OPDIVO (nivolumab)

OPDIVO (nivolumab) + YERVOY (ipilimumab)

| Ex-factory (excl. VAT) | | |
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| OPDIVO | 40 mg | €509,90 |
| OPDIVO | 100 mg | €1.274,75 |
| OPDIVO | 240 mg | €3.059,65 |

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions. **NAME OF THE MEDICINAL PRODUCT OPDIVO** 10 mg/mL concentrate for solution for infusion. **QUALITATIVE AND QUANTITATIVE COMPOSITION** Each mL of concentrate contains 10 mg of nivolumab. One vial of 4 mL contains 40 mg of nivolumab. One vial of 10 mL contains 100 mg of nivolumab. One vial of 24 mL contains 240 mg of nivolumab. Nivolumab is produced in Chinese hamster ovary cells by recombinant DNA technology. Excipient with known effect Each mL of concentrate contains 0.1 mmol (or 2.5 mg) sodium. For the full list of excipients, see section 6.1. **PHARMACEUTICAL FORM** Concentrate for solution for infusion (sterile concentrate). Clear to opalescent, colourless to pale yellow liquid that may contain few light particles. The solution has a pH of approximately 6.0 and an osmolality of approximately 340 mOsm/kg. **CLINICAL PARTICULARS 4.1 Therapeutic indications** 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). Adjuvant treatment of melanoma OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 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. OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see section 5.1). 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 recurrent or metastatic 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. **4.2 Posology and method of administration** Treatment must be initiated and supervised by physicians experienced in the treatment of cancer. *Posology OPDIVO as monotherapy* The recommended dose of OPDIVO is either nivolumab 240 mg every 2 weeks **or** 480 mg every 4 weeks (see section 5.1) depending on the indication, as presented in Table 1 . Table 1: Recommended dose and infusion time for intravenous administration of nivolumab monotherapy Recommended dose and infusion time per indication*: Melanoma (advanced or adjuvant treatment): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; Renal Cell Carcinoma: 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; Non-Small Cell Lung Cancer: 240 mg every 2 weeks over 30 minutes; Classical Hodgkin lymphoma: 240 mg every 2 weeks over 30 minutes; Squamous Cell Cancer of the Head and Neck: 240 mg every 2 weeks over 30 minutes; Urothelial Carcinoma: 240 mg every 2 weeks over 30 minutes *As per monotherapy indication in section 4.1. If melanoma or RCC patients need to be switched from the 240 mg every 2 weeks schedule to the 480 mg every 4 weeks schedule, the first 480 mg dose should be administered two weeks after the last 240 mg dose. Conversely, if patients need to be switched from the 480 mg every 4 weeks schedule to the 240 mg every 2 weeks schedule, the first 240 mg dose should be administered four weeks after the last 480 mg dose. *OPDIVO in combination with ipilimumab Melanoma* The recommended dose is 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, as presented in Table 2. For the monotherapy phase, the first dose of nivolumab should be administered; 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; or 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks. Table 2: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab *Nivolumab:* Combination phase, every 3 weeks for 4 dosing cycles: 1 mg/kg over 30 minutes / Monotherapy phase: 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; *Ipilimumab:* Combination phase, every 3 weeks for 4 dosing cycles: 3 mg/kg over 90 minutes. *Renal Cell Carcinoma* The recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks or at 480 mg every 4 weeks, as presented in Table 3. For the monotherapy phase, the first dose of nivolumab should be administered; 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; or 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks. Table 3: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab *Nivolumab:* Combination phase, every 3 weeks for 4 dosing cycles: 3 mg/kg over 30 minutes / Monotherapy phase: 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; *Ipilimumab:* Combination phase, every 3 weeks for 4 dosing cycles: 1 mg/kg over 30 minutes. *Duration of treatment*. Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab, should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. For adjuvant therapy, the maximum treatment duration with OPDIVO is 12 months. Atypical responses (i.e., an initial transient increase in tumour size or small new lesions within the first few months followed by tumour shrinkage) have been observed. It is recommended to continue treatment with nivolumab or nivolumab in combination with ipilimumab for clinically stable patients with initial evidence of disease progression until disease progression is confirmed. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 4. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4. Table 4: Recommended treatment modifications for OPDIVO or OPDIVO in combination with ipilimumab Immune-related adverse reaction: *Immune-related pneumonitis: Severity:* Grade 2 pneumonitis; *Treatment modification:* Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete; *Severity:* Grade 3 or 4 pneumonitis; *Treatment modification:* Permanently discontinue treatment; *Immune-related colitis: Severity:* Grade 2 diarrhoea or colitis; *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete; *Severity:* Grade 3 diarrhoea or colitis - OPDIVO monotherapy; *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids is complete; *Severity:* Grade 3 diarrhoea or colitis - OPDIVO+ipilimumab[a]; *Treatment modification:* Permanently discontinue treatment; *Severity:* Grade 4 diarrhoea or colitis; *Treatment modification:* Permanently discontinue treatment; *Immune-related hepatitis: Severity:* Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin; *Treatment modification:* Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete; *Severity:* Grade 3 or 4 elevation in AST, ALT, or total bilirubin; *Treatment modification:* Permanently discontinue treatment; *Immune-related nephritis and renal dysfunction: Severity:* Grade 2 or 3 creatinine elevation; *Treatment modification:* Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete; *Severity:* Grade 4 creatinine elevation; *Treatment modification:* Permanently discontinue treatment; *Immune-related endocrinopathies: Severity:* Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis, Grade 2 adrenal insufficiency, Grade 3 diabetes; *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. Treatment should be continued in the presence of hormone replacement therapy[b] as long as no symptoms are present; *Severity:* Grade 4 hypothyroidism, Grade 4 hyperthyroidism, Grade 4 hypophysitis, Grade 3 or 4 adrenal insufficiency, Grade 4 diabetes; *Treatment modification:* Permanently discontinue treatment; *Immune-related skin adverse reactions: Severity:* Grade 3 rash; *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids is complete; *Severity:* Grade 4 rash; *Treatment modification:* Permanently discontinue treatment; *Severity:* Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN); *Treatment modification:* Permanently discontinue treatment (see section 4.4); *Immune-related myocarditis Severity:* Grade 2 myocarditis *Treatment modification:* Withhold dose(s) until symptoms resolve and management with corticosteroids is completec; *Severity: Grade 3 or 4 myocarditis Treatment modification:* Permanently discontinue treatment. *Other immune-related adverse reactions: Severity:* Grade 3 (first occurrence); *Treatment modification:* Withhold dose(s); *Severity:* Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification ; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day; *Treatment modification:* Permanently discontinue treatment Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4). [a] During administration of the second phase of treatment (nivolumab monotherapy) following combination treatment, permanently discontinue treatment if Grade 3 diarrhoea or colitis occurs. [b]Recommendation for the use of hormone replacement therapy is provided in section 4.4. [c] The safety of re-initiating nivolumab or nivolumab in combination with ipilimumab therapy in patients previously experiencing immune-related myocarditis is not known. OPDIVO or OPDIVO in combination with ipilimumab should be permanently discontinued for: Grade 4 or recurrent Grade 3 adverse reactions; Persistent Grade 2 or 3 adverse reactions despite management. Patients treated with OPDIVO must be given the patient alert card and be informed about the risks of OPDIVO (see also package leaflet). When OPDIVO is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If dosing is resumed after a delay, either the combination treatment or OPDIVO monotherapy could be resumed based on the evaluation of the individual patient. *Special populations Paediatric population* The safety and efficacy of OPDIVO in children below 18 years of age have not been established. No data are available. *Elderly* No dose adjustment is required for elderly patients (≥ 65 years) (see section 5.2). Data from SCCHN, adjuvant melanoma and first-line RCC patients 75 years of age or older are too limited to draw conclusions on this population (see sections 4.8 and 5.1). *Renal impairment* Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population. *Hepatic impairment* Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment. Method of administration OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 or 60 minutes depending on the dose (see Tables 1, 2 and 3). The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm. OPDIVO must not be administered as an intravenous push or bolus injection. The total dose of OPDIVO required can be infused directly as a 10 mg/mL solution or can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection (see section 6.6). When administered in combination with ipilimumab, OPDIVO should be given first followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion. For instructions on the preparation and handling of the medicinal product before administration, see section 6.6. **4.3 Contraindications** Hypersensitivity to the active substance or to any of the excipients listed in section 6.1. **4.8 Undesirable effects** Nivolumab as monotherapy (see section 4.2) 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. *Adjuvant treatment of melanoma* In the dataset of nivolumab 3 mg/kg as monotherapy for the adjuvant treatment of melanoma (n = 452), the most frequent adverse reactions (≥ 10%) were fatigue (46%), rash (29%), diarrhoea (24%), pruritus (23%), nausea (15%), arthralgia (13%), musculoskeletal pain (11%), and hypothyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Tabulated summary of adverse reactions Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 2578) are presented in Table 5. 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 5: Adverse reactions with nivolumab monotherapy *Infections and infestations:* Common: upper respiratory tract infection; Uncommon: pneumonia[a], bronchitis; Not known: aseptic meningitis[h]; *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]; Uncommon: eosinophilia; *Immune system disorders:* Common: infusion related reaction[c], hypersensitivity[c]; Rare: anaphylactic reaction[c]; Not known: solid organ transplant rejection[h]; sarcoidosis[h]; *Endocrine disorders:* Common: hypothyroidism, hyperthyroidism; Uncommon: adrenal insufficiency, hypopituitarism, hypophysitis, thyroiditis, diabetes mellitus; Rare: diabetic ketoacidosis; Not known: hypoparathyroidism[h] *Metabolism and nutrition disorders:* Common: decreased appetite; Uncommon: dehydration, metabolic acidosis; Not known: tumour lysis syndrome[i]; *Hepatobiliary disorders:* Uncommon: hepatitis[c]; Rare: cholestasis; *Nervous system disorders:* Common: peripheral neuropathy, headache, dizziness; Uncommon: polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis); Rare: Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c]; *Eye disorders:* Uncommon: uveitis, blurred vision, dry eye; Not known: Vogt-Koyanagi-Harada syndrome[h]; *Cardiac disorders:* Uncommon: tachycardia, pericardial disorders[j]; Rare: arrhythmia (including ventricular arrhythmia)[d], atrial fibrillation, myocarditis[a,j]; *Vascular disorders:* Common: hypertension; Uncommon: vasculitis; *Respiratory, thoracic and mediastinal disorders:* Common: pneumonitis[a,c], dyspnoea[a], cough; Uncommon: pleural effusion; Rare: lung infiltration; *Gastrointestinal disorders:* Very common: diarrhoea, nausea; Common: colitis[a], stomatitis, vomiting, abdominal pain, constipation, dry mouth; Uncommon: pancreatitis, gastritis; Rare: duodenal ulcer; *Skin and subcutaneous tissue disorders:* Very common: rash[e], pruritus; Common: vitiligo, dry skin, erythema, alopecia; Uncommon: erythema multiforme, psoriasis, rosacea, urticaria; Rare: toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[a,f]; *Musculoskeletal and connective tissue disorders:* Common: musculoskeletal pain[g], arthralgia; Uncommon: polymyalgia rheumatica, arthritis; Rare: Sjogren's syndrome, myopathy, myositis (including polymyositis)[a,j], rhabdomyolysis[a,c]; *Renal and urinary disorders:* Uncommon: tubulointerstitial nephritis, renal failure (including acute kidney injury)[a,c]; *General disorders and administration site conditions:* Very common: fatigue; Common: pyrexia, oedema (including peripheral oedema); Uncommon: 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[k], hypercalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia; Common: increased total bilirubin, hypoglycaemia, 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. [j] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome. [k] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia. The overall safety profile of nivolumab 3 mg/kg for the adjuvant treatment of melanoma (n = 452) was consistent with that established across tumour types for nivolumab monotherapy. *Nivolumab in combination with ipilimumab* (see section 4.2) Summary of the safety profile When nivolumab is administered in combination with ipilimumab, refer to the Summary of Product Characteristics for ipilimumab prior to initiation of treatment. For additional information on the safety profile of ipilimumab monotherapy, please refer to the ipilimumab SmPC. *Melanoma* 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. *RCC* In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC (n = 547), with a minimum follow-up of 17.5 months, the most frequent adverse reactions (≥ 10%) were fatigue (48%), rash (34%), pruritus (28%), diarrhoea (27%), nausea (20%), hypothyroidism (16%), musculoskeletal pain (15%), arthralgia (14%), decreased appetite (14%), pyrexia (14%), vomiting (11%), hyperthyroidism (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Among the patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in CA209214, 169/547 (31%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 382 patients in this group who continued treatment in the single-agent phase, 144 (38%) 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 1 mg/kg in combination with ipilimumab 3 mg/kg (n = 448) and for patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg (n = 547) are presented in Table 6. 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 6: Adverse reactions with nivolumab in combination with ipilimumab Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg*: *Infections and infestations:* Common: pneumonia, upper respiratory tract infection; Uncommon: bronchitis; Not known aseptic meningitis[h]; *Blood and lymphatic system disorders:* Common: eosinophilia; *Immune system disorders:* Common: infusion related reaction, hypersensitivity; Uncommon: sarcoidosis; Not known: solid organ transplant rejection[h]; *Endocrine disorders:* Very common: hypothyroidism; Common: adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis; Uncommon: diabetic ketoacidosis[c], diabetes mellitus[c]: Not known: hypoparathyroidism[h]; *Metabolism and nutrition disorders: Very* common: decreased appetite; Common: dehydration; Not known: tumour lysis syndrome[i]; *Hepatobiliary disorders:* Common: hepatitis[c]; *Nervous system disorders: Very* common: headache; Common: peripheral neuropathy, dizziness; Uncommon: Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c]; *Eye disorders:* Common: uveitis, blurred vision; Not known: Vogt-Koyanagi-Harada syndrome[h]; *Cardiac disorders:* Common: tachycardia, Uncommon: arrhythmia (including ventricular arrhythmia)[a,d], atrial fibrillation, myocarditis[a,j]; Not known: pericardial disorders[i]; *Vascular disorders:* Common: hypertension; *Respiratory, thoracic and mediastinal disorders:* Very common: dyspnoea; Common: pneumonitis[a,c], pulmonary embolism[a], cough; Uncommon: pleural effusion; *Gastrointestinal disorders:* Very common: colitis[a], diarrhoea, vomiting, nausea, abdominal pain; Common: stomatitis, pancreatitis, constipation, dry mouth; Uncommon: , intestinal perforation[a], gastritis, duodenitis; *Skin and subcutaneous tissue disorders:* Very common: rash[e], pruritus; Common:

vitiligo, dry skin, erythema, alopecia, urticaria; Uncommon: psoriasis; Rare: toxic epidermal necrolysis[a,f], Stevens-Johnson syndrome[f] ; *Musculoskeletal and connective tissue disorders:* Very common: arthralgia; Common: musculoskeletal pain[g] ; Uncommon: spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,e], rhabdomyolysis[a,f]; *Renal and urinary disorders:* Common: renal failure (including acute kidney injury)[a,c], Uncommon: tubulointerstitial nephritis; *General disorders and administration site conditions:* Very common: fatigue, pyrexia; Common: oedema (including peripheral oedema), pain; Uncommon: chest pain; *Investigations*[b]: Very common: increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia[c], hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia, thrombocytopaenia, anaemia[k], hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia; Common: hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased; Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg**: *Infections and infestations:* Common: pneumonia, upper respiratory tract infection, conjunctivitis; Uncommon: bronchitis, aseptic meningitis; *Blood and lymphatic system disorders:* Uncommon: eosinophilia; *Immune system disorders:* Common: infusion related reaction, hypersensitivity; *Endocrine disorders:* Very common: hypothyroidism, hyperthyroidism; Common: adrenal insufficiency[c], hypophysitis[c], thyroiditis, diabetes mellitus[c]; Uncommon: diabetic ketoacidosis[c], hypopituitarism; Not known: hypoparathyroidism[h]; *Metabolism and nutrition disorders:* Very common: decreased appetite; Common: dehydration; Uncommon: metabolic acidosis; *Hepatobiliary disorders*: Common: hepatitis[c]; *Nervous system disorders:* Common: headache, peripheral neuropathy, dizziness; Uncommon: polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis[c]; *Eye disorders:* Common: blurred vision; Uncommon: uveitis; *Cardiac disorders:* Common: tachycardia; Uncommon: arrhythmia (including ventricular arrhythmia), myocarditis[c]; *Vascular disorders:* Common: hypertension; *Respiratory, thoracic and mediastinal disorders:* Common: pneumonitis, dyspnoea; pleural effusion, cough; *Gastrointestinal disorders:* Very common: diarrhoea, vomiting, nausea; Common: colitis, stomatitis, pancreatitis, abdominal pain, constipation, dry mouth; Uncommon: gastritis; *Skin and subcutaneous tissue disorders:* Very common: rash[e], pruritus; Common: dry skin, erythema, urticaria; Uncommon: Stevens-Johnson syndrome, vitiligo, erythema multiforme, alopecia, psoriasis; *Musculoskeletal and connective tissue disorders:* Very common: musculoskeletal pain[g], arthralgia; Common: arthritis, muscle spasms, muscular weakness; Uncommon: polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis; *Renal and urinary disorders:* Common: renal failure (including acute kidney injury)[a,c]; Uncommon: tubulointerstitial nephritis; *General disorders and administration site conditions:* Very common: fatigue, pyrexia; Common: oedema (including peripheral oedema), pain, chest pain, chills; *Investigations*[b]: Very common: increased AST, increased ALT, increased total bilirubin, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemia[c], hypoglycaemia, lymphopaenia, leucopoenia, neutropaenia[c], thrombocytopaenia, anaemia[k], hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hypomagnesaemia, hyponatraemia; Common: hypermagnesaemia, hypernatraemia, weight decreased. *nivolumab in combination with ipilimumab for the first 4 doses then followed by nivolumab monotherapy in melanoma. **nivolumab in combination with ipilimumab for the first 4 doses then followed by nivolumab monotherapy in RCC. [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. [j] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome. [k] Anaemia is a composite term which includes, among other causes, haemolytic anaemia and autoimmune anaemia. 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. Table 7 presents the percentage for immune-related adverse reactions who were permanently discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Table 7 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4. Table 7: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen : Nivolumab 3 mg/kg monotherapy : *Immune-related adverse reaction leading to permanent discontinuation:* Pneumonitis 1.2%; Colitis 0.8%; Hepatitis 1.0%; Nephritis and Renal Dysfunction 0.3%; Endocrinopathies 0.1%; Skin 0.3%; Hypersensitivity/Infusion Reaction 0.2%; *Immune-related adverse reaction requiring high-dose corticosteroids*[a,b]: Pneumonitis 69%; Colitis 15%; Hepatitis 21%; Nephritis and Renal Dysfunction 27%; Endocrinopawthies 7%; Skin 4%; Hypersensitivity/Infusion Reaction 20%; Nivolumab 1 mg/kg in Combination with Ipilimumab 3 mg/kg *Immune-related adverse reaction leading to permanent discontinuation:* Pneumonitis 2.0%; Colitis 16%; Hepatitis 9%; Nephritis and Renal Dysfunction 1.1%; Endocrinopathies 2.7%; Skin 0.9%; Hypersensitivity/Infusion Reaction 0%; *Immune-related adverse reaction requiring high-dose corticosteroids*[a,b]: Pneumonitis 63%; Colitis 46%; Hepatitis 46%; Nephritis and Renal Dysfunction 17%; Endocrinopathies 27%; Skin 7%; Hypersensitivity/Infusion Reaction 6%; Nivolumab 3 mg/kg in Combination with Ipilimumab 1 mg/kg *Immune-related adverse reaction leading to permanent discontinuation:* Pneumonitis 2.2%; Colitis 4.0%; Hepatitis 4.4%; Nephritis and Renal Dysfunction 1.3%; Endocrinopathies 2.9%; Skin 1.5%; Hypersensitivity/Infusion Reaction 0%; *Immune-related adverse reaction requiring high-dose corticosteroids*[a,b]: Pneumonitis 59%; Colitis 26%; Hepatitis 35%; Nephritis and Renal Dysfunction 27%; Endocrinopathies 25%; Skin 7%; Hypersensitivity/Infusion Reaction 9%. [a] at least 40 mg daily prednisone equivalents; [b] frequency is based on the number of patients who experienced the immune-related adverse reaction. *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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, 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). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of pneumonitis including interstitial lung disease was 6.2% (34/547). Grade 2 and Grade 3 cases were reported in 3.1% (17/547) and 1.1% (6/547), of patients, respectively. No Grade 4 or 5 cases were reported in this study. Median time to onset was 2.6 months (range: 0.25-20.6). Resolution occurred in 31 patients (91.2%) with a median time to resolution of 6.1 weeks (range: 0.7-85.9+). *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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, 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+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of diarrhoea or colitis was 28.2% (154/547). Grade 2 and Grade 3 cases were reported in 10.4% (57/547) and 4.9% (27/547) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 1.2 months (range: 0.0-24.7). Resolution occurred in 140 patients (91.5%) with a median time to resolution of 2.4 weeks (range: 0.1-103.1+). *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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, 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). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of liver function test abnormalities was 18.5% (101/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (26/547), 6.6% (36/547), and 1.6% (9/547) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.0 months (range: 0.4-26.8). Resolution occurred in 86 patients (85.1%) with a median time to resolution of 6.1 weeks (range: 0.1+-82.9+). *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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, 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+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of nephritis or renal dysfunction was 8.8% (48/547). Grade 2, Grade 3, and Grade 4 cases were reported in 4.4% (24/547), 0.7% (4/547), and 0.5% (3/547) of patients, respectively. No Grade 5 cases were reported. Median time to onset was 2.1 months (range: 0.0-16.1). Resolution occurred in 37 patients (77.1%) with a median time to resolution of 13.2 weeks (range: 0.1+-106.0+). *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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, 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. In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of thyroid disorders was 27.2% (149/547). Grade 2 and Grade 3 thyroid disorders were reported in 15.7% (86/547) and 1.3% (7/547) of patients, respectively. Hypophysitis occurred in 4.0% (22/547) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.5% (3/547), 2.4% (13/547), and 0.4% (2/547) of patients, respectively. Grade 2 hypopituitarism occurred in 0.4% (2/547) of patients. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.9% (16/547), 2.2% (12/547) and 0.4% (2/547) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (3 Grade 2, 2 Grade 3, and 3 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. No Grade 5 endocrinopathy was reported. Median time to onset of these endocrinopathies was 1.9 months (range: 0.0-22.3). Resolution occurred in 76 patients (42.7%). Time to resolution ranged from 0.4 to 130.3+ 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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, 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+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the incidence of rash was 48.8% (267/547). Grade 2 and Grade 3 cases were reported in 13.7% (75/547) and 3.7% (20/547) of patients, respectively. No Grade 4 or 5 cases were reported. Median time to onset was 0.9 months (range: 0.0-17.9). Resolution occurred in 192 patients (72.2%) with a median time to resolution of 11.6 weeks (range: 0.1-126.7+). 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 1 mg/kg in combination with ipilimumab 3 mg/kg, 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. In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg//kg, the incidence of hypersensitivity/infusion reactions was 4.0% (22/547); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.4% (13/547) of patients. No Grade 3-5 cases were reported. *Complications of allogeneic HSCT in classical Hodgkin Lymphoma. Rapid onset of GVHD has been reported with nivolumab use before and after allogeneic HSCT (see section 4.4).* 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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, 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. In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.0% for anaemia (all Grade 3), 0.7% for thrombocytopaenia, 0.6% for leucopoenia, 5.1% for lymphopaenia, 1.1% for neutropaenia, 2.0% for increased alkaline phosphatase, 4.8% for increased AST, 6.5% for increased ALT, 1.1% for increased total bilirubin, 2.1% for increased creatinine, 7.2% for hyperglycaemia, 1.8% for hypoglycemia, 12.2% for increased amylase, 20.1% for increased lipase, 0.4% for hypocalcaemia, 1.3% for hypercalcaemia, 2.4% for hyperkalemia, 1.1% for hypermagnesaemia, 0.4% for hypomagnesaemia 1.9% for hypokalaemia, and 9.9% 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 the patients who were treated with nivolumab in combination with ipilimumab and evaluable for the presence of anti-nivolumab antibodies, the incidence of anti-nivolumab antibodies was 26.0% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks and 37.8% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. The incidence of neutralising antibodies against nivolumab was 0.5% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks and 4.6% with nivolumab 1 mg/kg and ipilimumab 3 mg/kg every 3 weeks. Of patients evaluable for the presence of anti-ipilimumab antibodies, the incidence of anti-ipilimumab antibodies ranged from 6.3 to 8.4% and neutralising antibodies against ipilimumab ranged from 0 to 0.3%. Although the clearance of nivolumab was increased by 20% 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 SCCHN and adjuvant melanoma 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. **MARKETING AUTHORISATION HOLDER** Bristol-Myers Squibb Pharma EEIG. Plaza 254. Blanchardstown Corporate Park 2. Dublin 15, D15 T867. Ireland. **MARKETING AUTHORISATION NUMBER(S)** EU/1/15/1014/001 EU/1/15/1014/002 EU/1/15/1014/003 **DATE OF REVISION OF THE TEXT** 20 January 2020. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu