Opdivo (nivolumab) améliore le bénéfice de survie à 3 ans chez les patients souffrant d'un carcinome à cellules rénales avancé après un traitement antérieur

Opdivo *est le premier inhibiteur de PD-1 à démontrer un bénéfice sur le plan de la survie à trois ans dans le carcinome à cellules rénales (CCR) avancé, l'étude CheckMate -025 de phase 3 ayant démontré qu'il diminue de 26% le risque de mortalité par rapport à l'évérolimus*

(Braine-l'Alleud, le 28 novembre, 2017) – Bristol-Myers Squibb (NYSE: BMY) a annoncé aujourd'hui une actualisation de la survie globale (SG) à trois ans suite à l'étude de phase 3 CheckMate-025 qui comparait des patients traités par Opdivo (nivolumab) et par l'évérolimus dans le carcinome à cellules rénales avancé après un traitement antérieur. Ces données démontrent pour la première fois qu'un inhibiteur de PD-1 s'accompagne d'une survie durable à trois ans dans le CCR à un stade avancé, après un traitement antérieur. Aucun nouveau signal mettant en cause la tolérance du produit n'a été observé et les données montrent un profil de tolérance qui correspond aux résultats observés après deux ans. Les résultats de l'étude CheckMate -025 ont été présentés le 4 novembre dernier au 16ème *International Kidney Cancer Symposium* qui a eu lieu à Miami (Floride).

La durée médiane de la survie globale (SG), principal critère de jugement dans cette étude, était de 25,8 mois avec *Opdivo* contre 19,7 mois avec l'évérolimus (HR 0,74; IC à 95,45%: 0,63 à 0,88; p: 0,0005). La SG à trois ans était de 39% pour *Opdivo* et de 30% pour l'évérolimus. Le profil de tolérance d'*Opdivo* concordait avec celui des rapports précédents.

Comme le déclare le Dr Padmanee Sharma, directeur scientifique, département d'immunothérapie du *MD Anderson Cancer Center* : "Les résultats actualisés de l'étude CheckMate -025 valident le bénéfice sur le plan de la survie globale et le profil de tolérance d'Opdivo. En outre, ils apportent un soutien supplémentaire à cette option thérapeutique en tant que traitement standard destiné aux patients souffrant d'un carcinome à cellules rénales avancé après un traitement antérieur. »

À 36 mois, *Opdivo* montrait un taux de réponse objective (TRO), critère de jugement secondaire, de 26% versus 5% avec l'évérolimus (IC à 95% : 3,82 à 10,06). La durée médiane de la réponse était de 12,3 mois (IC à 95% : 9,1 à 18,2) avec *Opdivo* et de 12 mois (IC à 95% : 6,4 à 21,7) avec l'évérolimus. La durée médiane de la survie sans progression (SSP), également critère de jugement secondaire, était de 4,2 mois avec *Opdivo* et de 4,5 mois avec l'évérolimus (HR 0,85; IC à 95% : 0,73 à 0,99; p: 0,0371).

Le Dr Arvin Yang, responsable du développement, mélanome et cancers uro-génitaux chez Bristol-Myers Squibb l'affirme : "les résultats de l'étude CheckMate -025 renforcent l'importance d'Opdivo en tant que traitement standard dans le carcinome à cellules rénales avancé après un traitement antérieur, les données à trois montrant un bénéfice continu sur le plan de la survie qui s'améliore de plus de six mois par rapport à l'évérolimus". Et d'ajouter : "s'appuyant sur les données de survie globale à deux ans, sans précédent, issues de cette étude, ce sont les premiers résultats sur le taux de survie globale à trois ans avec un inhibiteur de PD-1 dans le carcinome à cellules rénales avancé, ce qui met en valeur notre engagement continu à améliorer les taux de survie des personnes vivant avec la forme de cancer du rein de l'adulte la plus courante dans le monde."

Quelques mots sur l'étude CheckMate -025

CheckMate -025 est une étude de phase 3 randomisée, réalisée en ouvert, comparant *Opdivo* et évérolimus chez des patients souffrant d'un carcinome à cellules rénales avancé après un traitement anti-angiogénique antérieur. Les patients (n = 803) recevaient soit *Opdivo* (n = 406) à raison de 3 mg/kg injecté par voie intraveineuse (IV) toutes les deux semaines, soit l'évérolimus (n = 397) à raison de 10 mg par voie orale, une fois par jour, et ce, jusqu'à progression de la maladie ou apparition d'une toxicité inacceptable. La survie globale (SG) était le principal critère de jugement de cette étude. Les critères de jugement secondaires étaient le taux de réponse objective (TRO), la survie sans progression (SSP), la qualité de vie (QV) et la tolérance. La qualité de vie rapportée par le patient était mesurée à l'aide de l'échelle FKSI-DRS (*Functional Assessment of Cancer Therapy–Kidney Symptom Index–Disease Related Symptoms*) et du questionnaire EuroQol EQ-5D (*European Quality of Life -5 Dimensions).*

Avec un suivi de minimum trois ans, l'incidence et le type d'effets indésirables (EI) liés au traitement concordaient avec l'analyse primaire. Dans le groupe « *Opdivo* », 21% des patients ont présenté des effets indésirables de grade 3/4 liés au traitement versus 37% des patients dans le groupe « évérolimus ». Des effets indésirables liés au traitement ayant entraîné l'arrêt du traitement sont survenus chez 8% des patients du groupe « Opdivo » et chez 13% des patients du groupe « évérolimus ». Les effets indésirables de grade 3/4 les plus fréquemment observés dans le groupe « Opdivo » étaient de nature hépatique (3%) et digestive (2%). Dans le groupe « évérolimus », les effets indésirables de grade 3/4 les plus fréquemment observés étaient de nature respiratoire (3%), digestive (2%) et cutanée (1%). À trois ans, aucun décès lié au traitement n'avait été signalé dans le groupe « *Opdivo »* mais deux décès liés au traitement avaient été rapportés dans le groupe « évérolimus ».

Quelques mots sur le carcinome à cellules rénales

Le carcinome à cellules rénales (CCR) est le type de cancer du rein le plus fréquent chez l'adulte. Il est responsable chaque année de plus de 100 000 décès dans le monde. Le CCR à cellules claires est le type de CCR le plus courant et représente 80% à 90% de l'ensemble des cas de CCR. Le CCR est environ deux fois plus fréquent chez l'homme que chez la femme, l'incidence la plus élevée s'observant en Amérique du Nord et en Europe. À l'échelle mondiale, le taux de survie à cinq ans est de 12,1% chez les personnes atteintes d'un cancer du rein métastatique ou à un stade avancé.

Bristol-Myers Squibb & l'immuno-oncologie: la recherche en oncologie évolue

Chez Bristol-Myers Squibb, le patient est au cœur de toutes nos actions. Nous visons à concentrer tous nos efforts en matière de traitements anticancéreux sur la recherche et le développement de médicaments transformationnels en immuno-oncologie (I-O) qui pourraient potentiellement améliorer les résultats chez les patients atteints de cancers difficiles à traiter.

Nous sommes à la pointe des connaissances scientifiques en immuno-oncologie grâce à notre vaste portefeuille de produits d'investigation et de médicaments approuvés. Notre programme de développement clinique diversifié étudie de larges populations de patients pour plus de 50 types de cancer, avec 14 produits au stade de développement clinique, conçus pour cibler différentes voies du système immunitaire. Notre expertise solide et nos concepts d'essais cliniques innovants nous permettent de progresser en I-O/IO, IO/chimiothérapie, I-O/thérapies ciblées et I-O/radiothérapie pour de nombreux types de tumeurs et de fournir à court terme et de manière urgente, une nouvelle vague de traitements. Nous continuons également à mener des recherches pionnières afin de mieux comprendre le rôle des biomarqueurs immunitaires et la façon dont la biologie des tumeurs des patients peut être utilisée pour guider les décisions thérapeutiques tout au long de leur trajet.

Nous sommes conscients que pour que l'immuno-oncologie tienne ses promesses pour les nombreux patients qui peuvent bénéficier de ces traitements, nous devons non seulement être innovants mais également agir en étroite collaboration avec les meilleurs experts dans ce domaine. Nos partenariats avec le monde universitaire, les gouvernements, les groupes de sensibilisation et les entreprises de

biotechnologie soutiennent notre objectif commun d'offrir de nouvelles options thérapeutiques pour faire avancer les normes en matière de pratique clinique.

Quelques mots sur *Opdivo*

Opdivo est un inhibiteur du point de contrôle immunitaire PD-1 (*programmed death-1* ou mort cellulaire programmée 1) conçu pour exploiter de façon unique le système immunitaire de l'organisme pour restaurer l'immunité antitumorale. En exploitant le propre système immunitaire de l'organisme pour combattre le cancer, *Opdivo* est devenu une option thérapeutique majeure dans de nombreux cancers.

Le programme phare de développement mondial d'*Opdivo* s'appuie sur l'expertise scientifique de Bristol-Myers Squibb dans le domaine de l'immuno-oncologie et est composé d'un large éventail d'études cliniques à toutes les phases de développement, y compris des études de phase 3 dans plusieurs types de cancers. Actuellement, plus de 25 000 patients ont participé au programme de développement clinique d'*Opdivo*. Les études sur *Opdivo* ont permis de mieux comprendre le rôle potentiel des biomarqueurs dans le traitement des patients, et plus précisément la façon dont *Opdivo* pourrait aider les patients selon l'expression de la protéine PD-L1.

En juillet 2014, *Opdivo* était le premier inhibiteur du point de contrôle immunitaire PD-1 ayant reçu une autorisation réglementaire de mise sur le marché au niveau mondial. *Opdivo* est actuellement autorisé dans plus de 60 pays, dont les États-Unis, l'Union européenne et le Japon. En octobre 2015, les instances réglementaires ont approuvé l'association immuno-oncologique d'*Opdivo* plus *Yervoy* (de la même firme) dans le traitement du mélanome métastatique. Cette association est actuellement approuvée dans plus de 50 pays, y compris aux États-Unis et dans l'Union européenne.

A propos de la collaboration entre Bristol-Myers Squibb et Ono Pharmaceutical Co., Ltd.

En 2011, Bristol-Myers Squibb a élargi, par le biais d'un accord de coopération avec Ono Pharmaceutical Co., Ltd (Ono), ses droits territoriaux au développement et à la commercialisation mondiale d'Opdivo, sauf au Japon, en Corée du Sud et à Taïwan où Ono conservait en tout temps tous les droits sur ce médicament. Le 23 juillet 2014, Bristol-Myers Squibb et Ono ont élargi leur accord de collaboration stratégique pour développer et commercialiser conjointement plusieurs immunothérapies – seules et en associations thérapeutiques – pour les patients atteints d'un cancer au Japon, en Corée du Sud et à Taïwan.

A propos de Bristol-Myers Squibb Belgique

Bristol-Myers Squibb Belgique est une filiale indirecte appartenant en propriété exclusive à la Société Bristol-Myers Squibb, une société biopharmaceutique d'envergure mondiale dont la mission est de découvrir, de mettre au point et de fournir des médicaments novateurs ayant pour but d'aider les patients à combattre des maladies graves. Pour de plus amples renseignements, visitez le site www.bms.com/be ou suivez-nous sur 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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