OPDIVO®
(nivolumab)

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

1. NAME OF THE MEDICINAL PRODUCT OPDIVO 10 mg/mL concentrate for solution for infusion. **2. QUALITATIVE AND QUANTITATIVE COMPOSITION** Each mL of concentrate for solution for infusion 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 12 mL contains 120 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. **3. 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. **4. 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 in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation. OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults. Malignant pleural mesothelioma (MPM) OPDIVO in combination with ipilimumab is indicated for the first line treatment of adult patients with unresectable malignant pleural mesothelioma. 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). OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with 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. Mismatch repair deficient (dMMR) or microsatellite instability high (MSI-H) colorectal cancer (CRC) OPDIVO in combination with ipilimumab is indicated for the treatment of adult patients with mismatch repair deficient or microsatellite instability high metastatic colorectal cancer after prior fluoropyrimidine based combination chemotherapy (see section 5.1). Oesophageal squamous cell carcinoma (OSCC) OPDIVO as monotherapy is indicated for the treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma after prior fluoropyrimidine- and platinum-based combination chemotherapy. Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC) OPDIVO as monotherapy is indicated for the adjuvant treatment of adult patients with oesophageal or gastro-oesophageal junction cancer who have residual pathologic disease following prior neoadjuvant chemoradiotherapy (see section 5.1). **Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma** OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score (CPS) ≥ 5. **4.2 Posology and method of administration** Treatment must be initiated and supervised by physicians experienced in the treatment of cancer. PD-L1 testing If specified in the indication, patient selection for treatment with OPDIVO based on the tumour expression of PD-L1 should be confirmed by a validated test (see sections 4.1, 4.4, and 5.1). 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 Indication* Melanoma (advanced or adjuvant treatment), Renal cell carcinoma Recommended dose and infusion time : 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; Oesophageal or gastro-oesophageal junction cancer (adjuvant treatment) : 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 30 minutes for the first 16 weeks, followed by 480 mg every 4 weeks over 30 minutes; Non-small cell lung cancer, Classical Hodgkin lymphoma, Squamous cell cancer of the head and neck, Urothelial carcinoma, Oesophageal squamous cell carcinoma Recommended dose and infusion time : 240 mg every 2 weeks over 30 minutes *As per monotherapy indication in section 4.1. If melanoma or RCC, OC or GEJC 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 for melanoma 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 - Malignant pleural mesothelioma The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks. Treatment is continued for up to 24 months in patients without disease progression. Renal cell carcinoma and dMMR or MSI-H colorectal cancer 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 (RCC only), 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 (RCC only). Table 3: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for RCC and dMMR or MSI-H CRC 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 (RCC only) Ipilimumab Combination phase, every 3 weeks for 4 dosing cycles : 1 mg/kg over 30 minutes - *OPDIVO in combination with cabozantinib* *Renal cell carcinoma* The recommended dose is nivolumab administered intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks in combination with 40 mg cabozantinib administered orally every day. Table 4: Recommended doses and infusion times for intravenous administration of nivolumab in combination with oral administration of cabozantinib for RCC **Nivolumab** Combination phase: 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes **Cabozantinib** Combination phase: 40 mg once daily. *OPDIVO in combination with ipilimumab and chemotherapy* Non small cell lung cancer The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered intravenously every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. *OPDIVO in combination with chemotherapy* *Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma* The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks **or** 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. *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 (and up to maximum duration of therapy if specified for an indication). For adjuvant therapy, the maximum treatment duration with OPDIVO is 12 months. For OPDIVO in combination with cabozantinib, OPDIVO should be continued until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. Cabozantinib should be continued until disease progression or unacceptable toxicity. Refer to the Summary of Product Characteristics (SmPC) for cabozantinib. 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 for OPDIVO as monotherapy or in combination with other therapeutic agents. 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 5. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4. When nivolumab is administered in combination with other therapeutic agents, refer to the SmPC of these other combination therapeutic agents regarding dosing. Table 5: Recommended treatment modifications for OPDIVO or OPDIVO in combination **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 - 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. **NOTE**: for RCC patients treated with **OPDIVO in combination with cabozantinib** with liver enzyme elevations, see dosing guidelines following this table. **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, Severity : Grade 2 adrenal insufficiency Severity : 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 Severity : Grade 4 hyperthyroidism Severity : Grade 4 hypophysitis Severity : Grade 3 or 4 adrenal insufficiency Severity : 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 complete[c] 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 Severity : 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 as monotherapy or in combination with other therapeutic agents 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. When OPDIVO is administered in combination with chemotherapy, refer to the SmPC of the other combination therapy agents regarding dosing. Dose escalation or reduction is not recommended for OPDIVO. If any agents are withheld, the other agents may be continued. If dosing is resumed after a delay, either the combination treatment, OPDIVO monotherapy or chemotherapy alone could be resumed based on the evaluation of the individual patient. *OPDIVO in combination with cabozantinib in RCC* When OPDIVO is used in combination with cabozantinib, the above treatment modifications in Table 5 also apply to the OPDIVO component. In addition, for liver enzyme elevations, in patients with RCC being treated with OPDIVO in combination with cabozantinib: - If ALT or AST > 3 times ULN but ≤ 10 times ULN without concurrent total bilirubin ≥ 2 times ULN, both OPDIVO and cabozantinib should be withheld until these adverse reactions recover to Grades 0-1. Corticosteroid therapy may be considered. Rechallenge with a single medicine or rechallenge with both medicines after recovery may be considered. If rechallenging with cabozantinib, refer to cabozantinib SmPC. - If ALT or AST > 10 times ULN or > 3 times ULN with concurrent total bilirubin ≥ 2 times ULN, both OPDIVO and cabozantinib should be permanently discontinued and corticosteroid therapy may be considered. *Special populations* *Paediatric population* The safety and efficacy of OPDIVO in children below 18 years of age have not been established. Currently available data of OPDIVO as monotherapy or in combination with ipilimumab are described in sections 4.8 and 5.1 but no recommendation on a posology can be made. *Elderly* No dose adjustment is required for elderly patients (≥ 65 years) (see section 5.2). *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, 3 and 4). 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 mm. 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 and/or chemotherapy, OPDIVO should be given first followed by ipilimumab (if applicable) and then by chemotherapy 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 as monotherapy across tumour types (n = 3771) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (46%), musculoskeletal pain (31%), diarrhoea (26%), nausea (24%), cough (24%), rash (24%), dyspnoea (18%), pruritus (18%), decreased appetite (18%), constipation (17%), abdominal pain (16%), upper respiratory tract infection (16%), arthralgia (15%), pyrexia (14%), vomiting (14%), headache (13%) and oedema (11%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). With a minimum of 63 months follow-up in NSCLC, no new safety signals were identified. *Tabulated summary of adverse reactions* Adverse reactions reported in the pooled dataset for patients treated with nivolumab monotherapy (n = 3771) 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 monotherapy Nivolumab monotherapy Infections and infestations** Very common upper respiratory tract infection Common pneumonia[a], bronchitis Rare aseptic meningitis[i] Neoplasms benign, malignant and unspecified (including cysts and polyps) Rare histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)-Blood and lymphatic system disorders Uncommon eosinophilia Not known haemophagocytic lymphohistiocytosis Immune system disorders Common infusion related reaction[c], hypersensitivity (including anaphylactic reaction)[c] Uncommon sarcoidosis Not known solid organ transplant rejection[h] Endocrine disorders Common hypothyroidism, hyperthyroidism, thyroiditis Uncommon adrenal insufficiency[l], hypopituitarism, hypophysitis, diabetes mellitus Rare diabetic ketoacidosis, hypoparathyroidism[i] Metabolism and nutrition disorders Very common decreased appetite Common dehydration Uncommon metabolic acidosis Not known tumour lysis syndrome[i] Nervous system disorders Very common headache Common peripheral neuropathy, dizziness Uncommon polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis) Rare Guillain-Barré syndrome, demyelination, myasthenic syndrome, encephalitis[a,c,m] Eye disorders Common blurred vision, dry eye Uncommon uveitis Not known Vogt-Koyanagi-Harada syndrome[h] Cardiac disorders Common tachycardia, atrial fibrillation Uncommon pericardial disorders[j], arrhythmia (including ventricular arrhythmia)[d] Rare myocarditis[a,f] Vascular disorders Common hypertension Rare vasculitis Respiratory, thoracic and mediastinal disorders Very common dyspnoea[a], cough Common pneumonitis[a,c], pleural effusion Uncommon lung infiltration Gastrointestinal disorders Very common diarrhoea, vomiting, nausea, abdominal pain, constipation Common colitis[a], stomatitis, dry mouth Uncommon pancreatitis, gastritis Rare duodenal ulcer Hepatobiliary disorders Uncommon hepatitis[c], cholestasis 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], Not known lichen sclerosus, other lichen disorders Musculoskeletal and connective tissue disorders Very common musculoskeletal pain[g], arthralgia Common arthritis Uncommon polymyalgia rheumatica 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 Rare cystitis noninfective[i] General disorders and administration site conditions Very common fatigue, pyrexia, oedema[n] Common pain, chest pain Investigations[b] Very common lymphopaenia, hyperglycaemiac, anaemia[k], increased AST, hyponatraemia, hypoalbuminaemia, increased alkaline phosphatase, increased creatinine, increased ALT, increased lipase, hyperkalaemia, increased amylase, hypocalcaemia, leucopoenia, hypomagnesaemia, neutropaenia[a,b], thrombocytopaenia, hypokalaemia, hypoglycaemia, hypercalcaemia Common increased total bilirubin, hypernatraemia, hypermagnesaemia, weight decreased Adverse reaction frequencies may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease. [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 reactions 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 reactions 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, myalgia intercostal, 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, haemoglobin decreased, iron deficiency anaemia and red blood cell count decreased. [l] Includes adrenal insufficiency and secondary adrenocortical insufficiency. [m] Includes encephalitis and limbic encephalitis. [n] Includes generalised oedema, oedema peripheral, peripheral swelling and swelling. 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 SmPC 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. With a minimum of 60 months follow up from study CA209067, no new safety signals were identified. *RCC and dMMR or MSI-H CRC* In the pooled dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg across tumour types (n = 666), with a minimum follow-up ranging from17.5 to 27.6 months, the most frequent adverse reactions (≥ 10%) were fatigue (58%), diarrhoea (41%), musculoskeletal pain (39%), rash (38%), pruritus (35%), nausea (30%), cough (29%), pyrexia (29%), abdominal pain (22%), arthralgia (22%), decreased appetite (22%), upper respiratory tract infection (21%) , vomiting (21%), headache (19%), dyspnoea (19%), hypothyroidism (18%), constipation (18%), oedema (including peripheral oedema) (16%), dizziness (14%), hyperthyroidism (12%), dry skin (11%), hypertension (10%). 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, 194/666 (29%) had the first onset of Grade 3 or 4 adverse reactions during the initial combination phase. Among the 474 patients in this group who continued treatment in the single-agent phase, 168 (35%) experienced at least one Grade 3 or 4 adverse reaction during the single-agent phase. *MPM* In the dataset of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM (n = 300), with a minimum follow-up of 22,1 months, the most frequent adverse reactions (≥ 10%) were fatigue (43%), diarrhoea (31%), rash (30%), musculoskeletal pain (27%), nausea (24%), decreased appetite (24%), pruritus (21%), constipation (19%), and hypothyroidism (13%). 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 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma (n = 448), for patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI-H CRC (n = 666) , and for patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM (n = 300) are presented in Table 7. 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 7: Adverse reactions with nivolumab in combination with ipilimumab** Infections and infestations Very Common Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: upper respiratory tract infection Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: pneumonia, upper respiratory tract infection Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: pneumonia, bronchitis, conjunctivitis Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : bronchitis Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: aseptic meningitis Not known Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : aseptic meningitis[h] Blood and lymphatic system disorders Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: eosinophilia Uncommon Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: eosinophilia Not known Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: haemophagocytic lymphohistiocytosis Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: haemophagocytic lymphohistiocytosis Immune system disorders Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: infusion related reaction, hypersensitivity Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: infusion-related reaction, hypersensitivity Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: infusion-related reaction, hypersensitivity Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : sarcoidosis Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: sarcoidosis Not known Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : solid organ transplant rejection[h] Endocrine disorders Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: hypothyroidism-Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: hypothyroidism, hyperthyroidism Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: hypothyroidism Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: adrenal insufficiency, hypopituitarism, hypophysitis, hyperthyroidism, thyroiditis Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: adrenal insufficiency[c], hypophysitis[c], thyroiditis, diabetes mellitus[c] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: hyperthyroidism, adrenal insufficiency, hypophysitis, hypopituitarism Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : diabetic ketoacidosis[c], diabetes mellitus[c] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: diabetic ketoacidosis[c], hypopituitarism Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: thyroiditis Not known Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: hypoparathyroidism[h] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: hypoparathyroidism[h] Metabolism and nutrition disorders Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: decreased appetite-Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: decreased appetite Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: decreased appetite Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : dehydration Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: dehydration Uncommon Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: metabolic acidosis Not known Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: tumour lysis syndrome[i] Nervous system disorders Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : Headache Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: headache, dizziness Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : peripheral neuropathy, dizziness Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: peripheral neuropathyUncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: Guillain-Barré syndrome, polyneuropathy, neuritis, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis[c] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis[c] , encephalitis Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: encephalitis Eye disorders Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: uveitis, blurred vision Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: blurred vision Uncommon Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: uveitis Not known Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : Vogt-Koyanagi-Harada syndrome[h] Cardiac disorders Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : tachycardia Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: tachycardia Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : arrhythmia (including ventricular arrhythmia)[a,d], atrial fibrillation, myocarditis[a,f] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: arrhythmia (including ventricular arrhythmia), myocarditis[c] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: myocarditis Not known Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: pericardial disorders[j] Vascular disorders Very common Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: hypertension Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : hypertension Respiratory, thoracic and mediastinal disorders Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: dyspnoea Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: dyspnoea, cough Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: pneumonitis[a,c], pulmonary embolism[a], cough Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: pneumonitis, pleural effusion Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: pneumonitis Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma : pleural effusion Gastrointestinal disorders Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : colitis[a], diarrhoea, vomiting, nausea, abdominal pain Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: diarrhoea, vomiting, nausea, abdominal pain, constipation Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: diarrhoea, nausea, constipation Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : stomatitis, pancreatitis, constipation, dry mouth Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: colitis, stomatitis, pancreatitis, dry mouth, gastritis Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: colitis, pancreatitis Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: intestinal perforation[a], gastritis, duodenitis Hepatobiliary disorders Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: hepatitis[c] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: hepatitis[c] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: hepatitis Skin and subcutaneous tissue disorders Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: rash[e], pruritus Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: rash[e], pruritus, dry skin Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: rash[e], pruritus Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: vitiligo, dry skin, erythema, alopecia, urticaria Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: erythema, alopecia, urticaria Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: psoriasis Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: Stevens-Johnson syndrome, vitiligo, erythema multiforme, psoriasis Rare Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : toxic epidermal necrolysis[a,f] Stevens-Johnson syndrome[f] Not known Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: lichen sclerosus, other lichen disorders Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in melanoma*: lichen sclerosus, other lichen disorders Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: lichen sclerosus, other lichen disorders Musculoskeletal and connective tissue disorders Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : arthralgia Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: musculoskeletal pain[g], arthralgia Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: musculoskeletal pain[g] Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : musculoskeletal pain[g] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: arthritis, muscle spasms, muscular weakness Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: arthritis Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: spondyloarthropathy, Sjogren's syndrome, arthritis, myopathy, myositis (including polymyositis)[a,e], rhabdomyolysis[a,f] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: polymyalgia rheumatica, myositis (including polymyositis), rhabdomyolysis Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: myositis Renal and urinary disorders Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: renal failure (including acute kidney injury)[a,c] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: renal failure (including acute kidney injury)[c] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: acute kidney injury,

renal failure Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : tubulointerstitial nephritis, cystitis noninfective[i] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: tubulointerstitial nephritis, cystitis noninfective[i] Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: cystitis noninfective[i] General disorders and administration site conditions Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : fatigue, pyrexia Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: fatigue, pyrexia, oedema (including peripheral oedema) Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: fatigue Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: oedema (including peripheral oedema), pain Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: pain, chest pain, chills Uncommon Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma* : chest pain Investigations[b] Very common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: 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 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC **: 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 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: increased AST, increased ALT, increased alkaline phosphatase, increased lipase, increased amylase, increased creatinine, hyperglycaemiac, lymphopaenia, anaemiak, hypercalcaemia, hypocalcaemia, hyperkalaemia, hypokalaemia, hyponatraemia, hypomagnesaemia Common Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma*: hypercalcaemia, hypermagnesaemia, hypernatraemia, weight decreased Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg**: hypermagnesaemia, hypernatraemia, weight decreased Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM***: increased total bilirubin, hypoglycaemia, leucopoenia, neutropaeniac, thrombocytopaenia, hypernatraemia, hypermagnesaemia * 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 and dMMR or MSI H CRC. ***nivolumab in combination with ipilimumab in MPM. [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 reactions 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 reactions 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.

Nivolumab in combination with other therapeutic agents (see section 4.2)

Summary of the safety profile When nivolumab is administered in combination, refer to the SmPC for the respective combination therapy components prior to initiation of treatment. In the dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma (n = 782), with a minimum follow-up of 12.1 months, the most frequent adverse reactions were peripheral neuropathy (53%), nausea (48%), fatigue (44%), diarrhoea (39%), vomiting (31%), decreased appetite (29%), abdominal pain (27%), constipation (25%), musculoskeletal pain (20%), pyrexia (19%), rash (18%), stomatitis (17%), palmar-plantar erythrodysaesthesia syndrome (13%), cough (13%), oedema (including peripheral oedema) (12%), headache (11%), and upper respiratory tract infection (10%). Incidences of Grade 3-5 adverse reactions were 76% for nivolumab in combination with chemotherapy and 64% for chemotherapy alone. Median duration of therapy was 6.75 months (95% CI: 6.11, 7.36) for nivolumab in combination with chemotherapy and 4.86 months (95% CI: 4.47, 5.29) for chemotherapy. In the dataset of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of chemotherapy in NSCLC (n = 358), with a minimum follow-up of 6.5 months, the most frequent adverse reactions were fatigue (36%), nausea (26%), rash (25%), diarrhoea (20%), pruritus (18%), decreased appetite (16%), hypothyroidism (15%), and vomiting (13%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). Median duration of therapy was 6.1 months (95% CI 4.93, 7.06) for nivolumab in combination with ipilimumab and chemotherapy and 2.4 months (95% CI 2.30, 2.83) for chemotherapy.

Tabulated summary of adverse reactions Adverse reactions reported in the dataset for patients treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma (n = 782) and for patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of chemotherapy in NSCLC (n = 358) are presented in Table 8. 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 8:Adverse reactions with nivolumab in combination with other therapeutic agents

Infections and infestations Very common Nivolumab in combination with chemotherapy: upper respiratory tract infection Common Nivolumab in combination with chemotherapy: pneumonia Nivolumab in combination with ipilimumab and chemotherapy: conjunctivitis, pneumonia, respiratory tract infection Blood and lymphatic system disorders Common Nivolumab in combination with chemotherapy: febrile neutropaenia, eosinophilia Nivolumab in combination with ipilimumab and chemotherapy: febrile neutropaenia Uncommon Nivolumab in combination with ipilimumab and chemotherapy: eosinophilia Immune system disorders Common Nivolumab in combination with chemotherapy: hypersensitivity, infusion related reaction Nivolumab in combination with ipilimumab and chemotherapy: infusion-related reaction, hypersensitivity Endocrine disorders Very common Nivolumab in combination with ipilimumab and chemotherapy: hypothyroidism Common Nivolumab in combination with chemotherapy: hypothyroidism, hyperthyroidism Nivolumab in combination with ipilimumab and chemotherapy: hyperthyroidism, adrenal insufficiency, hypophysitis, thyroiditis Uncommon Nivolumab in combination with chemotherapy: hypopituitarism, adrenal insufficiency, hypophysitis, diabetes mellitus Nivolumab in combination with ipilimumab and chemotherapy: hypopituitarism, hypoparathyroidism Metabolism and nutrition disorders Very common Nivolumab in combination with chemotherapy: decreased appetite Nivolumab in combination with ipilimumab and chemotherapy: decreased appetite Common Nivolumab in combination with ipilimumab and chemotherapy: dehydration, hypoalbuminaemia, hypophosphataemia Nervous system disorders Very Common Nivolumab in combination with chemotherapy: peripheral neuropathy, headache Common Nivolumab in combination with chemotherapy: paraesthesia, dizziness Nivolumab in combination with ipilimumab and chemotherapy: peripheral neuropathy, dizziness Uncommon Nivolumab in combination with chemotherapy: Guillain-Barré syndrome Nivolumab in combination with ipilimumab and chemotherapy: polyneuropathy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis Eye disorders Common Nivolumab in combination with chemotherapy: dry eye, blurred vision Nivolumab in combination with ipilimumab and chemotherapy: dry eye Uncommon Nivolumab in combination with chemotherapy: uveitis Nivolumab in combination with ipilimumab and chemotherapy: blurred vision, episcleritis Cardiac disorders Common Nivolumab in combination with chemotherapy: tachycardia Uncommon Nivolumab in combination with chemotherapy: myocarditis Nivolumab in combination with ipilimumab and chemotherapy: tachycardia, atrial fibrillation, bradycardia Vascular disorders Common Nivolumab in combination with chemotherapy: thrombosis, hypertension Uncommon Nivolumab in combination with ipilimumab and chemotherapy: hypertension Respiratory, thoracic and mediastinal disorders Very common Nivolumab in combination with chemotherapy: cough Common Nivolumab in combination with chemotherapy: pneumonitis, dyspnoea Nivolumab in combination with ipilimumab and chemotherapy: pneumonitis, dyspnoea, cough Uncommon Nivolumab in combination with ipilimumab and chemotherapy: pleural effusion Gastrointestinal disorders Very common Nivolumab in combination with chemotherapy: diarrhoea, stomatitis, vomiting, nausea, abdominal pain, constipation Nivolumab in combination with ipilimumab and chemotherapy: nausea, diarrhoea, vomiting Common Nivolumab in combination with chemotherapy: colitis, dry mouth Nivolumab in combination with ipilimumab and chemotherapy: constipation, stomatitis, abdominal pain, colitis, dry mouth, pancreatitis Uncommon Nivolumab in combination with chemotherapy: pancreatitis Hepatobiliary disorders Common Nivolumab in combination with ipilimumab and chemotherapy: hepatitis Uncommon Nivolumab in combination with chemotherapy: hepatitis Skin and subcutaneous tissue disorders Very common Nivolumab in combination with chemotherapy: palmar-plantar erythrodysaesthesia syndrome, rash[a] Nivolumab in combination with ipilimumab and chemotherapy: rash[a], pruritus Common Nivolumab in combination with chemotherapy: pruritus, skin hyperpigmentation, alopecia, dry skin, erythema Nivolumab in combination with ipilimumab and chemotherapy: alopecia, dry skin, erythema, urticaria Uncommon Nivolumab in combination with ipilimumab and chemotherapy: psoriasis, Stevens-Johnson syndrome, vitiligo Not known Nivolumab in combination with ipilimumab and chemotherapy: lichen sclerosus, other lichen disorders Musculoskeletal and connective tissue disorders Very common Nivolumab in combination with chemotherapy: musculoskeletal pain[b] Common Nivolumab in combination with chemotherapy: arthralgia, muscular weakness Nivolumab in combination with ipilimumab and chemotherapy: musculoskeletal pain[b], arthralgia, arthritis Uncommon Nivolumab in combination with ipilimumab and chemotherapy: muscular weakness, muscle spasms, polymyalgia rheumatica Renal and urinary disorders Common Nivolumab in combination with chemotherapy: renal failure Nivolumab in combination with ipilimumab and chemotherapy: renal failure (including acute kidney injury) Uncommon Nivolumab in combination with chemotherapy: nephritis, cystitis noninfective[e] Nivolumab in combination with ipilimumab and chemotherapy: nephritis, cystitis noninfective[e] General disorders and administration site conditions Very common Nivolumab in combination with chemotherapy: fatigue, pyrexia, oedema (including peripheral oedema) Nivolumab in combination with ipilimumab and chemotherapy: fatigue Common Nivolumab in combination with ipilimumab and chemotherapy: pyrexia, oedema (including peripheral oedema) Uncommon Nivolumab in combination with ipilimumab and chemotherapy: chills, chest pain Investigations Very common Nivolumab in combination with chemotherapy: anaemia[c,d], thrombocytopaenia[c], leucopoenia[c], lymphopaenia[c], neutropaenia[c], increased transaminases[c], increased total bilirubin[c], increased creatinine[c], hypernatraemia[c], hyponatraemia[c], hyperkalaemia[c], hypokalaemia[c], hypocalcaemia[c], hypoglycaemia[c], hyperglycaemia[c], increased lipase, increased alkaline phosphatase, increased amylase Nivolumab in combination with ipilimumab and chemotherapy: anaemia[c,d], thrombocytopaenia[c], leucopoenia[c], lymphopaenia[c], neutropaenia[c], increased alkaline phophatases[c], increased transaminases[c], increased creatinine[c], increased amylase[c], increased lipase[c], hypokalaemia[c], hypomagnesaemia[c], hyponatraemia[c] Common Nivolumab in combination with chemotherapy: hypercalcaemia[c] Nivolumab in combination with ipilimumab and chemotherapy: increased total bilirubin[c], increased thyroid stimulating hormone Uncommon Nivolumab in combination with ipilimumab and chemotherapy: increased gamma-glutamyltransferase. [a] Rash is a composite term which includes maculopapular rash, rash erythematous, rash pruritic, rash macular, rash morbilliform, rash papular, rash generalised, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, drug eruption, and exfoliative rash, nodular rash, rash vesicular. [b] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, myalgia, neck pain, pain in extremity, spinal pain, and musculoskeletal discomfort. [c] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements. [d] Anaemia is a composite term which includes iron deficiency anaemia, and haemoglobin decreased. [e] Reported in clinical studies and in the post-marketing setting.

Nivolumab in combination with cabozantinib (see section 4.2)

Summary of the safety profile When nivolumab is administered in combination with cabozantinib, refer to the SmPC for cabozantinib prior to initiation of treatment. For additional information on the safety profile of cabozantinib monotherapy, please refer to the cabozantinib SmPC. *RCC* In the dataset of nivolumab 240 mg every 2 weeks in combination with cabozantinib 40 mg once daily in RCC (n =320), with a minimum follow-up of 16.0 months, the most frequent adverse reactions (≥ 10%) were diarrhoea (64.7%), fatigue (51.3%), palmar-plantar erythrodysaesthesia syndrome (40.0%), stomatitis (38.8%), musculoskeletal pain (37.5%), hypertension (37.2%), rash (36.3%), hypothyroidism (35.6%), decreased appetite (30.3%), nausea (28.8%), abdominal pain (25.0%), dysguesia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The majority of adverse reactions were mild to moderate (Grade 1 or 2).

Tabulated summary of adverse reactions Adverse reactions reported in the dataset for patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg (n = 320) are presented in Table 9. 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) , 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 9: Adverse reactions with nivolumab in combination with cabozantinib

Infections and infestations Very common upper respiratory tract infection Common pneumonia; Blood and lymphatic system disorders Common eosinophilia; Immune system disorders Common hypersensitivity (including anaphylactic reaction) Uncommon infusion related hypersensitivity reaction; Endocrine disorders Very common hypothyroidism, hyperthyroidism Common adrenal insufficiency Uncommon hypophysitis, thyroiditis; Metabolism and nutrition disorders Very common decreased appetite Common dehydration; Nervous system disorders Very common dysgeusia, dizziness, headache Common peripheral neuropathy Uncommon encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome; Ear and labyrinth disorders Common tinnitus; Eye disorders Common dry eye, blurred vision Uncommon uveitis; Cardiac disorders Common atrial fibrillation, tachycardia Uncommon myocarditis; Vascular disorders Very common hypertension Common thrombosis[a]; Respiratory, thoracic and mediastinal disorders Very common dysphonia, dyspnoea, cough Common pneumonitis, pulmonary embolism, pleural effusion, epistaxis; Gastrointestinal disorders Very common diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia Common colitis, gastritis, oral pain, dry mouth, haemorrhoids Uncommon pancreatitis, small intestine perforation[b], glossodynia; Hepatobiliary disorders Common hepatitis; Skin and subcutaneous tissue disorders Very common palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus Common alopecia, dry skin, erythema, hair colour change Uncommon psoriasis, urticaria Not known lichen sclerosus, other lichen disorders; Musculoskeletal and connective tissue disorders Very common musculoskeletal pain[d], arthralgia, muscle spasm Common arthritis Uncommon myopathy, osteonecrosis of the jaw, fistula; Renal and urinary disorders Very common proteinuria Common renal failure, acute kidney injury Uncommon nephritis Rare cystitis noninfective[f]; General disorders and administration site conditions Very common fatigue, pyrexia, oedema Commonpain, chest pain; Investigations[e] Very common anaemia, thrombocytopaenia, leucopoenia, lymphopaenia, neutropaenia, increased alkaline phosphatase, increased ALT, increased AST, increased total bilirubin, increased creatinine, increased amylase, increased lipase, hypokalaemia, hypomagnesaemia, hyponatraemia, hypocalcaemia, hypercalcaemia, hypoglycaemia, hypophosphataemia, hyperglycaemia, hyperkalaemia, hypermagnesaemia, hypernatraemia, weight decreased Common blood cholesterol increased, hypertriglyceridaemia Adverse reaction frequencies presented in Table 9 may not be fully attributable to nivolumab alone but may contain contributions from the underlying disease or from medicinal product used in combination. [a] Thrombosis is a composite term which includes portal vein thrombosis, pulmonary vein thrombosis, pulmonary thrombosis, aortic thrombosis, arterial thrombosis, deep vein thrombosis, pelvic vein thrombosis, vena cava thrombosis, venous thrombosis, limb venous thrombosis. [b] Fatal cases have been reported. [c] Rash is a composite term which includes dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, exfoliative rash, rash erythematous, rash follicular, rash macular, rash maculo-papular, rash papular, rash morbilliform, rash pruritic, and drug eruption. [d] Musculoskeletal pain is a composite term which includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, neck pain, pain in extremity, spinal pain. [e] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements (with the exception of weight decreased, blood cholesterol increased, and hypertriglyceridaemia). See "Description of selected adverse reactions; laboratory abnormalities" below [f] Reported in clinical studies and in the post-marketing setting.

Description of selected adverse reactions

Nivolumab or nivolumab in combination with other therapeutic agents 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 or cabozantinib than in those receiving nivolumab monotherapy. Tables 10 and 11 present the percentage for immune-related adverse reactions who were permanently discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Tables 10 and 11 present 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 10: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab monotherapy or nivolumab in combination with ipilimumab)

Immune-related adverse reaction leading to permanent discontinuation Pneumonitis Nivolumab 3 mg/kg or 240 mg monotherapy % : 1.4 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 2.0 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 2.3 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%: 2.3 Colitis Nivolumab 3 mg/kg or 240 mg monotherapy % : 1.0 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 16 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 3.6 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:5.0 Hepatitis Nivolumab 3 mg/kg or 240 mg monotherapy % : 0.9 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 9 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 4.5 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:3.7 Nephritis and renal dysfunction Nivolumab 3 mg/kg or 240 mg monotherapy % : 0.2 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 1.1 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 1.4 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:1.3 Endocrinopathies Nivolumab 3 mg/kg or 240 mg monotherapy % : 0.3 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 2.7 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 2.9 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%: 0.3 Skin Nivolumab 3 mg/kg or 240 mg monotherapy % : 0.6 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 0.9 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 1.2 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:0.7 Hypersensitivity/Infusion reaction Nivolumab 3 mg/kg or 240 mg monotherapy % : 0.1 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 0 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 0 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:1.7 ***Immune-related adverse reaction requiring high-dose corticosteroids[a,b]*** Pneumonitis Nivolumab 3 mg/kg or 240 mg monotherapy % : 67 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 63 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 58 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:70 Colitis Nivolumab 3 mg/kg or 240 mg monotherapy % : 13 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 46 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 24 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:33 Hepatitis Nivolumab 3 mg/kg or 240 mg monotherapy % : 20 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 46 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 36 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:42 Nephritis and renal dysfunction Nivolumab 3 mg/kg or 240 mg monotherapy % : 24 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 17 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 26 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:40 Endocrinopathies Nivolumab 3 mg/kg or 240 mg monotherapy % : 7 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 27 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 24 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:10 Skin Nivolumab 3 mg/kg or 240 mg monotherapy % : 3 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 7 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 8 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:8 Hypersensitivity/Infusion reaction Nivolumab 3 mg/kg or 240 mg monotherapy % : 18 Nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma %: 6 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC %: 12 Nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM%:17 [a] at least 40 mg daily prednisone equivalents [b] frequency is based on the number of patients who experienced the immune-related adverse reaction

Table 11: Immune related adverse reactions leading to permanent discontinuation or requiring high dose corticosteroids by dosing regimen (nivolumab in combination with other therapeutic agents)

Immune related adverse reaction leading to permanent discontinuation Pneumonitis Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 1.9 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 2.2 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 2.5 Colitis Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 2.8 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 4.2 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %:2.5 Hepatitis Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 1.2 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 3.4 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 4.1 Nephritis and renal dysfunction Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 1.2 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 1.4 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 0.6 Endocrinopathies Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 0.4 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 2.0 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 1.3 Skin Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 1.4 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 1.1 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 2.2 Hypersensitivity/Infusion reaction Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 3.3 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 0.6 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 0 ***Immune related adverse reaction requiring high dose corticosteroids[a,b]*** Pneumonitis Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 65 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 68 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 56 Colitis Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 8 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 20 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 8 Hepatitis Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 8.9 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 29 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 23 Nephritis and renal dysfunction Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 15.4 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 24 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 9 Endocrinopathies Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 5.6 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 8 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC 4.2 Skin Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 6.5 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 10 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 8 Hypersensitivity/Infusion reaction Nivolumab 240 mg or 360 mg in combination with chemotherapy %: 23.4 Nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy in NSCLC %: 29 Nivolumab 240 mg in combination with cabozantinib 40 mg in RCC %: 0 [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, was3.4% (128/3771). The majority of cases were Grade 1 or 2 in severity reported in 0.8% (31/3771) and 1.8% (67/3771) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (27/3771) and <0.1% (1/3771) of patients respectively. Grade 5 cases were reported in < 0.1% (2/3771) of patients in these studies. Median time to onset was 3.2 months (range: 0.2 19.6). Resolution occurred in 88 patients (68.8%) with a median time to resolution of 6.6 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 and dMMR or MSI H CRC, the incidence of pneumonitis including interstitial lung disease was 6.5% (43/666). Grade 2 and Grade 3 cases were reported in 3.3% (22/666) and 1.1% (7/666), of patients, respectively. Median time to onset was 2.7 months (range: 0.25-56.8). Resolution occurred in 39 patients (90.7%) with a median time to resolution of 6.1 weeks (range: 0.7-110.3+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of pneumonitis including interstitial lung disease was 6.7% (20/300). Grade 2 and Grade 3 cases were reported in 5.3% (16/300) and 0.7% (2/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.3 20.8). Resolution occurred in 16 patients (80%) with a median time to resolution of 6.1 weeks (range: 1.1 113.1+). In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, the incidence of pneumonitis including interstitial lung disease was 5.1% (40/782). Grade 2, Grade 3, and Grade 4 cases were reported in 2.3% (18/782), 1.4% (11/782), and 0.4% (3/782), of patients, respectively. Median time to onset was 23.9 weeks (range: 1.6-96.9). Resolution occurred in 28 patients (70%) with a median time to resolution of 10.1 weeks (range: 0.3+-121.3+). In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of pneumonitis including interstitial lung disease was 5.3% (19/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.1% (4/358), and 0.6% (2/358) of patients, respectively. Median time to onset was 18.1 weeks (range: 0.6-52.4). Resolution occurred in 14 patients (74%) with a median time to resolution of 4.3 weeks (range: 0.7-27.9+). In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC the incidence of pneumonitis including interstitial lung disease was 5.6% (18/320). Grade 2 and Grade 3 cases were reported in 1.9% (6/320) and 1.6% (5/320), of patients, respectively. Median time to onset was 26.9 weeks (range: 12.3-74.3 weeks). Resolution occurred in 14 patients (77.8%) with a median time to resolution of 7.5 weeks (range: 2.1-60.7+ weeks).

Immune-related colitis In patients treated with nivolumab monotherapy, the incidence of diarrhoea, colitis, or frequent bowel movements was 15.0% (566/3771). The majority of cases were Grade 1 or 2 in severity reported in 9. 7% (364/3771) and 3. 9% (146/3771) of patients respectively. Grade 3 and 4 cases were reported in 1. 5% (55/3771) and <0.1% (1/3771) of patients respectively. Median time to onset was 1.8 months (range: 0.0 26.6). Resolution occurred in 503 patients (89.8%) with a median time to resolution of 2.3 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. 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 and dMMR or MSI H CRC, the incidence of diarrhoea or colitis was 27.9% (186/666). Grade 2 and Grade 3 cases were reported in 9.6% (64/666) and 4.7% (31/666) of patients, respectively. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 170 patients (92.4%) with a median time to resolution of 2.2 weeks (range: 0.1-117.0+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of diarrhoea or colitis was 22.0% (66/300). Grade 2 and Grade 3 cases were reported in 7.3% (22/300) and 5.3% (16/300) of patients, respectively. Median time to onset was 3.9 months (range: 0.0 21.7). Resolution occurred in 62 patients (93.9%) with a median time to resolution of 3.1 weeks (range: 0.1 100.0+). In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, the incidence of diarrhoea or colitis was 33.5% (262/782). Grade 2, Grade 3, and Grade 4 cases were reported in 10.2% (80/782), 4.9% (38/782), and 0.6% (5/782) of patients, respectively. Median time to onset was 4.3 weeks (range: 0.1-93.6). Resolution occurred in 228 patients (87.4%) with a median time to resolution of 1.6 weeks (range: 0.1-117.6+). In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of diarrhoea or colitis was 22.3% (80/358). Grade 2, Grade 3, Grade 4, and Grade 5 cases were reported in 7% (25/358), 5% (18/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. Median time to onset was 5.1 weeks (range: 0.1-53.6). Resolution occurred in 70 patients (87.5%) with a median time to resolution of 1.4 weeks (range: 0.1-76.9+). In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of diarrhoea, colitis, frequent bowel movements or enteritis was 59.1% (189/320). Grade 2 and Grade 3 cases were reported in 25.6% (82/320) and 6.3% (20/320) of patients, respectively. Grade 4 were reported in 0.6% (2/320). Median time to onset was 12.9 weeks (range: 0.3-110.9 weeks). Resolution occurred in 143 patients (76.1%) with a median time to resolution of 12.9 weeks (range: 0.1-139.7+ weeks).

Immune-related hepatitis In patients treated with nivolumab monotherapy, the incidence of liver function test abnormalities was7.3% (277/3771). The majority of cases were Grade 1 or 2 in severity reported in 4.0% (150/3771) and 1.6% (62/3771) of patients respectively. Grade 3 and 4 cases were reported in 1.5% (55/3771) and 0.3% (10/3771) of patients, respectively. Median time to onset was 2.3 months (range: 0.0 27.6). Resolution occurred in 214 patients (78.4%) with a median time to resolution of 6.1 weeks (range: 0.1-126.4+) 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. 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 and dMMR or MSI H CRC, the incidence of liver function test abnormalities was 19.8% (132/666). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (32/666), 7.4% (49/666), and 1.5% (10/666) of patients, respectively. Median time to onset was 2.1 months (range: 0.3-36.6). Resolution occurred in 112 patients (84.8%) with a median time to resolution of 6.3 weeks (range: 0.1+-175.9+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of liver function test abnormalities was 12.0% (36/300). Grade 2, Grade 3, and Grade 4 cases were reported in 1.7% (5/300), 4.3% (13/300), and 1.0% (3/300) of patients, respectively. Median time to onset was 1.8 months (range: 0.5 20.3). Resolution occurred in 31 patients (86.1%) with a median time to resolution of 4.1 weeks (range: 1.0 78.3+). In patients treated with nivolumab 240 mg or 360 mg in combination chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, the incidence of liver function test abnormalities was 26% (203/782). Grade 2 and Grade 3 cases were reported in 9.0% (70/782) and 3.7% (29/782) of patients, respectively. Median time to onset was 7.9 weeks (range: 0.1-61.3). Resolution occurred in 156 patients (78%) with a median time to resolution of 10.1 weeks (range: 0.4-150.6+). In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of liver function test abnormalities was 13.4% (48/358). Grade 2, Grade 3, and Grade 4 cases were reported in 3.1% (11/358), 3.4% (12/358), and 1.1% (4/358) of patients, respectively. Median time to onset was 10.6 weeks (range: 1.1-68.3). Resolution occurred in 37 patients (80.4%) with a median time to resolution of 5 weeks (range: 0.3+-45.0+). In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of liver function test abnormalities was 41.6% (133/320). Grade 2, Grade 3, and Grade 4 cases were reported in 14.7% (47/320), 10.3% (33/320), and 0.6% (2/320) of patients, respectively. Median time to onset was 8.3 weeks (range: 0.1-107.9 weeks). Resolution occurred in 101 patients (75.9%) with a median time to resolution of 9.6 weeks (range: 0.1-89.3+ weeks).

Immune-related nephritis and renal dysfunction In patients treated with nivolumab monotherapy, the incidence of nephritis or renal dysfunction was 2.3% (87/3771). The majority of cases were Grade 1 or 2 in severity reported in 1.3% (49/3771) and 0.6% (24/3771) of patients respectively. Grade 3 and 4 cases were reported in 0.3% (13/3771) and <0.1% (1/3771) of patients, respectively. Median time to onset was 2.6 months (range: 0.0 18.2). Resolution occurred in 55 patients (66.3%) with a median time to resolution of 9.6 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. 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 and dMMR or MSI H CRC, the incidence of nephritis or renal dysfunction was 8.6% (57/666). Grade 2, Grade 3, and Grade 4 cases were reported in 3.8% (25/666), 0.6% (4/666), and 0.8% (5/666) of patients, respectively. Median time to onset was 2.1 months (range: 0.0-34.8). Resolution occurred in 45 patients (78.9%) with a median time to resolution of 10.0 weeks (range: 0.1+-106.0+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of renal dysfunction was 5.0% (15/300). Grade 2 and Grade 3 cases were reported in 2.0% (6/300) and 1.3% (4/300) of patients, respectively. Median time to onset was 3.6 months (range: 0.5 14.4). Resolution occurred in 12 patients (80.0%) with a median time to resolution of 6.1 weeks (range: 0.9 126.4+). In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, the incidence of nephritis or renal dysfunction was 3.3% (26/782). Grade 2, Grade 3, and Grade 4 cases were reported in 1% (8/782), 0.6% (5/782), and 0.1% (1/782) of patients, respectively. Median time to onset was 12.4 weeks (range: 1.7-59.4). Resolution occurred in 19 patients (73.1%) with a median time to resolution of 3.1 weeks (range: 0.1-42.4+). In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of nephritis or renal dysfunction was 7% (25/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 1.7% (6/358), and 0.6 (2/358) of patients, respectively. Median time to onset was 10.6 weeks (range: 0.1-51.3). Resolution occurred in 14 patients (56%) with a median time to resolution of 6.3 weeks (range: 0.1+-82.9+). In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of nephritis, immune mediated nephritis, renal failure, acute kidney injury, blood creatinine increased or blood urea increased was 10.0% (32/320). Grade 2 and Grade 3 cases were reported in 3.4% (11/320), and 1.3% (4/320) of patients, respectively. Median time to onset was 14.2 weeks (range: 2.1-87.1 weeks). Resolution occurred in 18 patients (58.1%) with a median time to resolution of 10.1 weeks (range: 0.6-90.9+ weeks).

Immune-related endocrinopathies In patients treated with nivolumab monotherapy, the incidence of thyroid disorders, including hypothyroidism or hyperthyroidism, was 12.0%(451/3771). The majority of cases were Grade 1 or 2 in severity reported in 5.8% (217/3771) and 6.0% (227/3771) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (7/3771) of patients. Hypophysitis (3

Grade 1, 5Grade 2, 7 Grade 3, and 1 Grade 4), hypopituitarism (5 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency and adrenocortical insufficiency acute) (1 Grade 1, 15 Grade 2, and 8 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus) (1 Grade1, 4 Grade 2 and 2 Grade 3), and diabetic ketoacidosis (2 Grade 3) were reported. Median time to onset of these endocrinopathies was 2.7 months (range: 0.3 29.1). Resolution occurred in 239 patients (48.7%). Time to resolution ranged from 0.4 to 150.0+ 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 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 and dMMR or MSI H CRC, the incidence of thyroid disorders was 26.9% (179/666). Grade 2 and Grade 3 thyroid disorders were reported in 15.3% (102/666) and 1.7% (11/666) of patients, respectively. Hypophysitis occurred in 3.9% (26/666) of patients. Grade 2, Grade 3, and Grade 4 cases were reported in 0.8% (5/666), 2.3% (15/666), and 0.3% (2/666) of patients, respectively. Grade 2 hypopituitarism occurred in 0.5% (3/666) of patients. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 3.5% (23/666), 2.0% (13/666) and 0.3% (2/666) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus (2 Grade 2, 1 Grade 3, and 2 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-27.2). Resolution occurred in 89 patients (41.4%). Time to resolution ranged from 0.4 to 257.1+ weeks. In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of thyroid disorders was 14% (43/300). Grade 2 and Grade 3 thyroid disorders were reported in 9.3% (28/300) and 1.3% (4/300) of patients, respectively. Hypophysitis occurred in 2% (6/300) of patients. Grade 2 cases were reported in 1.3% (4/300) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 1.0% (3/300) and 1.0% (3/300) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (5/300) and 0.3% (1/300) of patients, respectively. Median time to onset of these endocrinopathies was 2.8 months (range: 0.5 20.8). Resolution occurred in 17 patients (32.7%). Time to resolution ranged from 0.3 to 144.1+ weeks. In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, the incidence of thyroid disorders was 12.3% (96/782). Grade 2 thyroid disorder was reported in 6% (47/782) patients. Grade 3 hypophysitis occurred in 0.1% (1/782) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.3% (2/782) and 0.3% (2/782) of patients, respectively. Grade 2 and Grade 3 adrenal insufficiency occurred in 0.4% (3/782) and 0.1% (1/782) of patients, respectively. Grade 2 and Grade 3 diabetes mellitus including Type 1 diabetes mellitus were reported in 0.3% (2/782) of patients. Median time to onset of these endocrinopathies was 15.0 weeks (range: 2.0-124.3). Resolution occurred in 46 patients (43%). Time to resolution ranged from 0.4 to 139.1+ weeks. In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of thyroid disorders was 24% (86/358). Grade 2 and Grade 3 thyroid disorders were reported in 12.3% (44/358) and 0.3% (1/358) of patients, respectively. Hypophysitis occurred in 1.4% (5/358) of patients. Grade 2 and Grade 3 cases were reported in 0.6% (2/358) and 0.8% (3/358) of patients, respectively. Grade 2 hypopituitarism occurred in 0.3% (1/358) of patients. Grade 2 and Grade 3 adrenal insufficiency occurred in 1.7% (6/358) and 1.4% (5/358) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus was not reported. Median time to onset of these endocrinopathies was 12.1 weeks (range: 1.9-58.3). Resolution occurred in 30 patients (35.3%). Time to resolution ranged from 1.4 to 72.4+ weeks. In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of thyroid disorders was 43.1% (138/320). Grade 2 and Grade 3 thyroid disorders were reported in 23.1% (74/320) and 0.9% (3/320) of patients, respectively. Hypophysitis occurred in 0.6% (2/320) of patients, all Grade 2. Adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 4.7% (15/320) of patients. Grade 2 and Grade 3 adrenal insufficiency cases were reported in 2.2% (7/320) and 1.9% (6/320) of patients, respectively. Median time to onset of these endocrinopathies was 12.3 weeks (range: 2.0-89.7 weeks). Resolution occurred in 50 patients (35.2%). Time to resolution ranged from 0.9 to 132.0+ weeks. *Immune-related skin adverse reactions* In patients treated with nivolumab monotherapy, the incidence of rash was 28.4% (1072/3771). The majority of cases were Grade 1 in severity reported in 21.7% (818/3771) of patients. Grade 2 and Grade 3 cases were reported 5.4% (204/3771) and 1.3% (50/3771) of patients respectively. Median time to onset was 1.4 months (range: 0.0 27.9). Resolution occurred in 677 patients (63.7%) with a median time to resolution of 18.4 weeks (0.1 163.1+). 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. 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 and dMMR or MSI H CRC, the incidence of rash was 47.7% (318/666). Grade 2 and Grade 3 cases were reported in 13.7% (91/666) and 3.9% (26/666) of patients, respectively. Median time to onset was 1.0 months (range: 0.0-33.8). Resolution occurred in 228 patients (71.9%) with a median time to resolution of 12.1 weeks (range: 0.1-268.7+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of rash was 36.0% (108/300). Grade 2 and Grade 3 cases were reported in 10.3% (31/300) and 3.0% (9/300) of patients, respectively. Median time to onset was 1.6 months (range: 0.0 22.3). Resolution occurred in 71 patients (66.4%) with a median time to resolution of 12.1 weeks (range: 0.4 146.4+). In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, the incidence of rash was 27.4% (214/782). Grade 2 and Grade 3 cases were reported in 7% (55/782), and 3.3% (26/782) of patients, respectively. Median time to onset was 9.6 weeks (range: 0.1-97.4). Resolution occurred in 124 patients (57.9%) with a median time to resolution of 23.4 weeks (range: 0.1-153.6+). In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of rash was 37.7% (135/358). Grade 2, Grade 3, and Grade 4 cases were reported in 11.5% (41/358), 4.2% (14/358), and 0.3% (1/358) of patients, respectively. Median time to onset was 3.3 weeks (range: 0.1-83.1). Resolution occurred in 96 patients (71.6%) with a median time to resolution of 9.4 weeks (range: 0.1+-84.1+). In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of rash was 62.8% (201/320). Grade 2 and Grade 3 cases were reported in 23.1% (74/320) and 10.6% (34/320) of patients, respectively. Median time to onset was 6.14 weeks (range: 0.1-104.4 weeks). Resolution occurred in 137 patients (68.2%) with a median time to resolution of 18.1 weeks (range: 0.1-130.6+ weeks). 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 3.8% (144/3771), including 7 Grade 3 and 3 Grade 4 cases. In patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg in melanoma, 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. In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in RCC and dMMR or MSI H CRC, the incidence of hypersensitivity/infusion reactions was 3.8% (25/666); all were Grade 1 or 2 in severity. Grade 2 cases were reported in 2.4% (16/666) of patients. Median time to onset was 0.7 months (range: 0.0 22.6). Resolution occurred in 23 patients (92.0%) with a median time to resolution of 0.1 weeks (range: 0.1 79.1+). In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the incidence of hypersensitivity/infusion reactions was 12% (36/300); Grade 2 and Grade 3 cases were reported in 5.0% (15/300) and 1.3% (4/300) of patients, respectively. In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, the incidence of hypersensitivity/infusion reactions was 14.2% (111/782). Grade 2, Grade 3, and Grade 4 cases were reported in 8.8% (69/782), 1.9% (15/782) and 0.3% (2/782) of patients, respectively. In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the incidence of hypersensitivity/infusion reactions was 4.7% (17/358). Grade 2, Grade 3, and Grade 4 cases were reported in 2.2% (8/358), 0.3% (1/358), and 0.3% (1/358) of patients, respectively. In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the incidence of hypersensitivity/infusion reactions was 2.5% (8/320). All 8 patients were Grade 1 or 2 in severity. Grade 2 cases were reported in 0.3% (1/320) of patients. *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 62 evaluated patients from two cHL studies who underwent allogeneic HSCT after discontinuing nivolumab monotherapy, Grade 3 or 4 acute GVHD was reported in 17/62 patients (27.4%). Hyperacute GVHD, defined as acute GVHD occurring within 14 days after stem cell infusion, was reported in four 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. Steroids were used in four patients and three patients responded to steroids. Hepatic veno-occlusive disease occurred in two patients, one of whom died of GVHD and multi-organ failure. Nineteen of 62 patients (30.6%) died from complications of allogeneic HSCT after nivolumab. The 62 patients had a median follow-up from subsequent allogeneic HSCT of 38.5 months (range: 0-68 months). *Elevated liver enzymes when nivolumab is combined with cabozantinib in RCC* In a clinical study of previously untreated patients with RCC receiving nivolumab in combination with cabozantinib, a higher incidence of Grades 3 and 4 ALT increased (10.1%) and AST increased (8.2%) were observed relative to nivolumab monotherapy in patients with advanced RCC. In patients with Grade ≥2 increased ALT or AST (n=85): median time to onset was 10.1 weeks (range: 2.0 to 106.6 weeks), 26% received corticosteroids for median duration of 1.4 weeks (range: 0.9 to 75.3 weeks), and resolution to Grades 0-1 occurred in 91% with median time to resolution of 2.3 weeks (range: 0.4 to 108.1+ weeks). Among the 45 patients with Grade ≥2 increased ALT or AST who were rechallenged with either nivolumab (n=10) or cabozantinib (n=10) administered as a single agent or with both (n=25), recurrence of Grade ≥2 increased ALT or AST was observed in 3 patients receiving OPDIVO, 4 patients receiving cabozantinib, and 8 patients receiving both OPDIVO and cabozantinib. *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: 4.1% for anaemia (all Grade 3), 0.8% for thrombocytopaenia, 0.8% for leucopoenia, 10.3% for lymphopaenia, 1.0% for neutropaenia, 1.9% for increased alkaline phosphatase, 2.6% for increased AST, 2.3% for increased ALT, 1.0% for increased total bilirubin, 0.6% for increased creatinine, 2.7% for hyperglycaemia, 1.2% for hypoglycaemia, 3.5% for increased amylase, 6.7% for increased lipase, 5.3% for hyponatraemia, 1.4% for hyperkalaemia, 1.5% for hypokalaemia, 1.3% for hypercalcaemia, 0.6% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.7% for hypocalcaemia, 0.9% for hypoalbuminaemia, 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 hyperkalaemia, 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 and dMMR or MSI H CRC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.3% for anaemia (all Grade 3), 0.8% for thrombocytopaenia, 0.5% for leucopoenia, 5.3% for lymphopaenia, 1.1% for neutropaenia, 2.8% for increased alkaline phosphatase, 6.7% for increased AST, 7.8% for increased ALT, 1.8% for increased total bilirubin, 2.3% for increased creatinine, 7.2% for hyperglycaemia, 2.2% for hypoglycemia, 11.1% for increased amylase, 20.2% for increased lipase, 0.5% for hypocalcaemia, 1.2% for hypercalcaemia, 2.2% for hyperkalemia, 0.9% for hypermagnesaemia, 0.3% for hypomagnesaemia 2.2% for hypokalaemia, and 9.2% for hyponatraemia. In patients treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg in MPM, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 2.4% for anaemia, 1.0% each for thrombocytopaenia and leucopaenia, 8.4% for lymphopaenia, 1.3% for neutropaenia, 3.1% for increased alkaline phosphatase, 7.1% each for increased AST and increased ALT, 1.7% for increased total bilirubin, 0.3% for increased creatinine, 2.8% for hyperglycaemia, 5.4% for increased amylase, 12.8% for increased lipase, 0.7% for hypernatraemia, 8.1% for hyponatraemia, 4.1% for hyperkalaemia, 2.0% for hypokalaemia, and 0.3% for hypocalcaemia. In patients treated with nivolumab 240 mg or 360 mg in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 13.9% for anaemia, 6.8% for thrombocytopaenia, 11.8% leukopaenia, 12.2% for lymphopaenia, 29.3% neutropaenia, 4.6% for increased AST, 3.4% for increased ALT, 3.0% for increased bilirubin, 1.0% for increased creatinine, 0.5% for hypernatraemia, 6.3% for hyponatraemia, 1.4% for hyperkalaemia, 6.5% for hypokalaemia, 0.3% for hypercalcaemia, 1.6% for hypocalcaemia, 4.2% for hyperglycaemia, and 0.7% for hypoglycaemia. In patients treated with nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and chemotherapy in NSCLC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 9.2% for anaemia, 4.3% for thrombocytopaenia, 9.8% for leucopoenia, 5.8% for lymphopaenia, 14.7% for neutropaenia, 1.2% for increased alkaline phosphatase, 3.5% for increased AST, 4.3% for increased ALT, 0% for increased total bilirubin, 1.2% for increased creatinine, 7.1% for hyperglycaemia, 0% for hypoglycaemia, 6.7% for increased amylase, 11.9% for increased lipase, 1.4% for hypocalcaemia, 1.2% for hypercalcaemia, 1.7% for hyperkalaemia, 0.3% for hypermagnesaemia, 1.2% for hypomagnesaemia 3.5% for hypokalaemia, and 10.7% for hyponatraemia. In patients treated with nivolumab 240 mg in combination with cabozantinib 40 mg in RCC, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.5% for anaemia (all Grade 3), 0.3% for thrombocytopaenia, 0.3% for leucopoenia, 7.5% for lymphopaenia, 3.5% for neutropaenia, 3.2% for increased alkaline phosphatase, 8.2% for increased AST, 10.1% for increased ALT, 1.3% for increased total bilirubin, 1.3% for increased creatinine, 11.9% for increased amylase, 15.6% for increased lipase, 3.5% for hyperglycaemia, 0.8% for hypoglycaemia, 2.2% for hypocalcaemia, 0.3% for hypercalcaemia, 5.4% for hyperkalaemia, 4.2% for hypermagnesaemia, 1.9% for hypomagnesaemia 3.2% for hypokalaemia, 12.3% for hyponatraemia, and 21.2% for hypophosphataemia. *Immunogenicity* Of the 3224 patients who were treated with nivolumab monotherapy 3 mg/kg or 240 mg every 2 weeks and evaluable for the presence of anti product antibodies, 286 patients (8.9%) tested positive for treatment emergent anti product antibodies with sixteen patients (0.5%) testing positive for neutralising antibodies. Co-administration with chemotherapy did not affect nivolumab immunogenicity. Of the patients who were treated with nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy and evaluable for the presence of anti-product-antibodies, 8.8% tested positive for treatment emergent anti-product-antibodies with 0.3% tested 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, 25.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 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 0.8% with nivolumab 3 mg/kg and ipilimumab 1 mg/kg every 3 weeks, 0.7% with nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 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 13.7% and neutralising antibodies against ipilimumab ranged from 0 to 0.4%. Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-nivolumab antibodies or neutralising antibodies against nivolumab, the incidence of anti-nivolumab antibodies was 33.8% and the incidence of neutralising antibodies was 2.6%. Of the patients who were treated with nivolumab in combination with ipilimumab and chemotherapy and evaluable for the presence of anti-ipilimumab antibodies or neutralising antibodies against ipilimumab, the incidence of anti-ipilimumab antibodies was 7.5%, and the neutralising antibodies was 1.6%. 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. Paediatric population Only limited safety data of nivolumab as monotherapy or in combination with ipilimumab in children below 18 years of age are available (see section 5.1). No new safety signals were observed in clinical study CA209908 of 151 paediatric patients with high-grade primary central nervous system (CNS) malignancies, relative to data available in adult studies across indications. Elderly No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years). Data from SCCHN, adjuvant melanoma, and adjuvant OC or GEJC patients 75 years of age or older are too limited to draw conclusions on this population (see section 5.1). Data from dMMR or MSI H CRC patients 75 years of age or older are limited (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). In MPM patients, there was a higher rate of serious adverse reactions and discontinuation rate due to adverse reactions in patients 75 years of age or older (68% and 35%, respectively) relative to all patients who received nivolumab in combination with ipilimumab (54% and 28%, respectively). For patients treated with nivolumab in combination with cabozantinib, data from RCC patients 75 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 listed in Appendix V. **7. MARKETING AUTHORISATION HOLDER** Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Ireland **8. MARKETING AUTHORISATION NUMBER(S)** EU/1/15/1014/001 EU/1/15/1014/002 EU/1/15/1014/003 EU/1/15/1014/004 **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION** Date of first authorisation: 19 June 2015 Date of latest renewal: 23 April 2020 **10. DRUG DISPENSING CLASSIFICATION** Medicinal product subject to restricted medical prescription **11. DATE OF REVISION OF THE TEXT** 07 December 2021 Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu