Opdivo (nivolumab) toont een betere overleving na drie jaar voor patiënten met reeds eerder behandeld gevorderd niercelcarcinoom (RCC)

Opdivo *is de eerste PD-1-remmer waarmee een overlevingsvoordeel na drie jaar kan worden aangetoond bij gevorderd RCC. Daardoor daalt het sterfterisico met 26% in vergelijking tot everolimus in de fase 3 CheckMate -025 studie*

(Braine-l'Alleud, 28 november 2017) – Bristol-Myers Squibb (NYSE: BMY) kondigt een update aan van de totale overleving (OS) na drie jaar in zijn fase 3-studie CheckMate-025 bij patiënten die behandeld werden met *Opdivo* (nivolumab) versus everolimus omwille van een reeds eerder behandeld gevorderd niercelcarcinoom (RCC). Deze gegevens tonen, als allereerste ooit voor een PD-1-remmer, een duurzame overleving aan na drie jaar bij reeds eerder behandelde RCC. Er werden geen nieuwe veiligheidssignalen vastgesteld en de gegevens toonden een veiligheidsprofiel aan dat overeenkomt met de resultaten na twee jaar. De resultaten van CheckMate -025 werden op 4 november voorgesteld tijdens het 16de *International Kidney Cancer Symposium* (KCS) in Miami, Florida.

De mediane totale overleving, het primair eindpunt van deze studie, bedroeg voor *Opdivo* 25,8 maand, vergeleken met 19,7 maand voor everolimus (HR 0,74; 95,45% BI: 0,63 tot 0,88; p: 0,0005). De totale overleving na drie jaar was 39% voor *Opdivo* en 30% voor everolimus. Het veiligheidsprofiel van *Opdivo* stemde overeen met dat in voorgaande rapporten.

"De bijgewerkte resultaten van CheckMate -025 bekrachtigen het totale overlevingsvoordeel en het veiligheidsprofiel van *Opdivo* en blijven deze therapeutische keuze ondersteunen als standaardbehandeling voor patiënten met reeds eerder behandeld gevorderd niercelcarcinoom," zegt Padmanee Sharma, M.D., PhD., wetenschappelijk directeur, Immunotherapy Platform, MD Anderson Cancer Center.

Na 36 maand toonde *Opdivo* een objectief responscijfer (ORR), een secundair eindpunt, van 26% vergeleken met 5% voor everolimus (95% BI: 3,82 tot 10,06) en bedroeg de mediane responsduur voor *Opdivo* en voor everolimus respectievelijk 12,3 maand (95% BI: 9,1 tot 18,2) en 12 maand (95% BI: 6,4 tot 21,7). De mediane progressievrije overleving (PFS), een ander secundair eindpunt, was 4,2 maand voor *Opdivo* en 4,5 maand voor everolimus (HR 0,85; 95% BI: 0,73 tot 0,99; p: 0,0371).

"De gegevens van CheckMate -025 versterken *Opdivo* als standaardbehandeling bij reeds eerder behandeld gevorderd niercelcarcinoom, waarbij de gegevens na drie jaar een duurzaam

overlevingsvoordeel aantonen met *Opdivo*, wat meer dan zes maand beter is dan met everolimus," zegt Arvin Yang, M.D., Ph.D., hoofd ontwikkeling, melanoom en genito-urinaire kankers, Bristol-Myers Squibb. "Voortbouwend op de ongeziene totale overlevingsgegevens na twee jaar, zijn dit de eerste totale overlevingscijfers na drie jaar voor een PD-1-remmer bij gevorderd RCC. Zij vestigen de aandacht op onze voortdurende inzet voor de verbetering van de overlevingscijfers voor mensen met de meest voorkomende vorm van nierkanker bij volwassenen wereldwijd."

Over CheckMate -025

CheckMate -025 is een open-label, gerandomiseerde fase 3-studie met *Opdivo* versus everolimus bij patiënten met reeds eerder behandeld gevorderd niercelcarcinoom (RCC) na voorafgaande anti-angiogene behandeling. De patiënten (N=803) kregen hetzij *Opdivo* (N=406) 3 mg/kg intraveneus (IV) om de twee weken of everolimus (N=397) 10 mg oraal éénmaal daags tot ziekteprogressie of onaanvaardbare toxiciteit. Het primair eindpunt van de studie was de totale overleving (OS). De secundaire eindpunten waren het objectief responscijfer (ORR), de progressievrije overleving (PFS), de levenskwaliteit (QoL) en de veiligheid. De door patiënten gerapporteerde QoL werd gemeten aan de hand van de nier-specifieke *Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms* (FKSI-DRS) schaal en de *European Quality of Life* (EuroQol)-*5 Dimensions* (EQ-5D) vragenlijst.

Met een opvolging van ten minste drie jaar, waren de incidentie en het type behandelingsgerelateerde bijwerkingen samenhangend met de primaire analyse. In de *Opdivo*-groep ervoer 21% van de patiënten behandelingsgerelateerde graad 3/4 bijwerkingen en in de everolimus-groep 37%. Behandelingsgerelateerde bijwerkingen die aanleiding gaven tot stopzetting van de behandeling kwamen voor bij 8% van de patiënten in de *Opdivo*-groep en bij 13% van de patiënten in de everolimus-groep. De vaakst voorkomende graad 3/4 bijwerkingen in de *Opdivo*-groep waren van hepatische (3%) en gastro-intestinale (2%) aard. In de everolimus-groep waren de vaakst voorkomende graad 3/4 bijwerkingen van pulmonale (3%), gastro-intestinale (2%) en dermale (1%) aard. Er werden na drie jaar geen behandelingsgerelateerde overlijdens gemeld in de *Opdivo*-groep en twee behandelingsgerelateerde overlijdens in de everolimus-groep.

Over niercelcarcinoom

Niercelcarcinoom (RCC) is de vaakst voorkomende vorm van nierkanker bij volwassenen en is jaarlijks verantwoordelijk voor meer dan 100.000 doden wereldwijd. *Clear-cell* RCC is het meest

voorkomende type RCC en vertegenwoordigt 80% tot 90% van alle patiënten. RCC komt ongeveer tweemaal vaker voor bij mannen dan bij vrouwen, met de hoogste ziektecijfers in Noord-Amerika en in Europa. Wereldwijd bedraagt het overlevingscijfer na vijf jaar 12,1% voor personen met gemetastaseerde of gevorderde nierkanker.

Bristol-Myers Squibb & Immuno-Oncology: Vooruitgang in oncologisch onderzoek

Bij Bristol-Myers Squibb staan patiënten centraal in alles wat wij doen. Onze visie op de toekomst van de kankerzorg richt zich op het onderzoek en de ontwikkeling van transformationele Immuno-Oncologische (I-O) therapieën voor moeilijk te behandelen kankers om de uitkomsten voor deze patiënten mogelijks te kunnen verbeteren.

We zijn de leiders in wetenschappelijk inzicht in I-O dankzij onze uitgebreide portefeuille aan onderzoeks- en goedgekeurde geneesmiddelen. Ons gedifferentieerd programma voor klinische ontwikkeling onderzoekt brede patiëntenpopulaties met meer dan 50 types kanker met 14 moleculen in klinische onderzoeksfases, die ontworpen werden om verschillende banen van het immuunstelsel in het vizier te nemen. Onze diepgaande expertise en vernieuwende ontwerpen van onze klinische studies helpen ons om vooruitgang te boeken op vlak van I-O/I-O, I-O/chemotherapie, I-O/gerichte therapieën en I-O/radiotherapie bij meerdere tumoren en om spoedig de volgende stroom behandelingen aan te reiken. Wij blijven ook baanbrekend onderzoek verrichten voor een beter begrip van de rol van immunologische biomarkers en hoe de tumorbiologie van patiënten kan worden aangewend als leidraad voor behandelingsbeslissingen doorheen hun traject.

Wij weten dat, om de belofte van I-O waar te maken voor de vele patiënten die bij deze behandelingen baat kunnen hebben, niet enkel innovatie van onze kant vereist is, maar ook een nauwe samenwerking met topexperten uit het veld. Onze samenwerking met universiteiten, overheden, pleitbezorgers en biotechnologiebedrijven ondersteunt onze gezamenlijke doelstelling om nieuwe behandelingsmogelijkheden aan te bieden en zo de standaarden voor de klinische praktijk vooruit te helpen.

Over *Opdivo*

Opdivo is een "programmed death-1 (PD-1) immune checkpoint inhibitor" (remmer van de geprogrammeerde celdood-1-receptor) die ontwikkeld is om het eigen immuunsysteem op unieke wijze te wapenen teneinde de anti-tumor immuunrespons te helpen herstellen. Doordat *Opdivo* het eigen immuunsysteem wapent om kanker te bestrijden, vormt het een belangrijke behandelingsoptie voor meerdere kankertypes.

Het toonaangevende globale ontwikkelingsprogramma voor *Opdivo* is gebaseerd op de wetenschappelijke expertise van Bristol-Myers Squibb inzake immuno-oncologie en bestaat uit een brede waaier van klinische onderzoeken in alle fasen, waaronder fase 3, bij allerhande tumortypes. Tot dusver hebben meer dan 25.000 patiënten aan het klinische ontwikkelingsprogramma voor *Opdivo* deelgenomen. De onderzoeken met *Opdivo* hebben bijgedragen tot een beter inzicht in de mogelijke rol van biomerkers bij patiëntenzorg, vooral wat betreft de manier waarop zij voordeel uit *Opdivo* kunnen halen tijdens de volledige expressie van PD-L1.

In juli 2014 was *Opdivo* de eerste PD-1 immune checkpoint inhibitor die door regelgevende instanties wereldwijd werd goedgekeurd. Nu is *Opdivo* goedgekeurd in meer dan 60 landen, waaronder de Verenigde Staten, de Europese Unie en Japan. In oktober 2015 hebben regelgevende instanties de combinatietherapie *Opdivo* en *Yervoy* van het bedrijf als eerste immuno-oncologische combinatie goedgekeurd voor de behandeling van gemetastaseerde melanomen. Momenteel is ze goedgekeurd in meer dan 50 landen, waaronder de Verenigde Staten en de Europese Unie.

Over de samenwerking tussen Bristol-Myers Squibb en Ono Pharmaceutical Co., Ltd.

In 2011 breidde Bristol-Myers Squibb zijn territoriale rechten op de ontwikkeling en commercialisatie van Opdivo wereldwijd uit, met uitzondering van Japan, Zuid-Korea en Taiwan dankzij een samenwerkingsovereenkomst met Ono Pharmaceutical Co., Ltd (Ono), waarbij Ono op dat moment alle rechten op het product bleef behouden. Op 23 juli 2014 breidden Bristol-Myers Squibb en Ono hun strategische samenwerkingsovereenkomst uit om gezamenlijk verscheidene immunotherapieën– zowel afzonderlijke stoffen als combinatieschemata – te ontwikkelen en commercialiseren voor kankerpatiënten in Japan, Zuid-Korea en Taiwan.

# # #

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.com/be of volg ons op LinkedIn, Twitter, YouTube en Facebook.

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APPENDIX

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.

OPDIVO® (nivolumab) is indicated for the treatment of adult and pediatric (12 years and older) patients with microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. This indication is approved under accelerated approval based on overall response rate and

duration of response. 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 hepatocellular carcinoma (HCC) who have been previously treated with sorafenib. This indication is approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the 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. For patients without HCC, withhold OPDIVO for Grade 2 and permanently discontinue OPDIVO for Grade 3 or 4. For patients with HCC, withhold OPDIVO and administer corticosteroids if AST/ALT is within normal limits at baseline and increases to >3 and up to 5 times the upper limit of normal (ULN), if AST/ALT is >1 and up to 3 times ULN at baseline and increases to >5 and up to 10 times the ULN, and if AST/ALT is >3 and up to 5 times ULN at baseline and increases to >8 and up to 10 times the ULN. Permanently discontinue OPDIVO and administer corticosteroids if AST or ALT increases to >10 times the ULN or total bilirubin increases >3 times the ULN. 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 Checkmate 040, immune-mediated hepatitis requiring systemic corticosteroids occurred in 5% (8/154) of patients receiving OPDIVO.

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 the adverse reaction, permanently discontinue or withhold OPDIVO, administer high-dose corticosteroids, and, if appropriate, initiate hormone-replacement therapy. Across clinical trials of OPDIVO monotherapy or in combination with YERVOY, the following clinically significant immune-mediated adverse reactions, some with fatal outcome, occurred in <1.0% of patients receiving OPDIVO: myocarditis, rhabdomyolysis, myositis, 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), 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. In Checkmate 040, serious adverse reactions occurred in 49% of patients (n=154). The most frequent serious adverse reactions reported in at least 2% of patients were pyrexia, ascites, back pain, general physical health deterioration, abdominal pain, and pneumonia.

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 Checkmate 040, the most common adverse reactions (≥20%) in patients receiving OPDIVO (n=154) were fatigue (38%), musculoskeletal pain (36%), abdominal pain (34%), pruritus (27%), diarrhea (27%), rash (26%), cough (23%), and decreased appetite (22%). The most common adverse reactions (≥20%) in patients who received OPDIVO as a single agent were fatigue, rash, musculoskeletal pain, pruritus, diarrhea, nausea, asthenia, cough, dyspnea, constipation, decreased appetite, back pain, arthralgia, upper respiratory tract infection, and pyrexia.

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.**

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; **Checkmate 040** – hepatocellular carcinoma.

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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