Europese Commissie keurt *Opdivo* (nivolumab) van Bristol-Myers Squibb goed voor plaveiselcelcarcinoom van het hoofd-halsgebied bij volwassenen die tijdens of na platinumhoudende therapie progressie vertonen

Opdivo *is het eerste en enige immuno-oncologische middel dat Europese goedkeuring krijgt voor de behandeling van plaveiselcelcarcinoom van het hoofd-halsgebied bij volwassenen die tijdens of na platinumhoudende therapie progressie vertonen*

Voor het eerst in meer dan tien jaar wordt in Europa een behandeling voor plaveiselcelcarcinoom van het hoofd-halsgebied goedgekeurd

Opdivo *is nu door de EC goedgekeurd voor zeven indicaties in vijf verschillende tumortypes*

Brussel, 29 mei 2017 – Bristol-Myers Squibb Company (NYSE: BMY) kondigt aan dat de Europese Commissie (EC) *Opdivo* (nivolumab) heeft goedgekeurd als monotherapie voor de behandeling van plaveiselcelcarcinoom van het hoofd-halsgebied (squamous cell cancer of the head and neck, SCCHN) bij volwassenen die tijdens of na platinumhoudende therapie progressie vertonen. *Opdivo* is de eerste en enige immuno-oncologische (I-O) behandeling die in een fase 3-onderzoek de totale overlevingskansen (overall survival, OS) van deze patiënten significant verbeterde.

"Volwassen patiënten met plaveiselcelcarcinoom van het hoofd-halsgebied die tijdens of na platinumhoudende therapie progressie vertonen, vechten tegen een slopende en moeilijk te behandelen ziekte met een uiterst slechte prognose," aldus Kevin Harrington, M.D., Ph.D., professor in de biologische kankerbehandelingen aan het Institute of Cancer Research in Londen, en consultant klinisch oncoloog van de Royal Marsden NHS Foundation Trust in Londen. "Als een oncoloog die patiënten helpt om met deze vreselijke ziekte om te gaan, hoop ik dat nivolumab nu zo ruim mogelijk beschikbaar zal worden gemaakt, zodat het voor deze patiëntengroep een nieuwe behandelingsoptie biedt die hun totale overleving mogelijk kan verbeteren."

De goedkeuring was gebaseerd op resultaten van CheckMate -141, een globaal, open-label, gerandomiseerd fase 3-onderzoek dat in oktober vorig jaar werd gepubliceerd in *The New England Journal of Medicine*. Dit onderzoek evalueerde *Opdivo* versus de door de onderzoeker gekozen behandeling bij patiënten van 18 jaar en ouder met recidiverend of gemetastaseerd, platinum-refractair SCCHN bij wie de tumor progressie vertoonde tijdens of in de zes maanden na platinumhoudende therapie die werd toegediend in adjuvante, neo-adjuvante, primaire of

gemetastaseerde setting. De door de onderzoeker gekozen behandeling bestond uit methotrexaat, docetaxel of cetuximab. Het primaire eindpunt was de totale overleving. De secundaire eindpunten van het onderzoek waren de progressievrije overleving (progression-free survival, PFS) en het objectieve responspercentage (objective response rate, ORR).

"De goedkeuring van *Opdivo* door de Europese Commissie zorgt niet alleen voor de eerste nieuwe behandelingsoptie in 10 jaar voor patiënten met gevorderd carcinoom van het hoofd-halsgebied, maar is ook de eerste immuno-oncologische behandeling voor SCCHN," aldus Scott Cooke, General Manager Benelux van Bristol-Myers Squibb. "Bristol-Myers Squibb blijft zich inzetten om de overleving van kankerpatiënten te verbeteren, en nu *Opdivo* in Europa is goedgekeurd, zullen we met de Europese gezondheidsautoriteiten samenwerken om ervoor te zorgen dat deze patiënten er zo snel mogelijk gebruik van kunnen maken."

In de tussentijdse analyse van het centrale onderzoek toonde *Opdivo* een statistisch significante verbetering van de OS met 30% afname van het risico op overlijden (HR=0,70 [95% BI: 0,53-0,92; *p*=0,0101]), en een mediane OS van 7,5 maanden (95% BI: 5,5-9,1) voor *Opdivo* in vergelijking met 5,1 maanden (95% BI: 4,0-6,0) voor de groep die de door de onderzoeker gekozen behandeling kreeg. Er waren geen statistisch significante verschillen tussen de twee groepen voor de PFS (HR=0,89; 95% BI: 0,70-1,13) of het ORR (13,3% [95% BI: 9,3-18,3] vs. 5,8% [95% BI: 2,4-11,6] voor respectievelijk *Opdivo* en de keuze van de onderzoeker. De goedkeuring van de EC was gebaseerd op de meest recente onderzoeksresultaten, die op de 53e jaarlijkse bijeenkomst van de American Society of Clinical Oncology (ASCO) zullen worden voorgesteld.

De door de patiënt gerapporteerde uitkomsten (patient reported outcomes, PROs) werden beoordeeld aan de hand van de door de European Organization for Research and Treatment of Cancer (EORTC) opgestelde meetinstrumenten voor de levenskwaliteit: EORTC QLQ-C30, EORTC QLQ-H&N35 en 3-level EQ-5D. Met *Opdivo* behandelde patiënten toonden stabiele PROs, terwijl patiënten die de door de onderzoeker gekozen behandeling kregen, een significante vermindering vertoonden van functioneren (bv. fysiek, sociaal en rolfunctioneren) en gezondheidstoestand en meer symptomen hadden (zoals vermoeidheid, dyspneu, verlies van eetlust, pijn en sensorische problemen).

Het veiligheidsprofiel van *Opdivo* in CheckMate-141 was consistent met eerdere studies bij patiënten met melanoom en niet-kleincellig longcarcinoom. Ernstige ongewenste voorvallen

traden op bij 49% van de met *Opdivo* behandelde patiënten. De meest frequente ernstige ongewenste voorvallen die bij minstens 2% van de met *Opdivo* behandelde patiënten werden gemeld, waren longontsteking, dyspneu, aspiratiepneumonie, ademhalingsfalen, luchtweginfectie en sepsis.

Over kanker van het hoofd-halsgebied

Carcinomen die tot de groep van hoofd-halskanker worden gerekend, beginnen gewoonlijk in de plaveiselcellen die de bovenste laag vormen van de slijmvliezen in het hoofd en de hals, zoals de binnenkant van de mond, neus en keel. Hoofd-halskanker is de zevende meest voorkomende kanker wereldwijd en geschat wordt dat er elk jaar 400.000 tot 600.000 nieuwe gevallen en 223.000 tot 300.000 sterfgevallen zijn. Het overlevingspercentage na vijf jaar wordt geschat op minder dan 4% voor gemetastaseerde ziekte in stadium IV. Plaveiselcelcarcinoom van het hoofd-halsgebied (squamous cell cancer of the head and neck, SCCHN) vertegenwoordigt ongeveer 90% van alle carcinomen van het hoofd-halsgebied en verwacht wordt dat tussen 2012 en 2022 de incidentie wereldwijd met 17% zal stijgen. Risicofactoren voor SCCHN zijn onder meer roken en alcoholconsumptie. Ook een infectie met het humaan papillomavirus (HPV) vormt een risicofactor die tot een snelle toename van orofaryngeale SCCHN in Europa en Noord-Amerika leidt.

Over *Opdivo*

Opdivo is een geprogrammeerde celdood-1 (PD-1) immuun checkpointremmer die werd ontworpen om op een unieke manier het eigen immuunsysteem van het lichaam te wapenen en het helpen de immuunrespons tegen tumoren te herstellen. Door het eigen immuunsysteem tegen kanker van het lichaam te wapenen, is *Opdivo* een belangrijke behandelingsoptie geworden bij verschillende soorten kanker.

Het belangrijkste wereldwijde ontwikkelingsprogramma van *Opdivo* is gebaseerd op de wetenschappelijke expertise van Bristol-Myers Squibb in het domein van immuno-oncologie en omvat een brede waaier aan klinische onderzoeken in alle mogelijk fasen, inclusief fase 3, bij verschillende soorten tumor. Tot op heden zijn in het klinisch ontwikkelingsprogramma met *Opdivo* meer dan 25.000 patiënten geregistreerd. De onderzoeken naar *Opdivo* hebben bijgedragen tot het verkrijgen van meer inzicht in de mogelijke rol van biomarkers in patiëntenzorg, meer

bepaald in hoe patiënten baat kunnen hebben bij *Opdivo* over het continuüm van PD-L1-expressie heen.

In juli 2014 was *Opdivo* de eerste PD-1 immuun checkpointremmer ter wereld die wettelijke goedkeuring kreeg. *Opdivo* is momenteel goedgekeurd in meer dan 60 landen, inclusief de Verenigde Staten, de Europese Unie en Japan. In oktober 2015 was het combinatieregime *Opdivo + Yervoy* van het bedrijf de eerste immuno-oncologische combinatie die wettelijk werd goedgekeurd voor de behandeling van gemetastaseerd melanoom en dit is momenteel goedgekeurd in meer dan 50 landen, inclusief de Verenigde Staten en de Europese Unie.

DOOR DE AMERIKAANSE FDA GOEDGEKEURDE INDICATIES VOOR OPDIVO®

OPDIVO® (nivolumab) als monotherapie is geïndiceerd voor de behandeling van patiënten met een niet-reseceerbaar of gemetastaseerd melanoom met een BRAF V600 mutatie. Deze indicatie is goedgekeurd volgens een versnelde goedkeuringsprocedure op basis van de progressievrije overleving. Een definitieve goedkeuring voor deze indicatie is mogelijk na verificatie en beschrijving van het klinisch voordeel in de bevestigende onderzoeken.

OPDIVO® (nivolumab) als monotherapie is geïndiceerd voor de behandeling van patiënten met een niet-reseceerbaar of gemetastaseerd melanoom met het BRAF V600 wild type.

OPDIVO® (nivolumab), in combinatie met YERVOY® (ipilimumab), is geïndiceerd voor de behandeling van patiënten met een niet-reseceerbaar of gemetastaseerd melanoom. Deze indicatie is goedgekeurd volgens een versnelde goedkeuringsprocedure op basis van de progressievrije overleving. Een definitieve goedkeuring voor deze indicatie is mogelijk na verificatie en beschrijving van het klinisch voordeel in de bevestigende onderzoeken.

OPDIVO® (nivolumab) is geïndiceerd voor de behandeling van patiënten met gemetastaseerd niet-kleincellig longcarcinoom (non-small cell lung cancer, NSCLC) die tijdens of na platinumhoudende chemotherapie progressie vertonen. Patiënten met EGFR of ALK genomische tumorafwijkingen moeten voorafgaand aan de toediening van OPDIVO ziekteprogressie vertonen tijdens een door de FDA goedgekeurde behandeling voor deze afwijkingen.

OPDIVO® (nivolumab) is geïndiceerd voor de behandeling van patiënten met gevorderd niercelcarcinoom (renal cell carcinoma, RCC) die voordien anti-angiogene therapie hebben gekregen.

OPDIVO® (nivolumab) is geïndiceerd voor de behandeling van patiënten met klassiek Hodgkin lymfoom (classical Hodgkin lymphoma, cHL) dat recidiveert of progressie vertoont na autologe hematopoëtische stamceltransplantatie (HSCT) en behandeling met brentuximab vedotin na de transplantatie. Deze indicatie is goedgekeurd volgens een versnelde goedkeuringsprocedure op basis van het totale responspercentage. Een definitieve goedkeuring voor deze indicatie is

mogelijk na verificatie en beschrijving van het klinisch voordeel in de bevestigende onderzoeken.

OPDIVO® (nivolumab) geïndiceerd voor de behandeling van patiënten met recidiverend of gemetastaseerd plaveiselcelcarcinoom van het hoofd-halsgebied (squamous cell carcinoma of the head and neck, SCCHN) die tijdens of na platinumhoudende therapie progressie vertonen.

OPDIVO® (nivolumab) is geïndiceerd voor de behandeling van patiënten met lokaal gevorderd of gemetastaseerd urotheliaal carcinoom die tijdens of na platinumhoudende chemotherapie of binnen de 12 maanden na neoadjuvante of adjuvante behandeling platinumhoudende chemotherapie progressie vertonen. Deze indicatie is goedgekeurd volgens een versnelde goedkeuringsprocedure op basis van het tumorresponspercentage en de duur van de respons. Een definitieve goedkeuring voor deze indicatie is mogelijk na verificatie en beschrijving van het klinisch voordeel in de bevestigende onderzoeken.

# # #

Over Bristol-Myers Squibb
Bristol-Myers Squibb België is een indirecte dochteronderneming volledig in handen van de Bristol-Myers Squibb Company, een biofarmaceutische onderneming op wereldniveau met als missie: het ontdekken, ontwikkelen en leveren van innovatieve geneesmiddelen, teneinde patiënten te helpen in de strijd tegen ernstige ziekten. Voor meer informatie, bezoek de website www.bms.be.

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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 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 ≥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, 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 ≥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. 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, among all patients (safety population [n=263]) and the subset of patients in the efficacy population (n=95), respectively, the most common adverse reactions (≥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 (≥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%).

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; **Checkmate 275** - urothelial carcinoma.

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.

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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.