Bristol-Myers Squibb

La Commission européenne approuve *Opdivo* (nivolumab) de Bristol-Myers Squibb pour le carcinome urothélial localement avancé non résécable ou métastatique chez l'adulte après échec d'un précédent traitement à base de platine

Opdivo *est le premier et le seul agent immuno-oncologique à recevoir l'approbation européenne pour le traitement de ce type de cancer de la vessie*

Opdivo *est maintenant approuvé dans l'Union européenne pour huit indications dans six types de tumeur distincts*

(PRINCETON, New Jersey, 2 juin 2017) – Bristol-Myers Squibb Company (NYSE: BMY) a annoncé aujourd'hui que la Commission européenne (CE) a approuvé *Opdivo* (nivolumab) pour le traitement du carcinome urothélial localement avancé non résécable ou métastatique (CUm) chez l'adulte après échec d'un précédent traitement à base de platine. La décision de ce jour fait d'*Opdivo* le premier agent immuno-oncologique approuvé dans l'Union européenne pour le traitement de patients présentant ce type fréquent de cancer de la vessie.

« Les estimations pour le cancer de la vessie sont de 151 000 nouveaux cas diagnostiqués chaque année en Europe, mais les dernières décennies ont toutefois connu quelques progrès dans le traitement du cancer de la vessie avancé », a affirmé Prof. Dr Margitta Retz, directrice de la Division d'uro-oncologie du Département d'urologie, à l'Université technique de Munich, Allemagne. « L'approbation du nivolumab par la Commission européenne marque une avancée significative, avec un taux de réponse objective notable, et offre une option importante pour aider les patients atteints d'un cancer urothélial localement avancé non résécable ou métastatique précédemment traité. »

L'approbation s'est appuyée sur les résultats de CheckMate -275, une étude de phase II menée en ouvert, à un seul bras, multicentrique, évaluant *Opdivo* chez des patients présentant un cancer urothélial localement avancé ou métastatique (CUm) dont la maladie progresse pendant ou après un traitement par chimiothérapie à base de platine ou dont la maladie progresse dans les 12 mois qui suivent un traitement néo-adjuvant ou adjuvant par chimiothérapie à base de platine. Dans cette étude, 270 patients ont reçu 3 mg/kg d'*Opdivo* administré par voie intraveineuse toutes les deux semaines jusqu'à la progression de la maladie ou une toxicité inacceptable. Le critère de jugement principal de l'essai était le taux de réponse objective (TRO). Les critères d'évaluation secondaires comprenaient la survie sans progression (SSP) et la survie globale (SG). Dans l'essai, 20,0 % (IC à 95 % de 15,4 à 25,3 ; 54/270) des patients ont répondu au traitement par *Opdivo.* Le pourcentage de patients présentant une réponse complète était de 3,0 % (8/270) et le pourcentage de patients présentant une réponse partielle était de 17 % (46/270).

« Nous sommes heureux de l'approbation d'*Opdivo* par la Commission européenne pour les patients ayant un carcinome urothélial localement avancé non résécable ou métastatique précédemment traité, un grand nombre d'entre eux ayant nécessité une option thérapeutique supplémentaire », a déclaré Murdo Gordon, directeur général adjoint et délégué commercial en chef chez Bristol-Myers Squibb. « Avec cette deuxième approbation de l'UE pour *Opdivo* en l'espace de deux mois, Bristol-Myers Squibb prouve son engagement face aux besoins non satisfaits des patients atteints de cancer. Nous entendons coopérer étroitement avec les autorités de la santé de l'UE pour qu'*Opdivo* soit le plus tôt possible à la disposition des patients atteints de cette forme fréquente de cancer de la vessie. »

La moitié de la population globale des patients (46 %) de l'étude CheckMate -275 présentait une expression tumorale de PD-L1 ≥ 1 %, et l'efficacité a été observée tant chez les patients dont la tumeur exprimait PD-L1 que chez ceux sans expression de PD-L1. Le taux de réponse était de 25 % chez les patients avec une expression tumorale de PD-L1 ≥ 1 % (IC à 95 % de 17,7 à 33,6), et il était de 15,8 % (IC à 95 % de 10,3 à 22,7) chez les patients avec une expression tumorale de PD-L1 < 1 %. Chez tous les patients traités, la SSP médiane était de 2,0 mois, le taux de SG à 12 mois était de 41 % (IC à 95 % de 34,8 à 47,1) et la SG médiane était de 8,6 mois (IC à 95 % de 6,1 à 11,3).

Parmi les 270 patients qui ont reçu *Opdivo* dans l'étude CheckMate -275, 17,8 % ont développé un événement indésirable (EI) de grade 3 ou 4 en lien avec le traitement. Les EI de tous grades en lien avec le traitement qui ont été le plus fréquemment signalés étaient la fatigue (16,7 %), le prurit (9,3 %), la diarrhée (8,9 %), la diminution de l'appétit (8,1 %), l'hypothyroïdie (7,8 %), les nausées (7,0 %), l'asthénie (5,9 %), les rougeurs (5,9 %) et la fièvre (5,6 %). Les EI de grade 3-4 en lien avec le traitement qui ont été le plus fréquemment signalés étaient la fatigue (1,9 %), la diarrhée (1,9 %), l'asthénie (1,5 %) et les rougeurs (1,1 %). Dans l'ensemble, 4,8 % des patients ont arrêté le traitement en raison d'EI de tous grades en lien avec le traitement et 3,0 % ont arrêté le traitement en raison d'EI de grade 3-4 en lien avec le traitement. Le décès en lien avec le traitement est survenu chez quatre patients et était dû à une pneumonite ou à une insuffisance cardiovasculaire.

Au sujet du cancer de la vessie

Le cancer de la vessie, qui débute habituellement dans les cellules qui tapissent la paroi interne de la vessie, est le cinquième cancer le plus souvent diagnostiqué en Europe, le nombre de nouveaux cas étant estimé à 151 000 par an et le nombre de décès à 52 000 par an. Le carcinome urothélial est le type de cancer de la vessie le plus fréquent, représentant environ 90 % des cas. La majorité des cancers de la

vessie sont diagnostiqués à un stade précoce, mais les taux de récidive et de progression sont élevés, et environ 78 % des patients développeront une récidive dans les cinq ans. Les taux de survie varient en fonction du stade, du type de cancer et du moment où le diagnostic est posé. Pour le cancer de la vessie de stade IV, le taux de survie à cinq ans est de 15 %.

Bristol-Myers Squibb et l'immuno-oncologie : faire avancer la recherche en oncologie

Chez Bristol-Myers Squibb, les patients sont au centre de toutes nos activités. Notre vision pour le futur de la prise en charge du cancer se concentre sur la recherche et le développement de médicaments transformationnels en immuno-oncologie (I-O) pour des cancers difficiles à traiter, médicaments qui pourraient améliorer les résultats chez ces patients.

Nous sommes à la pointe des connaissances scientifiques en I-O grâce à notre portefeuille étendu de composés expérimentaux et d'agents approuvés. Notre programme de développement clinique différencié étudie de vastes populations de patients parmi plus de 50 types de cancers avec 14 molécules au stade clinique conçues pour cibler différentes voies du système immunitaire. Notre profonde expertise et nos conceptions innovantes dans les essais cliniques nous positionnent pour des traitements avancés I-O/I-O, I-O/chimiothérapie, I-O/thérapies ciblées et I-O/radiothérapies dans de nombreuses tumeurs et pour potentiellement apporter la nouvelle vague de traitements avec un sentiment d'urgence. Nous continuons aussi à être à la tête de la recherche qui contribuera à faciliter une connaissance plus approfondie du rôle des biomarqueurs immunologiques et de la manière dont la biologie tumorale individuelle des patients peut être utilisée comme guide dans les décisions thérapeutiques tout au long de leur parcours.

Nous comprenons que transformer en réalité la promesse que l'I-O représente pour les nombreux patients qui peuvent bénéficier de ces thérapies demande non seulement de l'innovation de notre part, mais aussi une étroite collaboration avec les principaux experts du domaine. Nos partenariats avec le monde universitaire, les gouvernements, les groupes de sensibilisation et les entreprises de biotechnologies soutiennent notre but commun d'apporter de nouvelles options de traitement pour faire avancer les standards de la pratique clinique.

Au sujet d'*Opdivo*

Opdivo est un inhibiteur des points de contrôle immunitaires de mort cellulaire programmée (programmed death-1, PD-1) qui est conçu pour utiliser uniquement le système immunitaire propre du

corps pour favoriser la restauration de la réponse immunitaire antitumorale. En employant le système immunitaire propre du corps pour lutter contre le cancer, *Opdivo* est devenu une option thérapeutique importante dans de nombreux cancers.

Le programme de développement mondial phare d'*Opdivo* se base sur l'expertise scientifique de Bristol-Myers Squibb dans le domaine de l'immuno-oncologie et inclut une vaste gamme d'essais cliniques de toutes phases, y compris des essais de phase III, dans divers types de tumeurs. A ce jour, le programme de développement clinique d'*Opdivo* a inclus plus de 25 000 patients. Les essais portant sur *Opdivo* ont contribué à comprendre plus profondément le rôle potentiel des biomarqueurs dans la prise en charge des patients, en particulier dans quelle mesure *Opdivo* peut bénéficier aux patients dans le continuum de l'expression de PD-L1.

En juillet 2014, *Opdivo* était le premier inhibiteur des points de contrôle immunitaires PD-1 à recevoir l'approbation réglementaire dans le monde. *Opdivo* est actuellement approuvé dans plus de 60 pays, dont les États-Unis, l'Union européenne et le Japon. En octobre 2015, le schéma thérapeutique de la firme associant *Opdivo* et *Yervoy* était la première association immuno-oncologique à recevoir l'approbation réglementaire pour le traitement du mélanome métastatique et est actuellement approuvé dans plus de 50 pays, dont les États-Unis et l'Union européenne.

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 adult patients with classical Hodgkin lymphoma (cHL) that has relapsed or progressed after autologous hematopoietic stem cell transplantation (HSCT) and brentuximab vedotin or after 3 or more lines of systemic therapy that includes autologous HSCT. 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.

OPDIVO® (nivolumab) is indicated for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

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), adrenocorticotropic 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 6.0% (16/266) of patients receiving OPDIVO. Immune-mediated pneumonitis occurred in 4.9% (13/266) of patients receiving OPDIVO: Grade 3 (n=1) and Grade 2 (n=12).

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 ≥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 ≥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 (≥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 ≥2% of patients were acute kidney injury, pleural effusion, pneumonia, diarrhea, and hypercalcemia. In Checkmate 205 and 039, adverse reactions leading to discontinuation occurred in 7% and dose delays due to adverse reactions occurred in 34% of patients (n=266). Serious adverse reactions occurred in 26% of patients. The most frequent serious adverse reactions reported in ≥1% of patients were pneumonia, infusion-related reaction, pyrexia, colitis or diarrhea, pleural effusion, pneumonitis, and rash. Eleven patients died from causes other than disease progression: 3 from adverse reactions within 30 days of the last OPDIVO dose, 2 from infection 8 to 9 months after completing OPDIVO, and 6 from complications of allogeneic HSCT. 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 infection, and sepsis. In Checkmate 275, serious adverse reactions occurred in 54% of patients receiving OPDIVO (n=270). The most frequent serious adverse reactions reported in at least 2% of patients receiving OPDIVO were urinary tract infection, sepsis, diarrhea, small intestine obstruction, and general physical health deterioration.

Common Adverse Reactions

In Checkmate 037, the most common adverse reaction (≥20%) reported with OPDIVO (n=268) was rash (21%). In Checkmate 066, the most common adverse reactions (≥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 (≥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 (≥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 (≥20%) in patients receiving OPDIVO (n=418) were fatigue, musculoskeletal pain, cough, dyspnea, and decreased appetite. In Checkmate 025, the most common adverse reactions (≥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, the most common adverse reactions (≥20%) reported in patients receiving OPDIVO (n=266) were upper respiratory tract infection (44%), fatigue (39%), cough (36%), diarrhea (33%), pyrexia (29%), musculoskeletal pain (26%), rash (24%), nausea (20%) and pruritus (20%). In Checkmate 141, the most common adverse reactions (≥10%) in patients receiving OPDIVO were cough and dyspnea at a higher incidence than investigator's choice. In Checkmate 275, the most common adverse reactions (≥ 20%) reported in patients receiving OPDIVO (n=270) were fatigue (46%), musculoskeletal pain (30%), nausea (22%), and decreased appetite (22%).

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

Please see U.S. Full Prescribing Information for OPDIVO and YERVOY, including **Boxed WARNING regarding immune-mediated adverse reactions for YERVOY.**

About the Bristol-Myers Squibb and Ono Pharmaceutical Co., Ltd. Collaboration

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., Ltd (Ono), Bristol-Myers Squibb expanded its territorial rights to develop and commercialize *Opdivo* globally except in Japan, South Korea and Taiwan, where Ono had retained all rights to the compound at the time. On July 23, 2014, Bristol-Myers Squibb and Ono further expanded the companies' strategic collaboration agreement to jointly develop and commercialize multiple immunotherapies – as single agents and combination regimens – for patients with cancer in Japan, South Korea and Taiwan.

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 or follow us on LinkedIn, Twitter, YouTube and Facebook.

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. 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, 2016 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.

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Contacts

Media:
Audrey Abernathy, 919-605-4521, audrey.abernathy@bms.com

Investors:
Tim Power, 609-252-7509, timothy.power@bms.com
Bill Szablewski, 609-252-5894, william.szablewski@bms.com