UPDATES ON ADJUVANT TREATMENT FOR MIUC AND FIRST-LINE THERAPY FOR ADVANCED UC

Management of muscle-invasive urothelial cancer (MIUC) after radical cystectomy (RC) depends on the risk for disease recurrence. Adjuvant cisplatin-based combination chemotherapy can only be administered to certain patients and the response rate is limited.
In the locally advanced or metastatic setting, first-line platinum-based chemotherapy has been the standard of care in platinum-eligible patients. However, durable outcomes are rare. Nevertheless, the treatment landscape of urothelial cancer (UC) is evolving with the advent of immune checkpoint inhibitors (ICIs) and antibody-drug conjugates. BMS organised and supported a meeting that addressed the latest changes. During the meeting *Prof. Sylvie Rottey, Prof. Karel Decaestecker, Dr. Alexander Decruyenaere, Dr. Daan De Maeseneer and Prof. Christof Vulsteke* discussed the newest data on adjuvant approaches for MIUC and first-line therapy for advanced UC.

ADJUVANT NIVOLUMAB IN PATIENTS WITH A HIGH RISK OF RECURRENCE AFTER RADICAL SURGERY

Prof. Karel Decaestecker, Maria Middelares/UZ Ghent

For cisplatin-fit patients with cT2-4N0M0 disease, the European Association of Urology (EAU) guidelines recommend neoadjuvant chemotherapy (NAC) followed by RC and adjuvant immunotherapy in selected patients or adjuvant chemotherapy in selected patients if no NAC was given.[1] In Belgium, adjuvant nivolumab is reimbursed since September 2023 for adult patients with MIUC with tumour cell PD-L1 expression ≥1%, who are at high risk of recurrence following radical surgery for MIUC. The approval and reimbursement was based on the initial outcomes of the multi-centre, double-blind, phase III CheckMate 274 trial.[2] In this trial, 709 patients with MIUC with a high risk of recurrence after radical surgery were randomised to receive either adjuvant nivolumab or placebo for up to 1 year.[2] A high risk of recurrence was defined as ypT2-4a or ypN+ disease after cisplatin-based NAC, or pT3-4a or pN+ disease in patients who did not receive cisplatin-based NAC and are ineligible for or refuse adjuvant cisplatin-based chemotherapy.[2] One of the primary endpoints, disease-free survival (DFS), continued to be significantly improved with nivolumab *versus* placebo in the PD-L1 ≥1% population at extended follow-up (median 52.6 *versus* 8.4 months, HR[95% CI]: 0.52[0.37-0.72]).[3] Also, median non-urothelial tract recurrence-free survival and distant metastasis-free survival were significantly better with nivolumab *versus* placebo in the PD-L1 ≥1% population.[3] Interim overall survival (OS) data favoured adjuvant nivolumab over placebo. In the PD- L1 ≥1% population, median OS was not reached with either treatment (HR[95% CI]: 0.56 [0.36-0.86]).[3]

For patients with upper tract UC (UTUC), the EAU guidelines strongly recommend offering platinum-based chemotherapy after radical nephroureterectomy (RNU) to eligible patients with pT2-4 and/or pN+ disease.[1] Postoperative bladder instillation of chemotherapy should be offered to lower the intravesical recurrence rate in patients without a history of bladder cancer. Adjuvant nivolumab should be discussed with patients unfit for, or who declined, platinum-based adjuvant chemotherapy for >pT3 and/or pN+ disease after prior RNU alone or >ypT2 and/or pN+ disease after prior NAC, followed by RNU.

CONCLUSION

In patients at high risk of recurrence after radical surgery for MIUC, adjuvant nivolumab improves DFS, non-urothelial tract recurrence-free survival and distant metastasis-free survival versus placebo in PD-L1 ≥1% populations. OS data from interim analysis favour adjuvant nivolumab over placebo.

COMBINING NIVOLUMAB WITH CISPLATIN-BASED CHEMOTHERAPY

Dr. Daan De Maeseneer, Sint Lucas Assebroek/UZ Ghent

The open-label, phase III CheckMate 901 trial evaluated the combination of nivolumab + gemcitabine with cisplatin (GemCis) *versus* GemCis alone in 608 previously untreated patients with unresectable or metastatic UC.[4] In both arms, GemCis was given for up to 6 cycles, and in the combination arm, nivolumab was given from the start of chemotherapy until disease progression, unacceptable toxicity, or for up to 2 years.[4] At a median follow-up of 33.6 months, the addition of nivolumab to GemCis significantly improved OS and progression-free survival (PFS) (median OS 21.7 *versus* 18.9 months, HR[95% CI]: 0.78 [0.63-0.96], p= 0.02; median PFS 7.9 *versus* 7.6 months, HR[95% CI]: 0.72[0.59-0.88], p= 0.001).[4] Objective response rate (ORR) was 57.6% in the combination arm (complete response 21.7%) *versus* 43.1% in the GemCis arm (complete response 11.8%).[4] Median duration of response (complete response) was 9.5 months (37.1 months) in the combination arm *versus* 7.3 months (13.2 months) in the GemCis arm.[4] A post-hoc analysis showed that in the subgroup of patients with lymph node only disease (N= 110), the ORR and complete response rates were 81.5% and 63.0% for nivolumab + GemCis, respectively, compared to 64.3% and 33.9% for GemCis, respectively.[5] A cisplatin to carboplatin switch occurred in 16.1% of patients in the nivolumab + GemCis arm *versus* 14.9% of patients in the GemCis arm.[4] In the combination arm, 35.5% of patients received subsequent systemic therapy *versus* 51.3% in the GemCis arm.[4] Avelumab or pembrolizumab was administered subsequently before disease progression in only 14.5% of patients in the GemCis arm.[4] Finally, the addition of nivolumab to GemCis appeared to have no impact on health-related quality of life *versus* GemCis alone.[6]

PATIENT CASE: 73-YEAR-OLD MAN

- Dysuria
- Former smoker (30 pack years), medical history of hypertension
- CT: bone and lung metastases (biopsy: compatible with UC)
- ECOG PS: 1
- No peripheral neuropathy (PNP), diabetes mellitus or an autoimmune disease
- Grade 1 audiometric hearing loss
- Glomerular filtration grade (GFR): 90 ml/min, cardiac ejection fraction: 60%
- PD-L1 expression: positive, no FGFR2/3 alteration

This patient was treated with nivolumab + GemCis and had partial response as best response. After 2 years of nivolumab*, treatment was stopped. After 6 months without therapy, progressive disease with new lung metastases was seen on CT. The panel would then opt for gemcitabine with carboplatin (GemCarbo) followed by immunotherapy, or treatment with enfortumab vedotin (EV). Dr. De Maeseneer mentioned that according to his experience, disease may relapse quickly during drug holidays with EV and patients usually don't tolerate EV well at rechallenge. Prof. Vulsteke commented to quickly adapt the EV dosing intervals, even when grade 1 neurotoxicity is seen.

CONCLUSION

Adding nivolumab to GemCis results in significantly better survival versus GemCis alone in patients with previously untreated locally advanced or metastatic UC, without negatively impacting quality of life.

MAINTENANCE AVELUMAB FOR LOCALLY ADVANCED OR METASTATIC UC

Dr. Alexander Decruyenaere, UZ Ghent

In the multi-centre, open-label, phase III JAVELIN Bladder 100 trial, 700 patients with unresectable locally advanced or metastatic UC who did not have disease progression during 4-6 cycles of first-line chemotherapy (GemCis or GemCarbo) were randomised to receive best supportive care (BSC) with or without maintenance avelumab.[7] Avelumab treatment was well-tolerated. The incidence of grade 3 immune-related adverse events

*fictive case

(irAEs) was 7.0%, and no grade 4 or 5 irAEs were observed.[7] After a median follow-up of ≥38 months, median OS was 23.8 months for avelumab *versus* 15.0 months for BSC (HR[95% CI]: 0.76[0.63-0.91], p= 0.0036).[7] A subgroup analysis of the JAVELIN Bladder 100 trial confirmed improved OS with avelumab *versus* BSC regardless of prior chemotherapy regimen (cisplatin *versus* carboplatin) and regardless of best response to first-line therapy (complete or partial response *versus* stable disease).[7] However, an OS benefit was not so clear in patients with visceral disease nor in patients with UTUC.[7] Importantly, the study was not powered for these subgroup analyses. Furthermore, avelumab also prolonged PFS *versus* BSC with a 10-20% PFS benefit between both arms over time (median 5.5 *versus* 2.1 months, HR[95% CI]: 0.54[0.46-0.64], p< 0.001).[7] Similar median OS and PFS were observed in the real-world French AVENANCE and US PATRIOT-II studies.[8,9] It should be noted that in the subgroup of patients who discontinued study therapy due to progressive disease, only 52.9% of patients in the BSC arm received a PD-L1/PD-1 inhibitor, the standard of care in second line, and 24.7% of patients did not receive subsequent drug therapy.[7] Dr. Decruyenaere ended his talk by mentioning that every patient with locally advanced or metastatic UC should be exposed early to ICI.[10]

PATIENT CASE: 71-YEAR-OLD MAN

March 2024:

- Voiding lower urinary tract symptoms
- Physical examination: mild suprapubic tenderness but no palpable masses
- Digital rectal examination: prostate enlargement without irregularities
- Urinalysis: microscopic haematuria without pyuria
- PSA: normal
- TRUS: prostate volume of 58 ml

April 2024:

- Cystoscopy: benign prostatic hyperplasia following TUR of the prostate and high-grade pT1 UC (no detrusor) on TUR of the bladder (TURB)

May 2024:

- CT chest/abdomen: thickened anterior bladder wall (cN0cM0)
- Advice: re-TURB

July 2024:

- Patient went for a second opinion
- MRI and PET-CT: bone metastasis (pelvis) and lung metastasis
- No comorbidities and good performance status
- eGFR: >90 ml/min
- Creatinine levels: 0.75 mg/dl

For this patient and in the current reimbursement setting in Belgium, the attendees would consider GemCis or GemCarbo followed by maintenance avelumab ± metastasis-directed therapy (MDT), or GemCis + nivolumab ± MDT. In the ideal setting (all treatment options available and reimbursed), the attendees would also consider EV + pembrolizumab ± MDT. If the patient would have baseline grade 2 peripheral neuropathy (PNP), the attendees were unsure if EV + pembrolizumab should be administered as these patients were excluded from clinical studies and PNP might worsen (cumulative effect). If possible, EV + pembrolizumab could be started but a dose reduction or discontinuation of EV treatment might be required, and monitoring for PNP symptoms should be continued. If the disease would be very limited, the panel would not administer EV + pembrolizumab due to the risk of worsening PNP. If the patient would have baseline type 2 diabetes mellitus (HbA1c 8.0%), a referral to the endocrinologist should be considered before starting treatment with EV + pembrolizumab.

In clinical practice, this patient received 3 cycles of GemCis + nivolumab and obtained partial response (lung lesions resolved, bladder and bone lesion shrinked). The sixth cycle is ongoing. If the patient would have confirmed partial response after 6 cycles of systemic therapy, with only a sclerotic bone lesion, the attendees would re-

commend cystoscopy (and biopsy) first, followed by maintenance nivolumab for up to 2 years. During nivolumab treatment, cystoscopy every 3 months would be considered. The idea to consider stereotactic body radiation therapy (SBRT) of the sclerotic bone lesion was suggested by a member of the audience as it is associated with low toxicity. However, other attendees mentioned it would be difficult to evaluate the effect of SBRT.

CONCLUSION

Avelumab maintenance therapy following GemCis or GemCarbo is well-tolerated and showed PFS and OS benefits versus BSC. Every patient with unresectable locally advanced or metastatic UC should be exposed early to ICI.

COMBINING EV WITH PEMBROLIZUMAB

Prof. Christof Vulsteke, Maria Middelares Ghent

The open-label, phase III EV-302/KEYNOTE-A39 trial randomised 886 previously untreated patients with locally advanced or metastatic UC to EV + pembrolizumab or platinum-based chemotherapy.[11] After a median follow-up of 17.2 months, EV + pembrolizumab significantly prolonged PFS and OS *versus* chemotherapy (median PFS 12.5 *versus* 6.3 months, HR[95% CI]: 0.45[0.38-0.54], p< 0.001; median OS 31.5 *versus* 16.1 months, HR[95% CI]: 0.47[0.38-0.58], p< 0.001).[11] The OS benefit was consistent with the overall population regardless of cisplatin eligibility, PD-L1 expression status, or Nectin-4 expression status.[11,12] The ORR was 67.7% in the EV + pembrolizumab arm *versus* 44.4% in the chemotherapy arm.[11] Median duration of response was not reached with EV + pembrolizumab compared to 7.0 months with chemotherapy.[11] Grade ≥3 treatment-related adverse events (TRAEs) occurred in 55.9% and 69.5% of patients treated with EV + pembrolizumab *versus* chemotherapy, respectively.[11] The most common TRAEs of any grade with EV + pembrolizumab included peripheral sensory neuropathy (50.0%), pruritus (39.8%), alopecia (33.2%) and maculopapular rash (32.7%).[11] Prof. Vulsteke emphasised to carefully check a patient for skin toxicity, especially during the first two months of treatment, and to obtain the advice of a dermatologist. Furthermore, PNP should be checked carefully, and treatment should be withheld if grade 2 PNP occurs. Outside the setting of a clinical trial, the combination of EV + pembrolizumab is not yet available in Belgium.

PATIENT CASE: 75-YEAR-OLD MAN

July 2021:

- Haematuria
- TURB: pT2 UC (no divergent histology)
- CT thorax/abdomen: multiple suspicious pelvic and distant lymph nodes
- PET-CT: pT2 cN3M1a
- Enrolled in EV-302 trial, randomised to EV+pembrolizumab
  - 6 cycles – complete remission
  - Treatment stopped due to multiple toxicities, including *Campylobacter coli/jejuni,* auto-immune colitis and auto-immune pneumonitis. Long hospitalisation was required.

October 2024:

- Still in complete remission

CONCLUSION

Treatment with EV + pembrolizumab resulted in significant OS and PFS benefits versus platinum-based chemotherapy for patients with previously untreated locally advanced or metastatic UC. The most frequently observed TRAEs concern skin toxicity and PNP, specific monitoring for these AEs should be set in place. Outside the setting of a clinical trial, the combination of EV + pembrolizumab is not yet reimbursed in Belgium.

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OPDIVO (nivolumab)

Ex-factory (excl. VAT)		
OPDIVO	40 mg	€509,90
OPDIVO	100 mg	€1.274,75
OPDIVO	120 mg	€1.529,83
OPDIVO	240 mg	€3.059,65

Ex-factory (excl. VAT)	
YERVOY 50 mg	€4.250,00
YERVOY 200 mg	€17.000,00

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 and adolescents 12 years of age and older. 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 and adolescents 12 years of age and older with Stage IIB or IIC melanoma, or 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. Neoadjuvant treatment of NSCLC OPDIVO in combination with platinum-based chemotherapy is indicated for the neoadjuvant treatment of resectable non-small cell lung cancer at high risk of recurrence in adult patients whose tumours have PD-L1 expression ≥ 1% (see section 5.1 for selection criteria). 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 in combination with cisplatin and gemcitabine is indicated for the first-line treatment of adult patients with unresectable or metastatic 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. Adjuvant treatment of urothelial carcinoma OPDIVO as monotherapy is indicated for the adjuvant treatment of adults with muscle invasive urothelial carcinoma (MIUC) with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection of MIUC (see section 5.1). 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 in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%. OPDIVO in combination with fluoropyrimidine- and platinum-based combination chemotherapy is indicated for the first-line treatment of adult patients with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma with tumour cell PD-L1 expression ≥ 1%. 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 depending on the indication and population (see sections 5.1 and 5.2), as presented in Table 1. Table 1: Recommended dose and infusion time for intravenous administration of nivolumab monotherapy Indication* : Recommended dose and infusion time Melanoma (advanced or adjuvant treatment) Adults and adolescents (12 years of age and older and weighing at least 50 kg): : 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes or over 30 minutes (adjuvant melanoma, see section 5.1) Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes. Renal cell carcinoma, Muscle invasive urothelial carcinoma (MIUC) (adjuvant treatment): 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, RCC, OC, GEJC or MIUC (adjuvant treatment) 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* In adults and adolescents 12 years of age and older and weighing at least 50 kg, 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 (see sections 5.1 and 5.2), 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. In adolescents 12 years of age and older and weighing less than 50 kg, 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 3 mg/kg every 2 weeks **or** 6 mg/kg every 4 weeks (see sections 5.1 and 5.2), 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 3 mg/kg every 2 weeks; **or** 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 6 mg/kg 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 Adults and adolescents 12 years of age and older: 1 mg/kg over 30 minutes. Monotherapy phase Adults and adolescents (12 years of age and older and weighing at least 50 kg): 240 mg every 2 weeks over 30 minutes or 480 mg every 4 weeks over 60 minutes; Adolescents (12 years of age and older and weighing less than 50 kg): 3 mg/kg every 2 weeks over 30 minutes or 6 mg/kg every 4 weeks over 60 minutes **Ipilimumab** Combination phase, every 3 weeks for 4 dosing cycles Adults and adolescents 12 years of age and older : 3 mg/kg over 30 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 - *Oesophageal squamous cell carcinoma* The recommended dose is either 3 mg/kg nivolumab every 2 weeks or 360 mg nivolumab every 3 weeks administered intravenously over 30 minutes in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes 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 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 Neoadjuvant treatment of non-small cell lung cancer* The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with platinum-based chemotherapy every 3 weeks for 3 cycles (see section 5.1). *Oesophageal squamous cell carcinoma The recommended dose of nivolumab is 240 mg every 2 weeks or 480 mg every 4 weeks administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression. 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. *First-line treatment of unresectable or metastatic urothelial carcinoma* The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with cisplatin and gemcitabine every 3 weeks for up to 6 cycles followed by nivolumab monotherapy administered intravenously at either 240 mg every 2 weeks over 30 minutes **or** at 480 mg every 4 weeks over 30 minutes (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months from first dose, whichever comes first. *Duration of treatment* Treatment with OPDIVO, either as a monotherapy or in combination with ipilimumab or other therapeutic agents, 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. 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 establishedexcept in adolescents 12 years of age and older with melanoma. Currently available data of OPDIVO as monotherapy or in combination with ipilimumab are described in sections 4.2, 4.8, 5.1 and 5.2. *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 = 4646) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (44%), musculoskeletal pain (28%), diarrhoea (26%), rash (24%), cough (22%), nausea (22%), pruritus (19%), decreased appetite (17%), arthralgia (17%), constipation (16%), dyspnoea (16%), abdominal pain (15%), upper respiratory tract infection (15%), pyrexia (13%), headache (13%) , anaemia (13%) and vomiting (12%). The majority of adverse reactions were mild to moderate (Grade 1 or 2). The incidence of Grade 3-5 adverse reactions was 44%, with 0.3% fatal adverse reactions attributed to study drug. 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 = 4646) 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 Neoplasms benign, malignant and unspecified (including cysts and polyps) Rare: histiocytic necrotising lymphadenitis (Kikuchi lymphadenitis)-Blood and lymphatic system disorders Very common: lymphopaenia[b], anaemia[b,j], leucopoenia[b], neutropaenia[a,b], thrombocytopaenia[b] ; Uncommon: eosinophilia; Not known: haemophagocytic lymphohistiocytosis Immune system disorders Common: infusion related reaction (including cytokine release syndrome), hypersensitivity (including anaphylactic reaction); Uncommon: sarcoidosis; Not known: solid organ transplant rejection[f] Endocrine disorders Common: hypothyroidism, hyperthyroidism, thyroiditis; Uncommon: adrenal insufficiency[i], hypopituitarism, hypophysitis, diabetes mellitus; Rare: diabetic ketoacidosis, hypoparathyroidism Metabolism and nutrition disorders Very common: decreased appetite, hyperglycaemia[b] ; Common: dehydration, weight decreased, hypoglycaemia[b] ; Uncommon: metabolic acidosis; Not known: tumour lysis syndrome[g] 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,k] ; Not known myelitis (including transverse myelitis) Eye disorders Common: blurred vision, dry eye; Uncommon: uveitis; Not known: Vogt-Koyanagi-Harada syndrome[e] Cardiac disorders Common: tachycardia, atrial fibrillation; Uncommon: myocarditis[a] ,pericardial disorders[h] ,arrhythmia (including ventricular arrhythmia) Vascular disorders Common: hypertension; Rare: vasculitis Respiratory, thoracic and mediastinal disorders Very common: dyspnoea[a], cough; Common: pneumonitis[a], 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, pancreatic exocrine insufficiency, coeliac disease Hepatobiliary disorders Uncommon: hepatitis , cholestasis Skin and subcutaneous tissue disorders Very common: rash[c], pruritus; Common: vitiligo, dry skin, erythema, alopecia; Uncommon: psoriasis, rosacea, erythema multiforme, urticaria; Rare: toxic epidermal necrolysis[a,d] Stevens-Johnson syndrome[a]; Not known: lichen sclerosus[g], other lichen disorders Musculoskeletal and connective tissue disorders Very common: musculoskeletal pain[e], arthralgia; Common: arthritis; Uncommon: polymyalgia rheumatica; Rare: Sjogren's syndrome, myopathy, myositis (including polymyositis)[a], rhabdomyolysis[a,d] Renal and urinary disorders Common: renal failure (including acute kidney injury) [a] ; Rare: tubulointerstitial nephritis, cystitis noninfective General disorders and administration site conditions Very common: fatigue, pyrexia; Common: pain, chest pain, oedema[f] Investigations[b] Very common: increased AST, hyponatraemia, hypoalbuminaemia, increased alkaline phosphatase, increased creatinine, increased ALT, increased lipase, hyperkalaemia, increased amylase, hypocalcaemia, hypomagnesaemia, hypokalaemia, hypercalcaemia; Common: increased total bilirubin, hypernatraemia, hypermagnesaemia Adverse reaction frequencies presented in Table 6 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] Rash is a composite term which includes rash maculopapular, rash erythematous, rash pruritic, rash follicular, rash macular, rash morbilliform, rash papular, rash pustular, rash vesicular, exfoliative rash, dermatitis, dermatitis acneiform, dermatitis allergic, dermatitis atopic, dermatitis bullous, dermatitis exfoliative, dermatitis psoriasiform, drug eruption and pemphigoid. [d] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure. [e] 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. [f] Post-marketing event (also see section 4.4). [g] Reported in clinical studies and in the post-marketing setting. [h] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome. [i] 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. [j] Includes adrenal insufficiency , adrenocortical insufficiency acute, and secondary adrenocortical insufficiency. [k] Includes encephalitis and limbic encephalitis. [l] Oedema is a composite term which includes generalised oedema, oedema peripheral, peripheral swelling and swelling. 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 other therapeutic agents for additional information on the safety profile,prior to initiation of treatment. *Nivolumab in combination with ipilimumab (with or without chemotherapy)* In the pooled dataset of nivolumab administered in combination with ipilimumab (with or without chemotherapy) across tumour types (n = 2094) with minimum follow-up ranging from 6 to 47 months, the most frequent adverse reactions (≥ 10%) were fatigue (50%), rash (38%), diarrhoea (37%), nausea (31%), pruritus (29%), musculoskeletal pain (28%), pyrexia (25%), cough (24%), decreased appetite (23%), vomiting (20%), dyspnoea (19%), constipation (19%), arthralgia (19%), abdominal pain (18%), hypothyroidism (16%), headache (16%), upper respiratory tract infection (15%), oedema (13%), and dizziness (11%). The incidence of Grade 3-5 adverse reactions was 67% for nivolumab in combination with ipilimumab (with or without chemotherapy), with 0.7% fatal adverse reactions attributed to study drug. Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, fatigue (62%), rash (57%), diarrhoea (52%), nausea (42%), pruritus (40%), pyrexia (36%), and headache (26%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate. Among patients treated with nivolumab 360 mg in combination with ipilimumab 1 mg/kg and chemotherapy, anaemia (32%) and neutropaenia (15%) were reported at an incidence rate ≥ 10% higher than the rates reported in the pooled dataset of nivolumab in combination with ipilimumab (with or without chemotherapy) incidence rate. *Nivolumab in combination with chemotherapy* In the pooled dataset of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy across tumour types (n = 1572), with a minimum follow-up ranging from 7.4 to 20 months for gastric, GEJ or oesophageal adenocarcinoma, OSCC, or urothelial carcinoma, or following 3 cycles of treatment for resectable NSCLC, the most frequent adverse reactions (≥ 10%) were nausea (51%), fatigue (41%), peripheral neuropathy (34%), decreased appetite (32%), constipation (31%), diarrhoea (30%), vomiting (26%), stomatitis (19%), abdominal pain (19%), rash (19%), musculoskeletal pain (18%), pyrexia (17%), oedema (including peripheral oedema) (13%), cough (12%), pruritus (11%), and hypoalbuminaemia (10%). Incidences of Grade 3-5 adverse reactions were 72% for nivolumab in combination with chemotherapy, with 1.3% fatal adverse reactions attributed to nivolumab in combination with chemotherapy. Median duration of therapy was 6.44 months (95% CI: 5.95, 6.80) for nivolumab in combination with chemotherapy, 4.34 months (95% CI: 4.04, 4.70) for chemotherapy for gastric, GEJ or oesophageal adenocarcinoma, or OSCC and 7.39 months (95% CI: 7.06, 8.38) for urothelial carcinoma. For resectable NSCLC, ninety-three percent (93%) of patients received 3 cycles of nivolumab in combination with chemotherapy. Nivolumab in combination with cabozantinib 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%), dysgeusia (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 incidence of Grade 3-5 adverse reactions was 78%, with 0.3% fatal adverse reactions attributed to study drug. *Tabulated summary of adverse reactions* Adverse reactions reported in the pooled dataset for patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy) (n = 2094), nivolumab in combination with chemotherapy (n = 1572), and nivolumab in combination with cabozantinib (n = 320) 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), 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 other therapeutic agents** Infections and infestations *Combination with ipilimumab (with or without chemotherapy)* Very common: upper respiratory tract infection, Common: pneumonia, bronchitis, conjunctivitis, Rare: aseptic meningitis *Combination with chemotherapy* Very common:;Common: upper respiratory tract infection, pneumonia[a]; Rare: *Combination with cabozantinib* Very common: upper respiratory tract infection; Common: pneumonia; Rare: Blood and lymphatic system disorders *Combination with ipilimumab (with or without chemotherapy)* Very common: anaemia[b,j], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]; Common: eosinophilia; Uncommon: febrile neutropaenia; Not known: haemophagocytic lymphohistiocytosis *Combination with chemotherapy* Very common: neutropaenia[b], anaemia[b,j], leucopoenia[b], lymphopaenia[b], thrombocytopaenia[b]; Common: febrile neutropaenia[a]; Uncommon: eosinophilia; Not know: *Combination with cabozantinib* Very common: anaemia[b], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b]; Common: eosinophilia ; Uncommon:; Not know: Immune system disorders *Combination with ipilimumab (with or without chemotherapy)* Common: infusion related reaction (including cytokine release syndrome), hypersensitivity; Uncommon:; Rare: sarcoidosis; Not known: solid organ transplant rejection[f] *Combination with chemotherapy* Common: hypersensitivity, infusion related reaction (including cytokine release syndrome); Uncommon:; Rare:; Not known: *Combination with cabozantinib* Common: hypersensitivity (including anaphylactic reaction); Uncommon: infusion related hypersensitivity reaction; Rare:; Not known: Endocrine disorders *Combination with ipilimumab (with or without chemotherapy)* Very common: hypothyroidism; Common: hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus; Uncommon: diabetic ketoacidosis; Rare: hypoparathyroidism *Combination with chemotherapy* Very common:, Common: hypothyroidism, hyperthyroidism, diabetes mellitus; Uncommon: adrenal insufficiency, thyroiditis, hypopituitarism, hypophysitis; Rare:; *Combination with cabozantinib* Very common: hypothyroidism, hyperthyroidism, Common: adrenal insufficiency, Uncommon: hypophysitis, thyroiditis; Rare: Metabolism and nutrition disorders *Combination with ipilimumab (with or without chemotherapy)* Very common: decreased appetite, hyperglycaemia[b], hypoglycaemia[b]; Common: dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased; Uncommon: metabolic acidosis; Rare:; Not known: tumour lysis syndrome[g] *Combination with chemotherapy* Very common: decreased appetite, hypoalbuminaemia, hyperglycaemia[b], hypoglycaemia[b]; Common: hypophosphataemia; Uncommon:; Rare: tumour lysis syndrome; Not known: *Combination with cabozantinib* Very common: decreased appetite, hypoglycaemia[b], hyperglycaemia[a], weight decreased; Common: dehydration; Uncommon:; Rare: Nervous system disorders *Combination with ipilimumab (with or without chemotherapy)* Very common: headache, dizziness; Common: peripheral neuropathy; Uncommon: polyneuropathy, peroneal nerve palsy, autoimmune neuropathy (including facial and abducens nerve paresis), encephalitis, myasthenia gravis; Rare: Guillain-Barré syndrome, neuritis, myelitis (including transverse myelitis); *Not known: Combination with chemotherapy* Very common: peripheral neuropathy; Common: paraesthesia, dizziness, headache; Uncommon:; Rare: Guillain-Barré syndrome, encephalitis; Not known: myelitis (including transverse myelitis) *Combination with cabozantinib* Very common: dysgeusia, dizziness, headache; Common: peripheral neuropathy; Uncommon: encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome; Rare:; *Not known:* Ear and labyrinth disorders *Combination with ipilimumab (with or without chemotherapy)* *Combination with chemotherapy* Common: *Combination with cabozantinib* Common: tinnitus Eye disorders *Combination with ipilimumab (with or without chemotherapy)* Common: blurred vision, dry eye; Uncommon: uveitis, episcleritis; Rare: Vogt Koyanagi-Harada syndrome *Combination with chemotherapy* Common: dry eye, blurred vision; Uncommon: uveitis; Rare: *Combination with cabozantinib* Common: dry eye, blurred vision; Uncommon: uveitis; Rare: Cardiac disorders *Combination with ipilimumab (with or without chemotherapy)* Common: tachycardia, atrial fibrillation; Uncommon: myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia; Not known: pericardial disorders[h] *Combination with chemotherapy* Common: tachycardia, atrial fibrillation; Uncommon: myocarditis; Not known: *Combination with cabozantinib* Common: atrial fibrillation, tachycardia; Uncommon: myocarditis; Not known: Vascular disorders *Combination with ipilimumab (with or without chemotherapy)* Very common:; Common: hypertension *Combination with chemotherapy* Very common:; Common: thrombosis[a, i], hypertension, vasculitis *Combination with cabozantinib* Very common: hypertension; Common: thrombosis[i] Respiratory, thoracic and mediastinal disorders *Combination with ipilimumab (with or without chemotherapy)* Very common: cough, dyspnoea; Common: pneumonitis[a], pulmonary embolism[a], pleural effusion *Combination with chemotherapy* Very common: cough; Common: pneumonitis[a], dyspnoea *Combination with cabozantinib* Very common: dysphonia, dyspnoea, cough; Common: pneumonitis, pulmonary embolism, pleural effusion, epistaxis Gastrointestinal disorders *Combination with ipilimumab (with or without chemotherapy)* Very common: diarrhoea, vomiting, nausea, abdominal pain, constipation; Common: colitis[a], pancreatitis, stomatitis, gastritis, dry mouth; Uncommon: duodenitis; Rare: intestinal perforation[a], pancreatic exocrine insufficiency, coeliac disease.; Not known: *Combination with chemotherapy* Very common: diarrhoea[a], stomatitis, vomiting, nausea, abdominal pain, constipation; Common: colitis, dry mouth; Uncommon: pancreatitis; Rare: ; Not known: pancreatic exocrine insufficiency, coeliac disease *Combination with cabozantinib* Very common: diarrhoea, vomiting, nausea, constipation, stomatitis, abdominal pain, dyspepsia; Common: colitis, gastritis, oral pain, dry mouth, haemorrhoids; Uncommon: pancreatitis, small intestine perforation[a], glossodynia; Rare: ; Not known: pancreatic exocrine insufficiency, coeliac disease Hepatobiliary disorders *Combination with ipilimumab (with or without chemotherapy)* Common: hepatitis; Uncommon: *Combination with chemotherapy* Common:; Uncommon: hepatitis *Combination with cabozantinib* Common: hepatitis; Uncommon: Skin and subcutaneous tissue disorders *Combination with ipilimumab (with or without chemotherapy)* Very common: rash[c], pruritus; Common: alopecia, vitiligo, urticaria, dry skin, erythema; Uncommon: Stevens-Johnson syndrome, erythema multiforme, psoriasis; Rare: toxic epidermal necrolysis[a,d], lichen sclerosus, other lichen disorders; Not known: *Combination with chemotherapy* Very common: rash[c], pruritus; Common: palmar-plantar erythrodysaesthesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema; Uncommon:, Rare:, Not known: *Combination with cabozantinib* Very common: palmar-plantar erythrodysaesthesia syndrome, rash[c], pruritus; Common: alopecia, dry skin, erythema, hair colour change; Uncommon: psoriasis, urticaria; Rare:; Not known: lichen sclerosus, other lichen disorders Musculoskeletal and connective tissue disorders *Combination with ipilimumab (with or without chemotherapy)* Very common: musculoskeletal pain[e], arthralgia; Common: muscle spasms, muscular weakness, arthritis; Uncommon: polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a]; Rare: spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a] *Combination with chemotherapy* Very common: musculoskeletal pain[e]; Common: arthralgia, muscular weakness; Uncommon:, Rare: *Combination with cabozantinib* Very common: musculoskeletal pain[e], arthralgia, muscle spasm; Common: arthritis; Uncommon: myopathy, osteonecrosis of the jaw, fistula; Rare: Renal and urinary disorders *Combination with ipilimumab (with or without chemotherapy)* Very common:, Common: renal failure (including acute kidney injury)[a]; Uncommon: tubulointerstitial nephritis, nephritis; Rare: cystitis noninfective *Combination with chemotherapy* Very common:; Common: renal failure[a]; Uncommon: cystitis noninfective, nephritis; Rare: *Combination with cabozantinib* Very common: proteinuria; Common: renal failure, acute kidney injury; Uncommon: nephritis; Rare: cystitis noninfective[g] General disorders and administration site conditions *Combination with ipilimumab (with or without chemotherapy)* Very common: fatigue, pyrexia, oedema (including peripheral oedema); Common: chest pain, pain, chills *Combination with chemotherapy* Very common: fatigue, pyrexia, oedema (including peripheral oedema); Common: malaise *Combination with cabozantinib* Very common: fatigue, pyrexia, oedema; Common: pain, chest pain Investigations *Combination with ipilimumab (with or without chemotherapy)* Very common: increased alkaline phosphatase[b], increased AST[b], increased ALT[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hyponatraemia[b], hyperkalaemia[b], hypokalaemia[b], hypercalcaemia[b], hypocalcaemia[b]; Common: hypernatraemia[b], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase *Combination with chemotherapy* Very common: hypocalcaemia[b], increased AST[b], increased ALT[b], hyponatraemia[b], increased amylase[b], hypomagnesaemia[b], increased alkaline phosphatase[b], hypokalaemia[b], increased creatinine[b], increased lipase[b], hyperkalaemia[b], increased total bilirubin[b]; Common: hypernatraemia[b], hypercalcaemia[b], hypermagnesaemia[b] *Combination with cabozantinib* Very common: increased alkaline phosphatase[b], increased ALT[b], increased AST[b], increased total bilirubin[b], increased creatinine[b], increased amylase[b], increased lipase[b], hypokalaemia[b], hypomagnesaemia[b], hyponatraemia[b], hypocalcaemia[b], hypercalcaemia[b], hypophosphataemia[b], hyperkalaemia[b], hypermagnesaemia[b], hypernatraemia[b]; Common: blood cholesterol increased, hypertriglyceridaemia Adverse reaction frequencies presented in Table 7 may not be fully attributable to nivolumab alone or in combination with other therapeutic agents, but may contain contributions from the underlying disease or from medicinal product used in combination. [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] 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, nodular rash, and pemphigoid. [d] Reported also in studies outside the pooled dataset. The frequency is based on the program-wide exposure. [e] 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. [f] Post-marketing event (also see section 4.4) .[g] Reported in clinical studies and in the post-marketing setting. [h] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome. [i] 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. [j] 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. 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 generally was required in a greater proportion of patients receiving nivolumab in combination other agents than in those receiving nivolumab monotherapy. Table 8 presents the percentage of patients with immune-related adverse reactions who were permanently discontinued from treatment by dosing regimen. Additionally, for patients who experienced an event, Table 8 presents the percentage of patients who required high-dose corticosteroids (at least 40 mg daily prednisone equivalents) by dosing regimen. The management guidelines for these adverse reactions are described in section 4.4. **Table 8: Immune-related adverse reactions leading to permanent discontinuation or requiring high-dose corticosteroids by dosing regimen (nivolumab monotherapy, nivolumab in combination with ipilimumab (with or without chemotherapy), nivolumab in combination with chemotherapy, or nivolumab in combination with cabozantinib) Nivolumab monotherapy%; Nivolumab in combination with ipilimumab (with or without chemotherapy)%; Nivolumab in combination with chemotherapy%; Nivolumab in combination with cabozantinib%** Immune-related adverse reaction leading to permanent discontinuation Pneumonitis: 1,4;2,5;1,8;2,5 Colitis: 1,2;6;1,8;2,5 Hepatitis: 1,1;5; 0,8;4,1 Nephritis and renal dysfunction: 0,3;1,2;3,3;0,6 Endocrinopathies: 0,5;2,0;0,6;1,3 Skin: 0,8;1,0;1,0;2,2 Hypersensitivity/Infusion reaction: 0,1;0,3;1,8;0 Immune-related adverse reaction requiring high-dose corticosteroids[a,b] Pneumonitis: 65;59;58;56 Colitis: 14;32;8;8 Hepatitis: 21;37;8;23 Nephritis and renal dysfunction: 22;27;7;9 Endocrinopathies: 5;20;5;4,2 Skin: 3,3;8;6;8 Hypersensitivity/Infusion reaction:18;16;22;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, was 3.3% (155/4646). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (42/4646) and 1.7% (77/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.7% (33/4646) and <0.1% (1/4646) of patients respectively. Six patients (0.1%) had a fatal outcome. Median time to onset was 15.1 weeks (range: 0.7-85.1). Resolution occurred in 107 patients (69.0%) with a median time to resolution of 6.7 weeks (range: 0.1+-109.1+); + denotes a censored observation. In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of pneumonitis including interstitial lung disease, was 6.9% (145/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 3.5% (73/2094), 1.1% (24/2094), and 0.4% (8/2094) of patients, respectively. Four patients (0.2%) had a fatal outcome. Median time to onset was 2.7 months (range: 0.1-56.8). Resolution occurred in 119 patients (82.1%) with a median time to resolution of 6.1 weeks (range: 0.3-149.3+). In patients treated with nivolumab in combination with chemotherapy, the incidence of pneumonitis including interstitial lung disease was 4.3%

(67/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 2.1% (33/1572), 0.9% (14/1572), and 0.2% (3/1572), of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 25 weeks (range: 1.6-96.9). Resolution occurred in 48 patients (71.6%) with a median time to resolution of 10.4 weeks (range: 0.3+-121.3+). In patients treated with nivolumab in combination with cabozantinib , 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 15.4% (716/4646). The majority of cases were Grade 1 or 2 in severity reported in 9. 9% (462/4646) and 4.0% (186/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (67/4646) and <0.1% (1/4646) of patients respectively. Median time to onset was 8.3 weeks(range:0.1-115.6). Resolution occurred in 639 patients (90.3%) with a median time to resolution of 2.9 weeks (range: 0.1 124.4+). In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of diarrhoea or colitis was 27.7% (580/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 8.8% (184/2094), 6.8% (142/2094), and 0.1% (3/2094), of patients, respectively. One patient (<0.1%) had a fatal outcome. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 577 patients (90.8%) with a median time to resolution of 2.7 weeks (range: 0.1-159.4+). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of diarrhoea or colitis was 46.7%, including Grade 2 (13.6%), Grade 3 (15.8%), and Grade 4 (0.4%). In patients treated with nivolumab in combination with chemotherapy, the incidence of diarrhoea or colitis was 24.0% (377/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 7.3% (115/1572), 3.2% (51/1572), and 0.4% (6/1572) of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 4.4 weeks (range: 0.1-93.6). Resolution occurred in 329 patients (87.7%) with a median time to resolution of 1.6 weeks (range: 0.1-212.3+). In patients treated with nivolumab in combination with cabozantinib, 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 was 8.0% (371/4646). The majority of cases were Grade 1 or 2 in severity reported in 4.3% (200/4646) and 1.8% (82/4646) of patients respectively. Grade 3 and 4 cases were reported in 1.6% (74/4646) and 0.3% (15/4646) of patients, respectively. Median time to onset was 10.6 weeks(range:0.1-132.0). Resolution occurred in 298 patients (81.4%) with a median time to resolution of 6.1 weeks (range: 0.1-126.4+) In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of liver function test abnormalities was 19.2% (402/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 4.2% (88/2094), 7.8% (163/2094), and 1.2% (25/2094) of patients, respectively. Median time to onset was 1.9 months (range: 0.0-36.6). Resolution occurred in 351 patients (87.8%) with a median time to resolution of 5.3 weeks (range: 0.1-175.9+). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of liver function test abnormalities was 30.1% including Grade 2 (6.9%), Grade 3 (15.8%), and Grade 4 (1.8%). In patients treated with nivolumab in combination with chemotherapy, the incidence of liver function test abnormalities was 18.6% (293/1572). Grade 2, Grade 3 and Grade 4 cases were reported in 5.6% (88/1572), 2.9% (45/1572) and < 0.1% (1/1572) of patients, respectively. Median time to onset was 7.7 weeks (range: 0.1-99.0). Resolution occurred in 231 patients (79.9%) with a median time to resolution of 7.4 weeks (range: 0.4-240.0+). In patients treated with nivolumab in combination with cabozantinib, 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 2.6% (121/4646). The majority of cases were Grade 1 or 2 in severity reported in 1.5% (69/4646) and 0.7% (32/4646) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (18/4646) and <0.1% (2/4646) of patients, respectively. Median time to onset was 12.1 weeks (range:0.1-79.1). Resolution occurred in 80 patients (69.0%) with a median time to resolution of 8.0 weeks (range: 0.3-79.1+). In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of nephritis or renal dysfunction was 6.1% (128/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 2.3% (49/2094), 1.0% (20/2094), and 0.5% (10/2094) of patients, respectively. Two patients (< 0.1%) had a fatal outcome. Median time to onset was 2.5 months (range: 0.0-34.8). Resolution occurred in 97 patients (75.8%) with a median time to resolution of 6.3 weeks (range: 0.1-172.1+). In patients treated with nivolumab in combination with chemotherapy, the incidence of nephritis or renal dysfunction was 10.8% (170/1572). Grade 2, Grade 3, and Grade 4 cases were reported in, 4.1% (64/1572), 1.5% (24/1572), and 0.1% (2/1572) of patients, respectively. Two patients (0.1%) had a fatal outcome. Median time to onset was 6.9 weeks (range: 0.1-60.7). Resolution occurred in 111 patients (65.3%) with a median time to resolution of 11.6 weeks (range: 0.1-226.0+). In patients treated with nivolumab in combination with cabozantinib, 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 13.0%(603/4646). The majority of cases were Grade 1 or 2 in severity reported in 6.6% (305/4646) and 6.2% (290/4646)) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (8/4646) of patients. Hypophysitis (3 Grade 1, 7 Grade 2, 9 Grade 3, and 1 Grade 4), hypopituitarism (6 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute and blood corticotrophin decreased) (2 Grade 1, 23 Grade 2, and 11 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) (1 Grade1, 3 Grade 2 and 8 Grade 3 and 2 Grade 4) were reported. Median time to onset of these endocrinopathies was 11.1 weeks(range:0.1-126.7). Resolution occurred in 323 patients (48.7%). Median time to resolution was 48.6 weeks (range:0.4 to 204.4+). In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of thyroid disorders was 22.9% (479/2094). Grade 2 and Grade 3 thyroid disorders were reported in 12.5% (261/2094) and 1.0% (21/2094) of patients, respectively. Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 2.0% (42/2094) and 1.6% (33/2094) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.8% ((16/2094)) and 0.5% ((11/2094)) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency) occurred in 2.3% (49/2094), 1.5% (32/2094) and 0.2% (4/2094) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus occurred in 0.1% (1/2094), 0.2% (4/2094), < 0.1% (1/2094), and 0.1 (3/2094) of patients, respectively, and Grade 4 diabetic ketoacidosis was reported in < 0.1% (2/2094) of patients. Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 201 patients (40.7%). Time to resolution ranged from 0.3 to 257.1+ weeks. In patients treated with nivolumab in combination with chemotherapy, the incidence of thyroid disorders was 12.7% (199/1572). Grade 2 thyroid disorder was reported in 6.2% (97/1572) patients. Grade 3 hypophysitis occurred in 0.1% (2/1572) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.2% (3/1572) and 0.3% (4/1572) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency occurred in 0.6% (9/1572), 0.2% (3/1572) and <0.1% (1/1572) of patients, respectively. One patient (<0.1%) had a fatal outcome due to adrenal insufficiency. Diabetes mellitus including Type 1 diabetes mellitus, fulminant Type 1 diabetes mellitus and diabetic ketoacidosis (3 Grade 2, 2 Grade 3 and 1 Grade 4) were reported. Median time to onset of these endocrinopathies was 14.7 weeks (range: 1.1-124.3). Resolution occurred in 81patients (37.2%). Time to resolution ranged from 0.4 to 233.6+ weeks. In patients treated with nivolumab in combination with cabozantinib, 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 30.0% (1396/4646). The majority of cases were Grade 1 in severity reported in 22.8% (1060/4646) of patients. Grade 2 and Grade 3 cases were reported 5.9% (274/4646) and 1.3% (62/4646) of patients respectively. Median time to onset was 6.7 weeks (range:0.1-121.1). Resolution occurred in 896 patients (64.6%) with a median time to resolution of 20.1 weeks (0.1 - 192.7+). In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of rash was 46.2% (968/2094). Grade 2, Grade 3, and Grade 4 cases were reported in 14.1% (296/2094), 4.6% (97/2094), and < 0.1% (2/2094) of patients, respectively. Median time to onset was 0.7 months (range: 0.0-33.8). Resolution occurred in 671 patients (69.6%) with a median time to resolution of 11.1 weeks (range: 0.1-268.7+). Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, the incidence of rash was 65.2%, including Grade 2 (20.3%) and Grade 3 (7.8%). In patients treated with nivolumab in combination with chemotherapy, the incidence of rash was 25.6% (402/1572). Grade 2 and Grade 3 cases were reported in 6.2% (97/1572), and 2.5% (39/1572)) of patients, respectively. Median time to onset was 7.0 weeks (range: 0.1-97.4). Resolution occurred in 273 patients (68.1%) with a median time to resolution of 12.3 weeks (range: 0.1-258.7+). In patients treated with nivolumab in combination with cabozantinib, 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 4.0% (188/4646), including 9 Grade 3 and 3 Grade 4 cases. In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of hypersensitivity/infusion reactions was 4.9% (103/2094). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 2.1% (44/2094), 2.5% (53/2094), 0.2% (5/2094), and < 0.1% (1/2094) of patients, respectively. Among patients with MPM treated with nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg, the incidence of hypersensitivity/infusion reactions was 12%. In patients treated with nivolumab in combination with chemotherapy, the incidence of hypersensitivity/infusion reactions was 8.5% (134/1572). Grade 2, Grade 3, and Grade 4 cases were reported in 4.8% (76/1572), 1.1% (18/1572) and 0.2% (3/1572) of patients, respectively. In patients treated with nivolumab in combination with cabozantinib , 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: 3.4% for anaemia (all Grade 3), 0.7% for thrombocytopaenia, 0.7% for leucopoenia, 8.7% for lymphopaenia, 0.9% for neutropaenia, 1.7% for increased alkaline phosphatase, 2.6% for increased AST, 2.3% for increased ALT, 0.8% for increased total bilirubin, 0.7% for increased creatinine, 2.0% for hyperglycaemia, 0.7% for hypoglycaemia, 3.8% for increased amylase, 6.9% for increased lipase, 4.7% for hyponatraemia, 1.6% for hyperkalaemia, 1.3% for hypokalaemia, 1.1% for hypercalcaemia, 0.6% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.6% for hypocalcaemia, 0.6% for hypoalbuminaemia, and <0.1% for hypernatraemia. In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 4.9% for anaemia, 1.5% for thrombocytopaenia, 2.3% for leucopoenia, 7.3% for lymphopaenia, 3.4% for neutropaenia, 2.9% for increased alkaline phosphatase, 7.3% for increased AST, 8.4% for increased ALT, 1.2% for increased total bilirubin, 1.6% for increased creatinine, 5.8% for hyperglycaemia, 0.9% for hypoglycaemia, 8.4% for increased amylase, 16.7% for increased lipase, 0.8% for hypocalcaemia, 0.2% for hypernatraemia, 1.0% for hypercalcaemia, 1.9% for hyperkalaemia, 0.5% for hypermagnesaemia, 3.4% for hypokalaemia, and 9.8% for hyponatraemia. Among patients treated with nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg, a higher proportion of patients experienced a worsening from baseline to Grade 3 or 4 increased ALT (15.3%). In patients treated with nivolumab in combination with chemotherapy, the proportion of patients who experienced a worsening from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 15.8% for anaemia, 6.9% for thrombocytopaenia, 12.2% leukopaenia, 14.6% for lymphopaenia, 27.6% neutropaenia, 2.4% for increased alkaline phosphatase, 3.4% for increased AST, 2.6% for increased ALT, 2.0% for increased bilirubin, 1.4% for increased creatinine, 4.5% for increased amylase, 5.2% for increased lipase, 0.5% for hypernatraemia, 8.8% for hyponatraemia, 1.9% for hyperkalaemia, 5.6% for hypokalaemia, 0.8% for hypercalcaemia, 1.9% for hypocalcaemia, 1.5% for hypermagnesaemia, 2.9% for hypomagnesaemia, 3.5% for hyperglycaemia, and 0.7% for hypoglycaemia. In patients treated with nivolumab in combination with cabozantinib , 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 3529 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, 328 patients (9.3%) tested positive for treatment emergent anti product antibodies with 21 patients (0.6%) 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, 7.5% tested positive for treatment emergent anti-product-antibodies with 0.5% 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, 24.9% 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, 1.5% 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 The safety of nivolumab as monotherapy (3 mg/kg every 2 weeks) and in combination with ipilimumab (nivolumab 1 mg/kg or 3 mg/kg in combination with ipilimumab 1 mg/kg every 3 weeks for the first 4 doses, followed by nivolumab 3 mg/kg as monotherapy every 2 weeks) was evaluated in 97 paediatric patients aged ≥ 1 year to < 18 years (including 53 patients 12 to < 18 years) with recurrent or refractory solid or haematological tumours, including advanced melanoma, in clinical study CA209070. The safety profile in paediatric patients was generally similar to that seen in adults treated with nivolumab as monotherapy or in combination with ipilimumab. No new safety signals were observed. Long-term safety data is unavailable on the use of nivolumab in adolescents 12 years of age and older. The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab monotherapy were fatigue (35.9%) and decreased appetite (21.9%). The majority of adverse reactions reported for nivolumab monotherapy were Grade 1 or 2 in severity. Twenty-one patients (33%) had one or more Grades 3 to 4 adverse reactions. The most common adverse reactions (reported in at least 20% of paediatric patients) treated with nivolumab in combination with ipilimumab were fatigue (33.3%) and rash maculo-papular (21.2%). The majority of adverse reactions reported for nivolumab in combination with ipilimumab were Grade 1 or 2 in severity. Ten patients (30%) had one or more Grades 3 to 4 adverse reactions. No new safety signals were observed in clinical study CA209908 of 151 paediatric patients with high-grade primary central nervous system (CNS) malignancies (see section 5.1), 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** 10 june 2024. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu