

**Interim Phase 1/2 Data Show Encouraging Clinical Benefit for Lirilumab in Combination With *Opdivo* (Nivolumab) in Patients With Advanced Platinum Refractory Squamous Cell Carcinoma of the Head and Neck**

*Objective response rate (ORR) was 24% in 29 evaluable patients and increased in inflamed (PD-L1 positive) tumors, with ORR of 41% in patients with  $\geq 1\%$  PD-L1 expression*

*No significant added toxicity over nivolumab monotherapy observed*

*First disclosure of data for clinical activity with the combination of anti-KIR and anti-PD-1 therapy will include results for diverse biomarker subgroups*

(PRINCETON, N.J., and MARSEILLE, France, November 12, 2016) – [Bristol-Myers Squibb Company](#) (NYSE:BMJ) and [Innate Pharma SA](#) (Euronext Paris: FR0010331421 – IPH) today announced an interim efficacy analysis from a Phase 1/2 study of the combination of lirilumab and *Opdivo* (nivolumab) in the cohort of advanced platinum refractory squamous cell carcinoma of the head and neck (SCCHN), including exploratory biomarker analyses of patient response by level of PD-L1 expression. Among 29 evaluable patients with SCCHN, the objective response rate (ORR), a secondary endpoint measured by Response Evaluation Criteria In Solid Tumors (RECIST), was 24% (n=7). Seventeen percent (n=5) of these evaluable patients had deep responses, with reductions in tumor burden greater than 80%. Early signals of enhanced clinical benefit were observed in PD-L1 positive tumors, with an ORR of 41% (7/17) in patients with  $\geq 1\%$  PD-L1 expression.

Lirilumab is directed against the inhibitory killer-cell immunoglobulin-like receptors (KIRs) expressed predominantly on natural killer (NK) cells, which belong to the innate immune system, while *Opdivo* blocks the inhibitory function of the PD-1 receptor on T cells. These data mark the first report of potential efficacy with an anti-KIR antibody in combination with an anti-PD-1 therapy, and were presented at a late-breaking oral presentation (abstract 456) at the Society for Immunotherapy of Cancer (SITC) 31 Annual Meeting on November 12 at 11:15 a.m. EST in National Harbor, Maryland.

Preliminary efficacy and exploratory biomarker analyses of patient response by biomarker subgroups were presented.

The safety profile associated with lirilumab in combination with *Opdivo* was generally consistent with that observed with *Opdivo* monotherapy. The overall rate of treatment-related adverse events (TRAEs) was reported as 72% (114/159) and the rate of Grade 3-4 TRAEs was 15% (24/159).

Discontinuations due to TRAEs occurred in 8% of patients (12/159). These safety data were also reported at the 2016 European Society for Medical Oncology (ESMO) Congress.

“The interim efficacy results indicate that targeting both the KIR and PD-1 pathways with lirilumab and *Opdivo*, respectively, may provide enhanced clinical activity, particularly in PD-L1 positive tumors, with deep and durable responses in some patients,” said Rom Leidner, Medical Oncologist, Earle A. Chiles Research Institute, Providence Cancer Center, and lead author of the study. “We look forward to continuing the study of this novel combination in patients with advanced platinum refractory squamous cell carcinoma of the head and neck, which is the seventh-leading cause of cancer globally.”

“The preliminary signals of anti-tumor activity we are seeing with the combination of lirilumab and *Opdivo* in head and neck cancer patients compare favorably to data previously presented on *Opdivo* monotherapy in a similar patient population. We are encouraged by the suggestion of enhanced benefit, particularly in inflamed tumors as defined by increasing PD-L1 expression,” said Tim Reilly, head of Oncology Early Assets Development at Bristol-Myers Squibb. “We aim to apply what we have been learning about these complementary mechanisms and biomarker subgroups to maximize the potential clinical benefit of lirilumab and *Opdivo* across a range of tumor types and are excited about continuing to expand our study of *Opdivo* with complementary pathways.”

“We are very encouraged by these interim efficacy data and are eagerly awaiting the next steps of the clinical development of the combination of lirilumab and *Opdivo*” said Pierre Dodion, Chief Medical Officer of Innate Pharma. “These clinical data constitute crucial progress that validates our pioneering work on the role of innate immunity and NK cells in cancer. They support our ambition to be at the forefront of developing novel combination immunotherapies.”

**About CA223-001: A Phase 1/2 Dose Escalation and Cohort Expansion Study of the Safety, Tolerability and Efficacy of Anti-KIR (Lirilumab) Administered in Combination With Anti-PD-1 (Nivolumab) in Advanced Refractory Solid Tumors**

CA223-001 is a Phase 1/2 dose escalation and cohort expansion study of lirilumab in combination with nivolumab in 159 patients with advanced solid tumors. In this trial, patients received lirilumab (0.1, 0.3, 1.0, or 3.0 mg/kg) once every 4 weeks and nivolumab (3 mg/kg) once every 2 weeks.

During dose escalation, patients with advanced solid tumors who progressed after  $\geq 1$  prior therapy received lirilumab 0.1–3.0 mg/kg once every 4 weeks (Q4W) plus nivolumab 3.0 mg/kg Q2W. Cohort expansion was initiated at the maximum dose of lirilumab 3.0 mg/kg Q4W plus nivolumab 3.0 mg/kg

Q2W in patients with advanced solid tumors. The data reported at SITC pertain to an expansion cohort in SCCHN. Key study endpoints include safety (primary), objective response rate (ORR), disease control rate (DCR), duration of response (DOR), and biomarker assessments.

The purpose of this Phase 1/2 open label study is to determine the safety of the combination of lirilumab and nivolumab and to explore the preliminary anti-tumor activity of the combination in patients with a range of advanced solid tumors.

### **About Lirilumab (IPH2102/BMS-986015):**

Lirilumab is a fully human monoclonal antibody that is designed to act as a checkpoint inhibitor by blocking the interaction between KIR2DL-1,-2,-3 inhibitory receptors and their ligands. Blocking these receptors facilitates activation of NK cells and potentially some subsets of T cells, ultimately leading to destruction of tumor cells.

Lirilumab is licensed to Bristol-Myers Squibb Company. As part of the agreement with Innate Pharma, Bristol-Myers Squibb holds exclusive worldwide rights to develop, manufacture and commercialize lirilumab and related compounds blocking KIR receptors, for all indications. Under the agreement, Innate Pharma conducts the development of lirilumab through Phase II in acute myeloid leukemia (“AML”).

Innate Pharma is currently testing lirilumab in a randomized, double-blind, placebo-controlled Phase II trial as maintenance treatment in elderly patients with AML in first complete remission (“EffiKIR” trial). In addition, lirilumab is also being evaluated by Bristol-Myers Squibb in clinical trials in combination with other agents in a variety of tumor types.

### **About Head & Neck Cancer**

Cancers that are known as head and neck cancers usually begin in the squamous cells that line the moist mucosal surfaces inside the head and neck, such as inside the mouth, the nose and the throat. Head and neck cancer is the seventh most common cancer globally, with an estimated 400,000 to 600,000 new cases per year and 223,000 to 300,000 deaths per year. The five-year survival rate is reported as less than 4% for metastatic Stage IV disease. Squamous cell carcinoma of the head and neck (SCCHN) accounts for approximately 90% of all head and neck cancers with global incidence expected to increase by 17% between 2012 and 2022. Risk factors for SCCHN include tobacco and alcohol consumption. The Human Papilloma Virus (HPV) infection is also a risk factor leading to rapid increase in oropharyngeal SCCHN in Europe and North America. Quality of life is often impacted for SCCHN patients, as physiological

function (breathing, swallowing, eating, drinking), personal characteristics (appearance, speaking, voice), sensory function (taste, smell, hearing), and psychological/social function can be affected.

### **About Opdivo**

*Opdivo* is a programmed death-1 (PD-1) immune checkpoint inhibitor that is designed to uniquely harness the body's own immune system to help restore anti-tumor immune response. By harnessing the body's own immune system to fight cancer, *Opdivo* has become an important treatment option across multiple cancers.

*Opdivo*'s leading global development program is based on Bristol-Myers Squibb's scientific expertise in the field of Immuno-Oncology and includes a broad range of clinical trials across all phases, including Phase 3, in a variety of tumor types. To date, the *Opdivo* clinical development program has enrolled more than 25,000 patients. The *Opdivo* trials have contributed to gaining a deeper understanding of the potential role of biomarkers in patient care, particularly regarding how patients may benefit from *Opdivo* across the continuum of PD-L1 expression.

In July 2014, *Opdivo* was the first PD-1 immune checkpoint inhibitor to receive regulatory approval anywhere in the world. *Opdivo* is currently approved in more than 57 countries, including the United States, the European Union and Japan. In October 2015, the company's *Opdivo* and *Yervoy* combination regimen was the first Immuno-Oncology combination to receive regulatory approval for the treatment of metastatic melanoma and is currently approved in more than 47 countries, including the United States and the European Union.

### **U.S. FDA APPROVED INDICATIONS FOR OPDIVO®**

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. This indication is approved under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials

OPDIVO® (nivolumab) as a single agent is indicated for the treatment of patients with BRAF V600 wild-type unresectable or metastatic melanoma.

OPDIVO® (nivolumab), in combination with YERVOY® (ipilimumab), is indicated for the treatment of patients with unresectable or metastatic melanoma. This indication is approved

under accelerated approval based on progression-free survival. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) with progression on or after platinum-based chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving OPDIVO.

OPDIVO® (nivolumab) is indicated for the treatment of patients with advanced renal cell carcinoma (RCC) who have received prior anti-angiogenic therapy.

OPDIVO® (nivolumab) is indicated for the treatment of patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and post-transplantation brentuximab vedotin. This indication is approved under accelerated approval based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

OPDIVO® (nivolumab) is indicated for the treatment of patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) with disease progression on or after platinum-based therapy.

## **IMPORTANT SAFETY INFORMATION**

### **WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS**

**YERVOY can result in severe and fatal immune-mediated adverse reactions. These immune-mediated reactions may involve any organ system; however, the most common severe immune-mediated adverse reactions are enterocolitis, hepatitis, dermatitis (including toxic epidermal necrolysis), neuropathy, and endocrinopathy. The majority of these immune-mediated reactions initially manifested during treatment; however, a minority occurred weeks to months after discontinuation of YERVOY.**

**Assess patients for signs and symptoms of enterocolitis, dermatitis, neuropathy, and endocrinopathy and evaluate clinical chemistries including liver function tests (LFTs), adrenocorticotrophic hormone (ACTH) level, and thyroid function tests at baseline and before each dose.**

**Permanently discontinue YERVOY and initiate systemic high-dose corticosteroid therapy for severe immune-mediated reactions.**

### **Immune-Mediated Pneumonitis**

OPDIVO can cause immune-mediated pneumonitis. Fatal cases have been reported. Monitor patients for signs with radiographic imaging and for symptoms of pneumonitis. Administer

corticosteroids for Grade 2 or more severe pneumonitis. Permanently discontinue for Grade 3 or 4 and withhold until resolution for Grade 2. In patients receiving OPDIVO monotherapy, fatal cases of immune-mediated pneumonitis have occurred. Immune-mediated pneumonitis occurred in 3.1% (61/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated pneumonitis occurred in 6% (25/407) of patients.

In Checkmate 205 and 039, pneumonitis, including interstitial lung disease, occurred in 4.9% (13/263) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 3.4% (9/263) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=8).

### **Immune-Mediated Colitis**

OPDIVO can cause immune-mediated colitis. Monitor patients for signs and symptoms of colitis. Administer corticosteroids for Grade 2 (of more than 5 days duration), 3, or 4 colitis. Withhold OPDIVO monotherapy for Grade 2 or 3 and permanently discontinue for Grade 4 or recurrent colitis upon re-initiation of OPDIVO. When administered with YERVOY, withhold OPDIVO and YERVOY for Grade 2 and permanently discontinue for Grade 3 or 4 or recurrent colitis. In patients receiving OPDIVO monotherapy, immune-mediated colitis occurred in 2.9% (58/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated colitis occurred in 26% (107/407) of patients including three fatal cases.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal (diarrhea of  $\geq 7$  stools above baseline, fever, ileus, peritoneal signs; Grade 3-5) immune-mediated enterocolitis occurred in 34 (7%) patients. Across all YERVOY-treated patients in that study (n=511), 5 (1%) developed intestinal perforation, 4 (0.8%) died as a result of complications, and 26 (5%) were hospitalized for severe enterocolitis.

### **Immune-Mediated Hepatitis**

OPDIVO can cause immune-mediated hepatitis. Monitor patients for abnormal liver tests prior to and periodically during treatment. Administer corticosteroids for Grade 2 or greater transaminase elevations. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 immune-mediated hepatitis. In patients receiving OPDIVO monotherapy, immune-mediated hepatitis occurred in 1.8% (35/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated hepatitis occurred in 13% (51/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal hepatotoxicity (AST or ALT elevations  $>5x$  the ULN or total bilirubin elevations  $>3x$  the ULN; Grade 3-5) occurred in 8 (2%) patients, with fatal hepatic failure in 0.2% and hospitalization in 0.4%.

### **Immune-Mediated Neuropathies**

In a separate Phase 3 study of YERVOY 3 mg/kg, 1 case of fatal Guillain-Barré syndrome and 1 case of severe (Grade 3) peripheral motor neuropathy were reported.

### **Immune-Mediated Endocrinopathies**

OPDIVO can cause immune-mediated hypophysitis, immune-mediated adrenal insufficiency, autoimmune thyroid disorders, and Type 1 diabetes mellitus. Monitor patients for signs and symptoms of hypophysitis, signs and symptoms of adrenal insufficiency, thyroid function prior to and periodically during treatment, and hyperglycemia. Administer hormone replacement as clinically indicated and corticosteroids for Grade 2 or greater hypophysitis. Withhold for Grade 2 or 3 and permanently discontinue for Grade 4 hypophysitis. Administer corticosteroids for Grade 3 or 4 adrenal insufficiency. Withhold for Grade 2 and permanently discontinue for Grade 3 or 4 adrenal insufficiency. Administer hormone-replacement therapy for hypothyroidism. Initiate medical management for control of hyperthyroidism. Withhold OPDIVO for Grade 3 and permanently discontinue for Grade 4 hyperglycemia.

In patients receiving OPDIVO monotherapy, hypophysitis occurred in 0.6% (12/1994) of patients. In patients receiving OPDIVO with YERVOY, hypophysitis occurred in 9% (36/407) of patients. In patients receiving OPDIVO monotherapy, adrenal insufficiency occurred in 1% (20/1994) of patients. In patients receiving OPDIVO with YERVOY, adrenal insufficiency occurred in 5% (21/407) of patients. In patients receiving OPDIVO monotherapy, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 9% (171/1994) of patients. Hyperthyroidism occurred in 2.7% (54/1994) of patients receiving OPDIVO monotherapy. In patients receiving OPDIVO with YERVOY, hypothyroidism or thyroiditis resulting in hypothyroidism occurred in 22% (89/407) of patients. Hyperthyroidism occurred in 8% (34/407) of patients receiving OPDIVO with YERVOY. In patients receiving OPDIVO monotherapy, diabetes occurred in 0.9% (17/1994) of patients. In patients receiving OPDIVO with YERVOY, diabetes occurred in 1.5% (6/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe to life-threatening immune-mediated endocrinopathies (requiring hospitalization, urgent medical intervention, or interfering with activities of daily living; Grade 3-4) occurred in 9 (1.8%) patients. All 9 patients had hypopituitarism, and some had additional concomitant endocrinopathies such as adrenal insufficiency, hypogonadism, and hypothyroidism. 6 of the 9 patients were hospitalized for severe endocrinopathies.

### **Immune-Mediated Nephritis and Renal Dysfunction**

OPDIVO can cause immune-mediated nephritis. Monitor patients for elevated serum creatinine prior to and periodically during treatment. Administer corticosteroids for Grades 2-4 increased serum creatinine. Withhold OPDIVO for Grade 2 or 3 and permanently discontinue for Grade 4 increased serum creatinine. In patients receiving OPDIVO monotherapy, immune-mediated nephritis and renal dysfunction occurred in 1.2% (23/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated nephritis and renal dysfunction occurred in 2.2% (9/407) of patients.

### **Immune-Mediated Skin Adverse Reactions and Dermatitis**

OPDIVO can cause immune-mediated rash, including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), some cases with fatal outcome. Administer corticosteroids for Grade 3 or 4 rash. Withhold for Grade 3 and permanently discontinue for Grade 4 rash. For

symptoms or signs of SJS or TEN, withhold OPDIVO and refer the patient for specialized care for assessment and treatment; if confirmed, permanently discontinue. In patients receiving OPDIVO monotherapy, immune-mediated rash occurred in 9% (171/1994) of patients. In patients receiving OPDIVO with YERVOY, immune-mediated rash occurred in 22.6% (92/407) of patients.

In a separate Phase 3 study of YERVOY 3 mg/kg, severe, life-threatening, or fatal immune-mediated dermatitis (eg, Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations; Grade 3-5) occurred in 13 (2.5%) patients. 1 (0.2%) patient died as a result of toxic epidermal necrolysis. 1 additional patient required hospitalization for severe dermatitis.

### **Immune-Mediated Encephalitis**

OPDIVO can cause immune-mediated encephalitis. Evaluation of patients with neurologic symptoms may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. Withhold OPDIVO in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out other causes. If other etiologies are ruled out, administer corticosteroids and permanently discontinue OPDIVO for immune-mediated encephalitis. In patients receiving OPDIVO monotherapy, encephalitis occurred in 0.2% (3/1994) of patients. Fatal limbic encephalitis occurred in one patient after 7.2 months of exposure despite discontinuation of OPDIVO and administration of corticosteroids. Encephalitis occurred in one patient receiving OPDIVO with YERVOY (0.2%) after 1.7 months of exposure.

### **Other Immune-Mediated Adverse Reactions**

Based on the severity of adverse reaction, permanently discontinue or withhold treatment, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO the following clinically significant immune-mediated adverse reactions occurred in <1.0% of patients receiving OPDIVO: uveitis, iritis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barré syndrome, hypopituitarism, systemic inflammatory response syndrome, gastritis, duodenitis, sarcoidosis, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), myositis, myocarditis, rhabdomyolysis, motor dysfunction, vasculitis, and myasthenic syndrome.

### **Infusion Reactions**

OPDIVO can cause severe infusion reactions, which have been reported in <1.0% of patients in clinical trials. Discontinue OPDIVO in patients with Grade 3 or 4 infusion reactions. Interrupt or slow the rate of infusion in patients with Grade 1 or 2. In patients receiving OPDIVO monotherapy, infusion-related reactions occurred in 6.4% (127/1994) of patients. In patients receiving OPDIVO with YERVOY, infusion-related reactions occurred in 2.5% (10/407) of patients.



## **Complications of Allogeneic HSCT after OPDIVO**

Complications, including fatal events, occurred in patients who received allogeneic HSCT after OPDIVO. Outcomes were evaluated in 17 patients from Checkmate 205 and 039, who underwent allogeneic HSCT after discontinuing OPDIVO (15 with reduced-intensity conditioning, 2 with myeloablative conditioning). Thirty-five percent (6/17) of patients died from complications of allogeneic HSCT after OPDIVO. Five deaths occurred in the setting of severe or refractory GVHD. Grade 3 or higher acute GVHD was reported in 29% (5/17) of patients. Hyperacute GVHD was reported in 20% (n=2) of patients. A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in 35% (n=6) of patients. Two cases of encephalitis were reported: Grade 3 (n=1) lymphocytic encephalitis without an identified infectious cause, and Grade 3 (n=1) suspected viral encephalitis. Hepatic veno-occlusive disease (VOD) occurred in one patient, who received reduced-intensity conditioned allogeneic HSCT and died of GVHD and multi-organ failure. Other cases of hepatic VOD after reduced-intensity conditioned allogeneic HSCT have also been reported in patients with lymphoma who received a PD-1 receptor blocking antibody before transplantation. Cases of fatal hyperacute GVHD have also been reported. These complications may occur despite intervening therapy between PD-1 blockade and allogeneic HSCT.

Follow patients closely for early evidence of transplant-related complications such as hyperacute GVHD, severe (Grade 3 to 4) acute GVHD, steroid-requiring febrile syndrome, hepatic VOD, and other immune-mediated adverse reactions, and intervene promptly.

## **Embryo-Fetal Toxicity**

Based on their mechanisms of action, OPDIVO and YERVOY can cause fetal harm when administered to a pregnant woman. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with an OPDIVO- or YERVOY- containing regimen and for at least 5 months after the last dose of OPDIVO.

## **Lactation**

It is not known whether OPDIVO or YERVOY is present in human milk. Because many drugs, including antibodies, are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from an OPDIVO-containing regimen, advise women to discontinue breastfeeding during treatment. Advise women to discontinue nursing during treatment with YERVOY and for 3 months following the final dose.

## **Serious Adverse Reactions**

In Checkmate 037, serious adverse reactions occurred in 41% of patients receiving OPDIVO (n=268). Grade 3 and 4 adverse reactions occurred in 42% of patients receiving OPDIVO. The most frequent Grade 3 and 4 adverse drug reactions reported in 2% to <5% of patients receiving OPDIVO were abdominal pain, hyponatremia, increased aspartate aminotransferase, and increased lipase. In Checkmate 066, serious adverse reactions occurred in 36% of patients receiving OPDIVO (n=206). Grade 3 and 4 adverse reactions occurred in 41% of patients

receiving OPDIVO. The most frequent Grade 3 and 4 adverse reactions reported in  $\geq 2\%$  of patients receiving OPDIVO were gamma-glutamyltransferase increase (3.9%) and diarrhea (3.4%). In Checkmate 067, serious adverse reactions (73% and 37%), adverse reactions leading to permanent discontinuation (43% and 14%) or to dosing delays (55% and 28%), and Grade 3 or 4 adverse reactions (72% and 44%) all occurred more frequently in the OPDIVO plus YERVOY arm (n=313) relative to the OPDIVO arm (n=313). The most frequent ( $\geq 10\%$ ) serious adverse reactions in the OPDIVO plus YERVOY arm and the OPDIVO arm, respectively, were diarrhea (13% and 2.6%), colitis (10% and 1.6%), and pyrexia (10% and 0.6%). In Checkmate 017 and 057, serious adverse reactions occurred in 46% of patients receiving OPDIVO (n=418). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, pulmonary embolism, dyspnea, pyrexia, pleural effusion, pneumonitis, and respiratory failure. In Checkmate 025, serious adverse reactions occurred in 47% of patients receiving OPDIVO (n=406). The most frequent serious adverse reactions reported in  $\geq 2\%$  of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, among all patients (safety population [n=263]), adverse reactions leading to discontinuation (4.2%) or to dosing delays (23%) occurred. The most frequent serious adverse reactions reported in  $\geq 1\%$  of patients were infusion-related reaction, pneumonia, pleural effusion, pyrexia, rash and pneumonitis. Ten patients died from causes other than disease progression, including 6 who died from complications of allogeneic HSCT. Serious adverse reactions occurred in 21% of patients in the safety population (n=263) and 27% of patients in the subset of patients evaluated for efficacy (efficacy population [n=95]). In Checkmate 141, serious adverse reactions occurred in 49% of patients receiving OPDIVO. The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were pneumonia, dyspnea, respiratory failure, respiratory tract infections, and sepsis.

### **Common Adverse Reactions**

In Checkmate 037, the most common adverse reaction ( $\geq 20\%$ ) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions ( $\geq 20\%$ ) reported with OPDIVO (n=206) vs dacarbazine (n=205) were fatigue (49% vs 39%), musculoskeletal pain (32% vs 25%), rash (28% vs 12%), and pruritus (23% vs 12%). In Checkmate 067, the most common ( $\geq 20\%$ ) adverse reactions in the OPDIVO plus YERVOY arm (n=313) were fatigue (59%), rash (53%), diarrhea (52%), nausea (40%), pyrexia (37%), vomiting (28%), and dyspnea (20%). The most common ( $\geq 20\%$ ) adverse reactions in the OPDIVO (n=313) arm were fatigue (53%), rash (40%), diarrhea (31%), and nausea (28%). In Checkmate 017 and 057, the most common adverse reactions ( $\geq 20\%$ ) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 025, the most common adverse reactions ( $\geq 20\%$ ) reported in patients receiving OPDIVO (n=406) vs everolimus (n=397) were asthenic conditions (56% vs 57%), cough (34% vs 38%), nausea (28% vs 29%), rash (28% vs 36%), dyspnea (27% vs 31%), diarrhea (25% vs 32%), constipation (23% vs 18%), decreased appetite (23% vs 30%), back pain (21% vs 16%), and arthralgia (20% vs 14%). In Checkmate 205 and 039, among all patients (safety population [n=263]) and the subset of patients in the efficacy population (n=95), respectively, the most common adverse reactions ( $\geq 20\%$ ) were fatigue (32% and 43%), upper respiratory tract infection (28% and 48%), pyrexia

(24% and 35%), diarrhea (23% and 30%), and cough (22% and 35%). In the subset of patients in the efficacy population (n=95), the most common adverse reactions also included rash (31%), musculoskeletal pain (27%), pruritus (25%), nausea (23%), arthralgia (21%), and peripheral neuropathy (21%). In Checkmate 141, the most common adverse reactions ( $\geq 10\%$ ) in patients receiving OPDIVO were cough and dyspnea at a higher incidence than investigator's choice.

In a separate Phase 3 study of YERVOY 3 mg/kg, the most common adverse reactions ( $\geq 5\%$ ) in patients who received YERVOY at 3 mg/kg were fatigue (41%), diarrhea (32%), pruritus (31%), rash (29%), and colitis (8%).

### **Checkmate Trials and Patient Populations**

**Checkmate 067** - advanced melanoma alone or in combination with YERVOY; **Checkmate 037 and 066** - advanced melanoma; **Checkmate 017** - squamous non-small cell lung cancer (NSCLC); **Checkmate 057** - non-squamous NSCLC; **Checkmate 025** - renal cell carcinoma; **Checkmate 205/039** - classical Hodgkin lymphoma; **Checkmate 141** – squamous cell carcinoma of the head and neck.

[Please see U.S. Full Prescribing Information for OPDIVO and YERVOY, including \*\*Boxed WARNING\*\* regarding immune-mediated adverse reactions for YERVOY.](#)

### **About Bristol-Myers Squibb**

Bristol-Myers Squibb is a global biopharmaceutical company whose mission is to discover, develop and deliver innovative medicines that help patients prevail over serious diseases. For more information about Bristol-Myers Squibb, visit us at [BMS.com](http://BMS.com) or follow us on [LinkedIn](#), [Twitter](#), [YouTube](#) and [Facebook](#).

### **Bristol-Myers Squibb: At the Forefront of Immuno-Oncology Science & Innovation**

At Bristol-Myers Squibb, patients are at the center of everything we do. Our vision for the future of cancer care is focused on researching and developing transformational Immuno-Oncology (I-O) medicines that will raise survival expectations in hard-to-treat cancers and will change the way patients live with cancer.

We are leading the scientific understanding of I-O through our extensive portfolio of investigational and approved agents – including the first combination of two I-O agents in metastatic melanoma – and our differentiated clinical development program, which is studying broad patient populations across more than 20 types of cancers with 12 clinical-stage molecules designed to target different immune system pathways. Our deep expertise and innovative clinical trial designs uniquely position us to advance the science of combinations across multiple tumors and potentially deliver the next

wave of I-O combination regimens with a sense of urgency. We also continue to pioneer research that will help facilitate a deeper understanding of the role of immune biomarkers and inform which patients will benefit most from I-O therapies.

We understand making the promise of I-O a reality for the many patients who may benefit from these therapies requires not only innovation on our part, but also close collaboration with leading experts in the field. Our partnerships with academia, government, advocacy and biotech companies support our collective goal of providing new treatment options to advance the standards of clinical practice.

### **Bristol-Myers Squibb Forward Looking Statement**

*This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that Opdivo, Yervoy or any of the compounds mentioned in this release will receive regulatory approval for an initial or additional indication. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Bristol-Myers Squibb's business, particularly those identified in the cautionary factors discussion in Bristol-Myers Squibb's Annual Report on Form 10-K for the year ended December 31, 2015 in our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Bristol-Myers Squibb undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events or otherwise.*

### **About Innate Pharma**

Innate Pharma S.A. is a clinical-stage biotechnology company with a focus on discovering and developing first-in-class therapeutic antibodies that harness the innate immune system to improve cancer treatment and clinical outcomes for patients.

Innate Pharma specializes in immuno-oncology, a new therapeutic field that is changing cancer treatment by mobilizing the power of the body's immune system to recognize and kill cancer cells.

The Company's aim is to become a commercial stage biopharmaceutical company in the area of immunotherapy and focused on serious unmet medical needs in cancer. Innate Pharma has pioneered the discovery and development of checkpoint inhibitors to activate the innate immune system. Innate Pharma's innovative approach has resulted in three first-in-class, clinical-stage antibodies targeting natural killer cell receptors that may address a broad range of solid and hematological cancer indications as well as additional preclinical product candidates and technologies. Targeting receptors involved in

innate immunity also creates opportunities for the Company to develop therapies for inflammatory diseases.

The Company's expertise and understanding of natural killer cell biology have enabled it to enter into major alliances with leaders in the biopharmaceutical industry including AstraZeneca, Bristol-Myers Squibb, Novo Nordisk A/S and Sanofi.

Based in Marseille, France, Innate Pharma has more than 140 employees and is listed on Euronext Paris. Learn more about Innate Pharma at [www.innate-pharma.com](http://www.innate-pharma.com).

About Innate Pharma shares:

ISIN code      FR0010331421  
Ticker code    IPH

### **Innate Pharma Forward-Looking Statements:**

This press release contains certain forward-looking statements. Although the company believes its expectations are based on reasonable assumptions, these forward-looking statements are subject to numerous risks and uncertainties, which could cause actual results to differ materially from those anticipated. For a discussion of risks and uncertainties which could cause the company's actual results, financial condition, performance or achievements to differ from those contained in the forward-looking statements, please refer to the Risk Factors ("Facteurs de Risque") section of the Document de Reference prospectus filed with the AMF, which is available on the AMF website (<http://www.amf-france.org>) or on Innate Pharma's website.

This press release and the information contained herein do not constitute an offer to sell or a solicitation of an offer to buy or subscribe to shares in Innate Pharma in any country.

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