD-1 immune checkpoint inhibitor that binds to the checkpoint receptor PD-1 (programmed death-1) expressed on activated T-cells. We are investigating whether by blocking this pathway, nivolumab would enable the immune system to resume its ability to recognize, attack and destroy cancer cells.

Bristol-Myers Squibb has a broad, global development program to study nivolumab in multiple tumor types consisting of more than 35 trials – as monotherapy or in combination with other therapies – in which more than 7,000 patients have been enrolled worldwide. Among these are several potentially registrational trials in non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma (RCC), head and neck cancer, glioblastoma and non-Hodgkin lymphoma. In 2013, the FDA granted Fast Track designation for nivolumab in NSCLC, melanoma and RCC. Last month, the FDA granted nivolumab Breakthrough Therapy Designation for the treatment of patients with Hodgkin lymphoma after failure of autologous stem cell transplant and brentuximab.

Yervoy, which is a recombinant, human monoclonal antibody, blocks the cytotoxic T- lymphocyte antigen-4 (CTLA-4). CTLA-4 is a negative regulator of T-cell activation. Ipilimumab binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation. The mechanism of action of ipilimumab's effect in patients with melanoma is indirect through T-cell mediated anti-tumor immune responses. On March 25, 2011, the FDA approved *Yervoy* 3 mg/kg monotherapy for patients with unresectable or metastatic melanoma. *Yervoy* is now approved in more than 40 countries.

Immuno-Oncology at Bristol-Myers Squibb

Surgery, radiation, cytotoxic or targeted therapies have represented the mainstay of cancer treatment over the last several decades, but long-term survival and a positive quality of life have remained elusive for many patients with advanced disease. To address this unmet medical need, Bristol-Myers Squibb is leading advances in a rapidly evolving field of cancer research and treatment known as immuno-oncology, which involves agents whose primary mechanism is to work directly with the body's immune system to fight cancer. This includes conducting research on the potential of combining immuno-oncology agents that target different and complementary pathways in the treatment of cancer.

Bristol-Myers Squibb is committed to advancing the science of immuno-oncology, with the goal of changing survival expectations and the way patients live with cancer.

About the Bristol-Myers Squibb and Ono Pharmaceutical Partnership

Through a collaboration agreement with Ono Pharmaceutical in 2011, Bristol-Myers Squibb expanded its territorial rights to develop and commercialize nivolumab (BMS-936558/ONO-4538) globally except in Japan, Korea and Taiwan where Ono has retained all rights to the compound.