Bristol-Myers Squibb krijgt een gunstig advies van het CHMP met de aanbeveling om *Opdivo* (nivolumab) goed te keuren als adjuvante behandeling voor volwassen patiënten met melanoom

Het eerste en enige PD-1-middel dat een positief advies van CHMP ontvangt in adjuvant kader

(Braine L'Alleud, 13 juli 2018) – Bristol-Myers Squibb Company (NYSE: BMY) kondigt aan dat het Comité voor geneesmiddelen voor menselijk gebruik (CHMP) van het Europees geneesmiddelenagentschap (EMA) aanbevolen heeft om de goedkeuring van de huidige indicaties van *Opdivo* (nivolumab) uit te breiden met de adjuvante behandeling van volwassen patiënten met melanoom met aantasting van de lymfeknopen of met gemetastaseerde ziekte en die een volledige resectie ondergaan hebben. Dit is de allereerste keer dat het CHMP een PD-1-remmer heeft aanbevolen als adjuvante behandeling voor eender welk kankertype. De aanbeveling van het CHMP zal nu beoordeeld worden door de Europese Commissie (EC), die bevoegd is voor de goedkeuring van geneesmiddelen in de Europese Unie (EU).

"Dit gunstig advies ondersteunt het potentieel van *Opdivo* als adjuvante behandeling ter voorkoming van recidive en van progressie tot een vergevorderd stadium," zei Arvin Yang, M.D., Ph.D., hoofd ontwikkeling melanoom en genito-urinaire kankers bij Bristol-Myers Squibb. "Wij kijken uit naar de nakende beslissing van de EC en de mogelijke kans om meer patiënten in de Europese Unie toegang te geven tot immunologische behandelingsmogelijkheden tegen kanker."

De aanbeveling van het CHMP is gestoeld op de gegevens van de fase 3-studie CheckMate-238, een nog lopende, gerandomiseerde, dubbelblinde studie van *Opdivo* 3 mg/kg tegenover *Yervoy* (ipilimumab) 10 mg/kg bij patiënten die een volledige resectie ondergaan hebben van hun stadium IIIB/C of stadium IV melanoom volgens de AJCC stadiëring 7de uitgave. In december 2017 breidde de Amerikaanse *Food and Drug Administration* (FDA) de goedkeuring van *Opdivo* uit met de adjuvante behandeling van patiënten met melanoom met aantasting van de lymfeknopen of met gemetastaseerde ziekte en die een volledige resectie ondergaan hebben.

Over CheckMate-238

CheckMate-238 is een lopende fase 3, gerandomiseerde, dubbelblinde studie van Opdivo tegenover Yervoy bij patiënten die een volledige resectie ondergaan hebben van hun stadium IIIB/C of stadium IV melanoom. In de studie werden 906 patiënten 1:1 gerandomiseerd op Opdivo 3 mg/kg om de twee weken (n=453) of op Yervoy 10 mg/kg (n=453) om de drie weken voor vier dosissen en vervolgens om de 12 weken, beginnende in week 24. De patiënten werden behandeld gedurende een periode gaande tot een jaar, totdat hun ziekte weerkeerde, tot onaanvaardbare toxiciteit optrad of tot zij hun toestemming introkken. Het primair eindpunt is recidivevrije overleving (RFS), gedefinieerd als de tijd tussen randomisatie en de datum van eerste recidive, van nieuw primair melanoom of van overlijden. Na het bereiken van het primair eindpunt zal de studie voortgezet worden om de totale overleving, een secundair eindpunt, te evalueren.

Adjuvante behandeling bij melanoom

Melanomen worden in vijf stadia ingedeeld (stadia 0 tot 4) in functie van de tumorgrootte of -dikte, hun eventuele uitzaaiing naar de lymfeknopen of andere organen en bepaalde andere kenmerken, zoals de groeisnelheid.

Een stadium III melanoom heeft de regionale lymfeknopen bereikt maar is nog niet uitgezaaid naar de lymfeknopen op afstand of naar andere delen van het lichaam (metastasering). Hiervoor is heelkundige verwijdering van de primaire tumor en van de aangetaste lymfeknopen vereist. Sommige patiënten kunnen ook behandeld worden met adjuvante therapie. Ondanks de heelkundige ingreep en eventuele adjuvante behandeling, ervaren de meeste patiënten recidive van hun ziekte of progressie tot gemetastaseerde ziekte. Binnen een bestek van vijf jaar ervaren de meeste patiënten met ziekte in stadium IIIB en IIIC (respectievelijk 68% en 89%) recidive van hun ziekte.

Bristol-Myers Squibb & immuno-oncologie: het oncologisch onderzoek stimuleren

In alles wat we bij Bristol-Myers Squibb doen, staat de patiënt centraal. Onze visie voor de toekomst van kankerzorg is gericht op onderzoek en ontwikkeling van transformationele immuno-oncologische (IO) geneesmiddelen voor hardnekkige kankers die de uitkomsten voor deze patiënten mogelijk zouden kunnen verbeteren.

Dankzij onze uitgebreide portfolio van experimentele en goedgekeurde middelen willen we de wetenschappelijke kennis over I-O vergroten. Ons gedifferentieerd klinisch ontwikkelingsprogramma, waaraan grote patiëntenpopulaties met meer dan 50 verschillende

kankertypes deelnemen, bestudeert 24 molecules in de klinische ontwikkelingsfase die ontworpen zijn om op verschillende signaalwegen van het immuunsysteem in te werken. Onze ruime expertise en de innovatieve opzet van onze klinische studies stellen ons in staat om vooruitgang te boeken in I-O/I-O, I-O/chemotherapie, I-O/doelgerichte therapieën en I-O/bestralingstherapieën voor verschillende tumortypes, en om eventueel de volgende golf van hoognodige behandelingen aan te bieden. Aan de hand van onze toonaangevende capaciteiten inzake translationeel onderzoek willen we het immunobiologisch onderzoek stimuleren en een aantal mogelijk voorspellende biomerkers identificeren, waaronder PD-L1, TMB, MSI-H/dMMR en LAG-3, zodat precisiegeneeskunde voor meer kankerpatiënten werkelijkheid kan worden.

Als we beloven om I-O werkelijkheid te maken voor de talrijke patiënten die hier voordeel uit kunnen halen, beseffen we dat hiervoor niet enkel onze innovatie, maar ook nauwe samenwerking met toonaangevende experts in het veld nodig is. Onze partnerschappen met de academische wereld, de overheid, belangenorganisaties en biotechnologische bedrijven ondersteunen ons gemeenschappelijke doel om nieuwe behandelingsopties aan te bieden die de klinische praktijk vooruithelpen.

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 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 of volg ons op LinkedIn, Twitter, YouTube en Facebook.

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EU-APPROVED INDICATIONS FOR OPDIVO®

Melanoma

OPDIVO as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.

Relative to nivolumab monotherapy, an increase in progression-free survival (PFS) and overall survival (OS) for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression (see sections 4.4 and 5.1).

Non-Small Cell Lung Cancer (NSCLC)

OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.

Renal Cell Carcinoma (RCC)

OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults.

Classical Hodgkin Lymphoma (cHL)

OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

Squamous Cell Cancer of the Head and Neck (SCCHN)

OPDIVO as monotherapy is indicated for the treatment of squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1).

Urothelial Carcinoma

OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

IMPORTANT SAFETY INFORMATION

WARNING: IMMUNE-MEDIATED ADVERSE REACTIONS

When nivolumab is administered in combination with ipilimumab, refer to the Summary of Product Characteristics for ipilimumab prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2).

Cardiac adverse events and pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with nivolumab or nivolumab in combination with ipilimumab may occur at any time during or after discontinuation of therapy.

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

Nivolumab or nivolumab in combination with ipilimumab should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Immune-related pneumonitis

Severe pneumonitis or interstitial lung disease, including fatal cases, has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of pneumonitis such as radiographic changes (e.g., focal ground glass opacities, patchy filtrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 pneumonitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents.

For Grade 2 (symptomatic) pneumonitis, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 2 to 4 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related colitis

Severe diarrhoea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Infectious and disease-related aetiologies should be ruled out.

For Grade 4 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Nivolumab monotherapy should be withheld for Grade 3 diarrhoea or colitis, and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab monotherapy

may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, nivolumab monotherapy must be permanently discontinued. Grade 3 diarrhoea or colitis observed with nivolumab in combination with ipilimumab requires permanent discontinuation of treatment and initiation of corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent diarrhoea or colitis should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related hepatitis

Severe hepatitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of hepatitis such as transaminase and total bilirubin elevations. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 transaminase or total bilirubin elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent elevations in these laboratory values should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related nephritis and renal dysfunction

Severe nephritis and renal dysfunction have been observed with monotherapy treatment or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for signs and symptoms of nephritis or renal dysfunction. Most patients present with asymptomatic increases in serum creatinine. Disease-related aetiologies should be ruled out.

For Grade 4 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For Grade 2 or 3 serum creatinine elevation, nivolumab or nivolumab in combination with ipilimumab should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents, and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

Immune-related endocrinopathies

Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), diabetes mellitus, and diabetic ketoacidosis have been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8).

Patients should be monitored for clinical signs and symptoms of endocrinopathies and for hyperglycaemia and changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation). Patients may present with fatigue, headache, mental status changes, abdominal pain, unusual bowel habits, and hypotension, or nonspecific symptoms which may resemble other causes such as brain metastasis or underlying disease. Unless an alternate aetiology has been identified, signs or symptoms of endocrinopathies should be considered immune-related.

For symptomatic hypothyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, nivolumab or nivolumab in combination with ipilimumab should be withheld and antithyroid medication should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the thyroid is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening hyperthyroidism or hypothyroidism.

For symptomatic Grade 2 adrenal insufficiency, nivolumab or nivolumab in combination with ipilimumab should be withheld, and physiologic corticosteroid replacement should be initiated as needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) adrenal insufficiency. Monitoring of adrenal function and hormone levels should continue to ensure appropriate corticosteroid replacement is utilised.

For symptomatic Grade 2 or 3 hypophysitis, nivolumab or nivolumab in combination with ipilimumab should be withheld, and hormone replacement should be initiated as needed. Corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents should also be considered if acute inflammation of the pituitary gland is suspected. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper, if needed. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening (Grade 4) hypophysitis. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

For symptomatic diabetes, nivolumab or nivolumab in combination with ipilimumab should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for life-threatening diabetes.

Immune-related skin adverse reactions

Severe rash has been observed with nivolumab in combination with ipilimumab and, less commonly, with nivolumab as monotherapy (see section 4.8). Nivolumab or nivolumab in combination with ipilimumab should be withheld for Grade 3 rash and discontinued for Grade 4 rash. Severe rash should be managed with high-dose corticosteroid at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Rare cases of SJS and TEN some of them with fatal outcome have been observed. If symptoms or signs of SJS or TEN appear, treatment with nivolumab or nivolumab in combination with ipilimumab should be discontinued and the patient referred to a specialised unit for assessment and treatment. If the patient has developed SJS or TEN with the use of nivolumab or nivolumab in combination with ipilimumab, permanent discontinuation of treatment is recommended (see section 4.2).

Caution should be used when considering the use of nivolumab in a patient who has previously experienced a severe or life-threatening skin adverse reaction on prior treatment with other immune-stimulatory anticancer agents.

Other immune-related adverse reactions

The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab monotherapy or nivolumab in combination with ipilimumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenic syndrome, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, and rhabdomyolysis. Cases of Vogt-Koyanagi-Harada syndrome have been reported post-marketing (see section 4.8).

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. Upon improvement, nivolumab or nivolumab in combination with ipilimumab may be resumed after corticosteroid taper. Nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Rare cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued (see section 4.2), and appropriate treatment instituted.

Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab versus the risk of possible organ rejection should be considered in these patients.

Infusion reactions

Severe infusion reactions have been reported in clinical trials of nivolumab or nivolumab in combination with ipilimumab (see section 4.8). In case of a severe or life-threatening infusion reaction, the nivolumab or nivolumab in combination with ipilimumab infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive nivolumab or nivolumab in combination with ipilimumab with close monitoring and use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Disease-specific precautions

Melanoma
Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials of nivolumab or nivolumab in combination with ipilimumab. Patients with ocular/uveal melanoma were excluded from clinical trials of melanoma. In addition, CA209037 excluded patients who have had a Grade 4 adverse reaction that was related to anti-CTLA-4 therapy (see section 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Relative to nivolumab monotherapy, an increase in PFS for the combination of nivolumab with ipilimumab is established only in patients with low tumour PD-L1 expression. The improvement in OS was similar between nivolumab in combination with ipilimumab and nivolumab monotherapy in patients with high tumour PD-L1 expression (PD-L1 ≥ 1%). Before initiating treatment with the combination, physicians are advised to carefully evaluate the individual patient and tumour characteristics, taking into consideration the observed benefits and the toxicity of the combination relative to nivolumab monotherapy (see sections 4.8 and 5.1).

Use of nivolumab in melanoma patients with rapidly progressing disease

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with rapidly progressing disease (see section 5.1).

Non-Small Cell Lung Cancer

Patients with a baseline performance score ≥ 2, active brain metastases or autoimmune disease, symptomatic interstitial lung disease, and patients who had been receiving systemic immunosuppressants prior to study entry were excluded from the clinical trials of NSCLC (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In non-squamous NSCLC, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were poorer prognostic factors and/or more aggressive disease combined with low or no tumour PD-L1 expression (see section 5.1).

Renal Cell Carcinoma

Patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the pivotal trial in RCC (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Classical Hodgkin Lymphoma

Patients with active autoimmune disease and symptomatic interstitial lung disease were excluded from clinical trials of cHL. In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Complications of allogeneic Haematopoietic Stem Cell Transplant (HSCT) in classical Hodgkin Lymphoma

Preliminary results from the follow-up of patients undergoing allogeneic HSCT after previous exposure to nivolumab showed a higher than expected number of cases of acute graft-versus-host-disease (aGVHD) and transplant related mortality (TRM). Until further data become available, careful consideration to the potential benefits of HSCT and the possible increased risk of transplant related complications should be made case by case (see section 4.8).

Head and Neck Cancer

Patients with a baseline performance score ≥ 2, active brain or leptomeningeal metastases, active autoimmune disease, medical conditions requiring systemic immunosuppression, or carcinoma of the nasopharynx or salivary gland as the primary tumour sites were excluded from the SCCHN clinical trial (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Physicians should consider the delayed onset of nivolumab effect before initiating treatment in patients with poorer prognostic features and/or aggressive disease. In head and neck cancer, a higher number of deaths within 3 months was observed in nivolumab compared to docetaxel. Factors associated with early deaths were ECOG performance status, fast progressive disease on prior platinum therapy and high tumour burden.

Urothelial Carcinoma

Patients with a baseline performance score ≥2, active brain metastases or leptomeningeal metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical trials of urothelial carcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab should be used with caution in these populations after careful consideration of the potential benefit-risk on an individual basis.

Patients on controlled sodium diet

Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

Patient Alert Card

All prescribers of OPDIVO must be familiar with the Physician Information and Management Guidelines. The prescriber must discuss the risks of OPDIVO therapy with the patient. The patient will be provided with the Patient Alert Card with each prescription.

Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of nivolumab in pregnant women. Studies in animals have shown embryofoetal toxicity (see section 5.3). Human IgG4 is known to cross the placental barrier and nivolumab is an IgG4; therefore, nivolumab has the potential to be transmitted from the mother to the developing foetus. Nivolumab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. Effective contraception should be used for at least 5 months following the last dose of nivolumab.

Breast-feeding

It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Studies to evaluate the effect of nivolumab on fertility have not been performed. Thus, the effect of nivolumab on male and female fertility is unknown.

Undesirable effects

Summary of the safety profile

In the pooled dataset of nivolumab 3 mg/kg as monotherapy across tumour types (n = 2578) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (30%), rash (17%), pruritus (13%), diarrhoea (13%), and nausea (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). With a minimum of 24 months follow-up in NSCLC, no new safety signals were identified.

In the pooled dataset of nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n = 448) with minimum follow-up ranging from 6 to 28 months, the most frequent adverse reactions (≥ 10%) were rash (52%), fatigue (46%), diarrhoea (43%), pruritus (36%), nausea (26%), pyrexia (19%), decreased appetite (16%), hypothyroidism (16%), colitis (15%), vomiting (14%), arthralgia (13%), abdominal pain (13%), headache (11%), and dyspnoea (10%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Among the patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in CA209067, 154/313 (49%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 147 patients in this group who continued treatment in the single-agent phase, 47 (32%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase.

Tabulated summary of adverse reactions

Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 2578) and for patients treated with nivolumab in combination with ipilimumab (n = 448) are presented in Table 4. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available post-marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 4: Adverse reactions

	Nivolumab monotherapy	Nivolumab in combination with ipilimumab
Infections and infestations		
Common	upper respiratory tract infection	pneumonia, upper respiratory tract infection
Uncommon	pneumonia[a], bronchitis	bronchitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)		
Rare	histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)	
Blood and lymphatic system disorders		
Very common	neutropaenia[a,b]	
Common		eosinophilia
Uncommon	eosinophilia	
Immune system disorders		
Common	infusion related reaction[c], hypersensitivity[c]	infusion related reaction, hypersensitivity
Uncommon		sarcoidosis
Rare	anaphylactic reaction[c]	
Not known	solid organ transplant rejection	solid organ transplant rejection
Endocrine disorders		
Very common		hypothyroidism
Common	hypothyroidism, hyperthyroidism	adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis
Uncommon	adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus	diabetic ketoacidosis[c], diabetes mellitus[c]
Rare	diabetic ketoacidosis	
Metabolism and nutrition disorders		
Very common		decreased appetite
Common	decreased appetite	dehydration
Uncommon	dehydration, metabolic acidosis	
Not known	tumour lysis syndrome[i]	tumour lysis syndrome[i]
Hepatobiliary disorders		
Common		hepatitis[c]
Uncommon	hepatitis[c]	
Rare	cholestasis	
Nervous system disorders		
Very common		headache
Common	peripheral neuropathy, headache, dizziness	peripheral neuropathy, dizziness

Uncommon	polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis)	Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c]
Rare	Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c]	
Eye disorders		
Common		uveitis, blurred vision
Uncommon	uveitis, blurred vision, dry eye	
Not known	Vogt-Koyanagi-Harada syndrome[h]	Vogt-Koyanagi-Harada syndrome[h]
Cardiac disorders		
Common		tachycardia
Uncommon	tachycardia	arrhythmia (including ventricular arrhythmia)[a,d], atrial fibrillation, myocarditis[a,f]
Rare	arrhythmia (including ventricular arrhythmia)[d], atrial fibrillation, myocarditis[a,f]	
Vascular disorders		
Common	hypertension	hypertension
Rare	vasculitis	
Respiratory, thoracic and mediastinal disorders		
Very common		dyspnoea
Common	pneumonitis[a,c], dyspnoea[a], cough	pneumonitis[a,c], pulmonary embolism[a], cough
Uncommon	pleural effusion	pleural effusion
Rare	lung infiltration	
Gastrointestinal disorders		
Very common	diarrhoea, nausea	colitis[a], diarrhoea, vomiting, nausea, abdominal pain
Common	colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth	stomatitis, pancreatitis, constipation, dry mouth
Uncommon	pancreatitis, gastritis	intestinal perforation[a], gastritis, duodenitis
Rare	duodenal ulcer	
Skin and subcutaneous tissue disorders		
Very common	rash[e], pruritus	rash[e], pruritus
Common	vitiligo, dry skin, erythema, alopecia	vitiligo, dry skin, erythema, alopecia, urticaria
Uncommon	erythema multiforme, psoriasis, rosacea, urticaria	psoriasis

Rare	toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[a,f]	toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[f]
Musculoskeletal and connective tissue disorders		
Very common		arthralgia
Common	musculoskeletal pain[g], arthralgia	musculoskeletal pain[g]
Uncommon	polymyalgia rheumatica, arthritis	spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,f], rhabdomyolysis[a,f]
Rare	Sjogren's syndrome, myopathy, myositis (including polymyositis)[a,f], rhabdomyolysis[a,f]	
Renal and urinary disorders		
Common		renal failure (including acute kidney injury)[a,c]
Uncommon	tubulointerstitial nephritis, renal failure (including acute kidney injury)[a,c]	tubulointerstitial nephritis
General disorders and administration site conditions		
Very common	fatigue	fatigue, pyrexia
Common	pyrexia, oedema (including peripheral oedema)	oedema (including peripheral oedema), pain
Uncommon	pain, chest pain	chest pain
Investigations[b]		
Very common	increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, hypocalcaemia, increased creatinine, hyperglycaemia[c], lymphopaenia, leucopoenia, thrombocytopaenia, anaemia, hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia	increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia[c], hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia
Common	increased total bilirubin, hypoglycaemia, hypermagnesaemia, hypernatraemia, weight decreased	hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased

[a] Fatal cases have been reported in completed or ongoing clinical studies

[b] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. See "Description of selected adverse reactions; laboratory abnormalities" below.

[c] Life-threatening cases have been reported in completed or ongoing clinical studies.

[d] The frequency of adverse events in the cardiac disorders system organ class regardless of causality was higher in the nivolumab group than in the chemotherapy group in post-CTLA4/BRAF inhibitor metastatic melanoma population. Incidence rates per 100 person-years of exposure were 9.3 vs. 0;

serious cardiac events were reported by 4.9% patients in the nivolumab group vs. 0 in the investigator´s choice group. The frequency of cardiac adverse events was lower in the nivolumab group than in the dacarbazine group in the metastatic melanoma without prior treatment population. All were considered not related to nivolumab by investigators except arrhythmia (atrial fibrillation, tachycardia and ventricular arrhythmia).

[e] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash papulosquamous, rash vesicular, rash generalised, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid.

[f] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure.

[g] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, and spinal pain.

[h] Post-marketing event (also see section 4.4).

[i] Reported in clinical studies and in the post-marketing setting.

Description of selected adverse reactions

Nivolumab or nivolumab in combination with ipilimumab is associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. Permanent discontinuation of treatment was required in a greater proportion of patients receiving nivolumab in combination with ipilimumab than in those receiving nivolumab monotherapy for immune-related colitis (16% and 0.8%, respectively), immune-related hepatitis (9% and 1%), and immune-related endocrinopathies (2.7% and 0.1%). Among patients who experienced an event, high-dose corticosteroids (at least 40 mg prednisone equivalents) were required in a greater proportion of patients receiving the combination regimen than in patients receiving nivolumab monotherapy for the management of immune-related colitis (46% and 15%, respectively), immune-related hepatitis (46% and 21%), immune-related endocrinopathies (27% and 7%, respectively), and immune-related skin adverse reaction (7% and 4%, respectively). The management guidelines for these adverse reactions are described in section 4.4.

Immune-related pneumonitis

In patients treated with nivolumab monotherapy, the incidence of pneumonitis, including interstitial lung disease and lung infiltration, was 3.4% (87/2578). The majority of cases were Grade 1 or 2 in severity reported in 0.8% (21/2578) and 1.7% (44/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (19/2578) and <0.1% (1/2578) of patients respectively. Grade 5 cases were reported in < 0.1% (2/2578) of patients in these studies. Median time to onset was 3.6 months (range: 0.2-19.6). Resolution occurred in 63 patients (72.4%) with a median time to resolution of 6.1 weeks (range: 0.1+-96.7+); + denotes a censored observation.

In patients treated with nivolumab in combination with ipilimumab, the incidence of pneumonitis including interstitial lung disease, was 7.8% (35/448). Grade 2, Grade 3, and Grade 4 cases were reported in 4.7% (21/448), 1.1% (5/448), and 0.2% (1/448) of patients, respectively. One of the Grade 3 pneumonitis cases worsened over 11 days with a fatal outcome. Median time to onset was 2.6 months (range: 0.7-12.6). Resolution occurred in 33 patients (94.3%) with a median time to resolution of 6.1 weeks (range: 0.3-35.1).

Immune-related colitis

In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 13.1% (339/2578). The majority of cases were Grade 1 or 2 in severity reported in 8.5% (220/2578) and 3.0% (78/2578) of patients respectively. Grade 3 cases were reported in 1.6% (41/2578) of patients. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.8 months (range: 0.0-26.6). Resolution occurred in 296 patients (88.1%) with a median time to resolution of 2.1 weeks (range: 0.1-124.4+).

In patients treated with nivolumab in combination with ipilimumab, the incidence of diarrhoea or colitis was 46.7% (209/448). Grade 2, Grade 3, and Grade 4 cases were reported in 13.6% (61/448), 15.8% (71/448), and 0.4% (2/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.2 months (range: 0.0-22.6). Resolution occurred in 186 patients (89.4%) with a median time to resolution of 3.0 weeks (range: 0.1-159.4+).

Immune-related hepatitis

In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was 6.7% (173/2578). The majority of cases were Grade 1 or 2 in severity reported in 3.5% (91/2578) and 1.2% (32/2578) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (41/2578) and 0.3% (9/2578) of patients, respectively. No Grade 5 cases were reported in these studies. Median time to onset was 2.1 months (range: 0.0-27.6). Resolution occurred in 132 patients (76.7%) with a median time to resolution of 5.9 weeks (range: 0.1-82.6+).

In patients treated with nivolumab in combination with ipilimumab, the incidence of liver function test abnormalities was 29.5% (132/448). Grade 2, Grade 3, and Grade 4 cases were reported in 6.7% (30/448), 15.4% (69/448), and 1.8% (8/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 1.5 months (range: 0.0-30.1). Resolution occurred in 124 patients (93.9%) with a median time to resolution of 5.1 weeks (range: 0.1-106.9).

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.8% (71/2578). The majority of cases were Grade 1 or 2 in severity reported in 1.6% (41/2578) and 0.7% (18/2578) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (11/2578) and <0.1% (1/2578) of patients, respectively. No Grade 5 nephritis or renal dysfunction was reported in these studies. Median time to onset was 2.3 months (range: 0.0-18.2). Resolution occurred in 42 patients (61.8%) with a median time to resolution of 12.1 weeks (range: 0.3-79.1+).

In patients treated with nivolumab in combination with ipilimumab, the incidence of nephritis or renal dysfunction was 5.1% (23/448). Grade 2, Grade 3, and Grade 4 cases were reported in 1.6% (7/448), 0.9% (4/448), and 0.7% (3/448) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.6 months (range: 0.5-21.8). Resolution occurred in 21 patients (91.3%) with a median time to resolution of 2.1 weeks (range: 0.1- 125.1+).

Immune-related endocrinopathies

In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 9.6% (248/2578). The majority of cases were Grade 1 or 2 in severity reported in 4.2% (107/2578) and 5.4% (139/2578) of patients, respectively. Grade 3 thyroid disorders were reported in < 0.1% (2/2578) of patients. Hypophysitis (1 Grade 1, 2 Grade 2, 5 Grade 3, and

1 Grade 4), hypopituitarism (4 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency) (1 Grade 1, 9 Grade 2, and 5 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus) (3 Grade 2 and 1 Grade 3), and diabetic ketoacidosis (2 Grade 3) were reported. No Grade 5 cases were reported in these studies. Median time to onset of these endocrinopathies was 2.8 months (range: 0.3-29.1). Resolution occurred in 117 patients (42.9%). Time to resolution ranged from 0.4 to 144.1+ weeks.

In patients treated with nivolumab in combination with ipilimumab, the incidence of thyroid disorders was 25.2% (113/448). Grade 2 and Grade 3 thyroid disorders were reported in 14.5% (65/448) and 1.3% (6/448) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 5.8% (26/448) and 2.0% (9/448) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.4% (2/448) and 0.7% (3/448) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 1.6% (7/448), 1.3% (6/448) and 0.2% (1/448) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus and Grade 4 diabetic ketoacidosis were each reported in 0.2% (1/448) of patients. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-28.1). Resolution occurred in 64 patients (45.4%). Time to resolution ranged from 0.4 to 155.4+ weeks.

Immune-related skin adverse reactions

In patients treated with nivolumab monotherapy, the incidence of rash was 26.4% (680/2578). The majority of cases were Grade 1 in severity reported in 20.1% (518/2578) of patients. Grade 2 and Grade 3 cases were reported in 5.1% (131/2578) and 1.2% (31/2578) of patients respectively. No Grade 4 or 5 cases were reported in these studies. Median time to onset was 1.4 months (range: 0.0-27.9). Resolution occurred in 428 patients (63.8%) with a median time to resolution of 17.1 weeks (0.1-150.0+).

In patients treated with nivolumab in combination with ipilimumab, the incidence of rash was 65.0% (291/448). Grade 2 and Grade 3 cases were reported in 20.3% (91/448) and 7.6% (34/448) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.5 months (range: 0.0-19.4). Resolution occurred in 191 patients (65.9%) with a median time to resolution of 11.4 weeks (range: 0.1-150.1+).

Rare cases of SJS and TEN some of them with fatal outcome have been observed (see sections 4.2 and 4.4).

Infusion reactions

In patients treated with nivolumab monotherapy, the incidence of hypersensitivity/infusion reactions was 4.7% (121/2578), including 6 Grade 3 and 2 Grade 4 cases.

In patients treated with nivolumab in combination with ipilimumab, the incidence of hypersensitivity/infusion reactions was 3.8% (17/448); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.2% (10/448) of patients. No Grade 3-5 cases were reported.

Complications of allogeneic HSCT in classical Hodgkin Lymphoma

In 49 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 13/49 patients (26.5%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in three patients (6%). A steroid-requiring febrile syndrome, without an identified infectious cause, was reported in six patients (12%) within the first 6 weeks post-transplantation, with three patients responding to steroids. Hepatic veno-occlusive disease occurred in one patient, who died of GVHD and multi-organ failure. Nine of 49 patients

(18.4%) died from complications of allogeneic HSCT after nivolumab. The 49 patients had a median follow-up from subsequent allogeneic HSCT of 5.6 months (range: 0-19 months).

Laboratory abnormalities

In patients treated with nivolumab monotherapy, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 5.2% for anaemia (all Grade 3), 1.0% for thrombocytopaenia, 1.0% for leucopoenia, 10.0% for lymphopaenia, 1.1% for neutropaenia, 2.1% for increased alkaline phosphatase, 2.7% for increased AST, 2.2% for increased ALT, 1.2% for increased total bilirubin, 0.9% for increased creatinine, 3.8% for hyperglycaemia, 1.0% for hypoglycaemia, 3.5% for increased amylase, 7.9% for increased lipase, 6.4% for hyponatraemia, 1.8% for hyperkalaemia, 1.5% for hypokalaemia, 1.2% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.5% for hypomagnesaemia, 0.7% for hypocalcaemia, and 0.1% for hypernatraemia.

In patients treated with nivolumab in combination with ipilimumab, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.8% for anaemia (all Grade 3), 1.2% for thrombocytopaenia, 0.5% for leucopoenia, 6.7% for lymphopaenia, 0.7% for neutropaenia, 4.3% for increased alkaline phosphatase, 12.4% for increased AST, 15.3% for increased ALT, 1.2% for increased total bilirubin, 2.4% for increased creatinine, 5.3% for hyperglycaemia, 8.7% for increased amylase, 19.5% for increased lipase, 1.2% for hypocalcaemia, 0.2% each for hypernatraemia and hypercalcaemia, 0.5% for hyperkalemia, 0.3% for hypermagnesaemia, 4.8% for hypokalaemia, and 9.5% for hyponatraemia.

Immunogenicity

Of the 2022 patients who were treated with nivolumab monotherapy 3 mg/kg every 2 weeks and evaluable for the presence of anti-product-antibodies, 231 patients (11.4%) tested positive for treatment-emergent anti-product-antibodies with fifteen patients (0.7 %) testing positive for neutralising antibodies.

Of 394 patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, 149 patients (37.8%) tested positive for treatment-emergent anti-nivolumab antibodies with 18 patients (4.6%) testing positive for neutralising antibodies.

Although the clearance of nivolumab was increased by 24% when anti-nivolumab-antibodies were present, there was no evidence of loss of efficacy or altered toxicity profile in the presence of nivolumab antibodies based on the pharmacokinetic and exposure-response analyses for both monotherapy and combination.

Elderly

No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from NSCLC and SCCHN patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from cHL patients 65 years of age or older are too limited to draw conclusions on this population (see section 5.1).

Hepatic or renal impairment

In the non-squamous NSCLC study (CA209057), the safety profile in patients with baseline renal or hepatic impairment was comparable to that in the overall population. These results should be interpreted with caution due to the small sample size within the subgroups.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

Please see EU Full prescribing information for Opdivo and Yervoy.

About the Bristol-Myers Squibb and Ono Pharmaceutical Collaboration

In 2011, through a collaboration agreement with Ono Pharmaceutical Co., 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, Ono and Bristol-Myers Squibb 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.

Over Bristol-Myers Squibb

Bristol-Myers Squibb is een wereldwijd actief biofarmaceutisch bedrijf met als missie het ontdekken, ontwikkelen en leveren van innovatieve geneesmiddelen die patiënten helpen om ernstige ziekten te overwinnen. Lees meer op BMS.com of volg ons op LinkedIn, Twitter, YouTube en Facebook.

Bristol-Myers Squibb Forward-Looking Statement

This press release contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding the research, development and commercialization of pharmaceutical products. Such forward-looking statements are based on current expectations and involve inherent risks and uncertainties, including factors that could delay, divert or change any of them, and could cause actual outcomes and results to differ materially from current expectations. No forward-looking statement can be guaranteed. Among other risks, there can be no guarantee that Opdivo will receive regulatory approval for the additional indication described herein. 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, 2017 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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