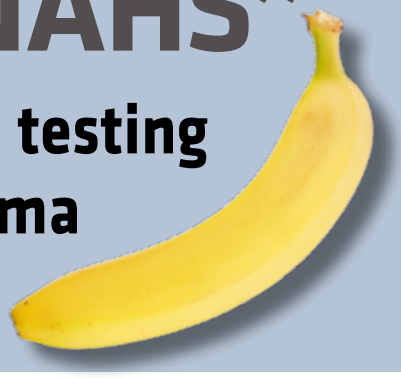
"I LIKE BANANAS, YOU LIKE BANAHNAHS"

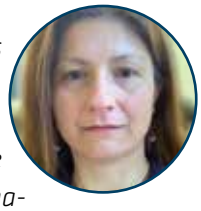
A pathologists' debate on PD-L1 testing in muscle-invasive urothelial carcinoma and upper gastro-intestinal cancers



As patients with a high expression of PD-L1 are more likely to obtain a response to anti-PD-L1 therapy, the detection of PD-L1 can be used as a predictive biomarker. However, all anti-PD-L1 therapy companies used distinct immunohistochemistry (IHC) assays for PD-L1 expression, as well as different scoring schemes for the readout, in their pivotal clinical trials.[1] As such, there have been years of debate and confusion on how we should deal with all these PD-L1 assays in clinical practice. Although implementing all available assays in each laboratory is impossible due to limited tumour tissue, turnaround time and high costs, there is no firm consensus on the potential interchangeability of the various assays. During a BMS supported satellite symposium at the Belgian Week of Pathology meeting in October 2022, *Prof. Nicky D'Haene (ULB Erasme), Dr. Vasiliki Siozopoulou (UZA)* and *Dr. Roberto Salgado (GZA-ZNA)* tried to solve this dilemma in an interactive debate. Below, their expert opinions and recommendations are summarised.

To open the debate, *Dr. Roberto Salgado* shed some light over the current situation in PD-L1 testing. Over the past decade, programmed death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors have gained momentum in a broad range of indications. In some indications, including non-small cell lung cancer, urothelial carcinoma, head and neck squamous cell carcinoma, triple-negative breast cancer, oesophageal squamous cell carcinoma, HER2-negative gastro-oesophageal junction cancer, HER2-negative gastric cancer and cervical cancer, the approval and reimbursement are restricted to PD-L1 expression thresholds. To determine if a patient is eligible for treatment with a PD-(L)1 inhibitor, pathology samples of the tumour need to be analysed by immunohistochemistry (IHC) to determine PD-L1 expression levels. However, pivotal clinical trials at the basis for approval of the PD-(L)1 inhibitors in the various cancer settings all use different PD-L1 scoring algorithms (tumour proportion score [TPS], combined positive score [CPS], expression on immune cells, *etc.*) and different cut-off values for readout. Furthermore, several commercially available kits and antibodies (28-8, 22C3, SP263 and SP142) are used as companion diagnostics throughout the clinical trials. As such, it is to no surprise to see that pathologists and oncologists are left behind with many questions and wonder whether a clinical trial validates an assay, or a biomarker.

What is the current situation in PD-L1 testing in MIUC and upper gastrointestinal cancers?



Dr. Siozopoulou: *"Based on the results of the CheckMate 274 trial, nivolumab got approved and reimbursed for the adjuvant treatment of muscle-invasive urothelial cancer (MIUC). The dual primary outcome measures of the trial were the disease-free survival (DFS) in the intention-to-treat population and in patients with tumour PD-L1 ≥1%. The latter was defined by the percentage of positive tumour cell membrane staining in a minimum of 100 evaluable tumour cells using the PD-L1 IHC 28-8 PharmDx immunohistochemistry assay (TPS ≥1%).[2]"*

Prof. D'Haene: *"In upper gastro-intestinal tract cancers, first-line treatment with immunotherapy is only recommended in specific settings. In contrast to the MIUC setting, in the gastrointestinal setting, immune checkpoint inhibitor use is linked to the cancer type and PD-L1 expression evaluation. As such, nivolumab plus chemotherapy is indicated for patients with oesophageal squamous cell carcinoma (ESCC) with a TPS ≥1% and for patients with HER2-negative oe-*

sophageal adenocarcinoma (EAC), gastro-oesophageal junction cancer (GEJC) or gastric adenocarcinoma (GC) with a CPS ≥5 (all 28-8 PharmDx assay).[3,4] Furthermore, pembrolizumab plus chemotherapy is indicated for patients with ESCC and a CPS ≥10 (22C3 assay) or HER2-negative patients with EAC or GEJC and a CPS ≥10 (22C3 assay).[5]"

Dr. Roberto Salgado concluded that companion diagnostics PD-L1 IHC assays thus seem to be developed in a "one assay, one drug" paradigm, which raises questions as to feasibility of using a specific PD-L1 assay for a certain drug or therapeutic indication. If pathologists are consistent, each laboratory would need to implement at least 5 different PD-L1-assays, all for the same biomarker. However, Dr. Salgado stressed that, in trials where outcomes were linked to PD-L1 expression, what is actually validated is PD-L1 as a biomarker for response to a certain drug, rather than the PD-L1 assay itself. In addition, neither the EMA nor the RIZIV/INAMI limit anti-PD-(L)1 treatment access to patients tested with a specific companion diagnostic assay. For patient selection, PD-L1 expression should only be confirmed by 'a validated test'.

Are PD-L1 IHC assays interchangeable?

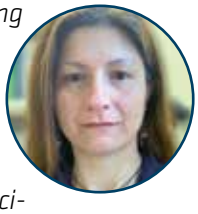
To date, many PD-L1 IHC assays have been implemented in laboratories around the globe, either as companion diagnostic kits or as Laboratory-Developed Tests (LDT), and the analytical concordance between assays has been evaluated in multiple studies. While the Blueprint PD-L1 immunohistochemistry project in real-world clinical lung cancer samples consolidated the analytical evidence for interchangeability of the 22C3, 28-8, and SP263 assays for these patients, there is no real consensus in the setting of MIUC and upper gastro-intestinal cancers. Nonetheless, there is some evidence from literature.

First of all, the concordance between 28-8-, 22C3-, and SP263-based assays in urothelial carcinoma was high when used to assess PD-L1 expression on tumour cells (TCs).[6] Also in the setting of upper gastro-intestinal cancers, several studies have confirmed the interchangeability between the 22C3, 28-8 and SP263 assays. One of these studies demonstrated that the inter-observer variability was higher than the inter-assay variability. In other words, differences in interpretation between pathologists generate more variability than technical differences between assays. This implies that well-trained pathologists are of utmost importance for a correct interpretation of the staining results.[7-10] Furthermore, the SP263, 28-8 and 22C3 assays all showed similar ranges of limit of detection, suggesting that they are of nearly equal sensitivity. In addition, properly designed and validated laboratory developed tests (LDT) perform equally to the original commercially available assays.[11] With the exception of the SP142 assay, **all commercially available as well as validated LDTs can thus be used interchangeably to measure PD-L1 levels in a daily practice setting.** This is similar to the situation of HER2, where there are 4 different Companion Diagnostics (CdX). Although these assays are not perfectly but nearly interchangeable, for a daily practice use this has never been an issue, since pathologists are never requested to use a particular HER2 CdX depending on the anti-HER2 drug used. Nonetheless, a clear communication between pathologists and oncologists is of utmost importance for a successful diagnosis. In this, the oncologist must clearly communicate to the pathologist(s) which type of information is required. For example, in case of ESCC, the oncologist should request both TPS and CPS values if it is unclear what drug he/she aims to use, while for urothelial cancer in the adjuvant setting, only TPS is sufficient. Based on this information, the pathologist can then decide upon the best assay, knowing that any validated PD-L1 IHC tests can be used, and make a complete report on the staining results, in which PD-L1 expression shall ideally be reported as continuous variables rather than thresholds. This information can then be used by the oncologists to determine the patient's eligibility for a certain PD-(L)1 inhibitor.

Table 1. PD-L1 scoring algorithms.

TPS/TC	$\frac{(\#PD\text{-}L1\ staining\ tumour\ cells)}{(Total\ \#\ viable\ tumour\ cells)} \times 100$
CPS	$\frac{(PD\text{-}L1\ staining\ cells\ @(tumour\ cells, lymphocytes, macrophages)}{(total\ \#\ viable\ tumour\ cells\ )} \times 100$
IC	$\frac{(tumour\ area\ occupied\ by\ PD\text{-}L1\ stained\ immune\ cell (lymphocytes, macrophages, dendritic\ cells, granulocytes)}{(total\ \#\ viable\ tumour\ cells)} \times 100$

Which sample should we test?



Dr. Siozopoulou: *"In the adjuvant setting of MIUC, the question is still open as to whether to use the biopsy sample or excision sample for PD-L1 staining. Thus far, there are no clear-cut criteria as to use one or the other. However, the biopsy specimen is usually better fixated than the excision material and fixation plays an important role in IHC. Therefore, I would prefer to stain the biopsy material if enough viable tumours cells are present (a minimum of 100 viable tumour cells is required). However, if the initial biopsy result is negative but the patient already received neoadjuvant chemotherapy, it*

Key messages for clinical practice
- In terms of analytical performance, the SP263, 28-8 and 22C3 PD-L1 IHC assays are highly comparable and can interchangeably be used in a daily practice setting
- Laboratory developed tests (LDT) to measure PD-L1 expression can also be used when properly validated
- A clear communication between pathologists and oncologists is of utmost importance for an appropriate assessment of PD-L1
- Pathologists should be adequately trained to correctly interpret staining results
- Inter- as well as intra-tumour variability in PD-L1 expression levels can be significant and sufficient cells and tumour area thus need to be present before drawing any conclusions on the results
- If both primary and metastatic tumour samples are available, the primary tumour should be preferred for PD-L1 assessment

may be worthwhile to perform an extra analysis on the excision biopsy. Finally, PD-L1 is very heterogeneously expressed from area to area within the same tumour, meaning that results can be false negative if only small samples/areas are analysed."

***Prof. D'Haene**: "In gastro-intestinal cancer, there is, as already described for other solid tumours, temporal and spatial heterogeneity of PD-L1 expression. In one study, biopsies showed a higher number of PD-L1 negative cases as compared to gastric surgical resection specimens. Out of patients with discrepant results between biopsy and gastrectomy, positive conversion (PD-L1 negative in biopsy and positive in resection) was more frequent than negative conversion.[12] Furthermore, another study observed that the baseline distant metastatic tumours have a lower PD-L1 positive rate than their matched baseline primary tumours. With regard to the situation pre- and post-treatment, there is temporal heterogeneity and no significant directional change in PD-L1 status after chemotherapy.[13] Finally, the primary gastric tumour seems to be more often PD-L1 positive than the metastatic tumour.[14] All together, sampling of the primary tumour is thus preferred."*

CONCLUSION

In terms of analytical comparability, the SP263, 28-8 and 22C3 assays are interchangeable and can be used to assess PD-L1, independent of the tumour type and the organ where the cancer arose. However, the training of the pathologist to score according to the corresponding scoring system is of utmost importance. Important to note is also that all clinical trials with anti-PD-L1 drugs validated the use of PD-L1 as a biomarker for response to a certain drug, rather than validating the used vendor-specific PD-L1 assay itself. The site of biopsy can also largely influence the staining outcomes. Indeed, in most tumour types is the metastatic setting an immune-deprived environment. Given the lower amount of immune cells, PD-L1 expression is often lower in a metastatic biopsy. Hence, testing the primary tumour is always preferred. Finally, neither the EMA nor the RIZIV/INAMI states that the exact same diagnostic assay as in the clinical trials should be used to claim the patient's eligibility for a certain PD-(L)1 inhibitor.

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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 melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection (see section 5.1). Non-small cell lung cancer (NSCLC) OPDIVO in combination with ipilimumab and 2 cycles of platinum-based chemotherapy is indicated for the first-line treatment of metastatic non-small cell lung cancer in adults whose tumours have no sensitising EGFR mutation or ALK translocation. OPDIVO as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults. Malignant pleural mesothelioma (MPM) OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with unresectable malignant pleural mesothelioma. Renal cell carcinoma (RCC) OPDIVO as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. OPDIVO in combination with ipilimumab is indicated for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma (see section 5.1). OPDIVO in combination with cabozantinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (see section 5.1). Classical Hodgkin lymphoma (cHL) OPDIVO as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin. Squamous cell cancer of the head and neck (SCCHN) OPDIVO as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy (see section 5.1). Urothelial carcinoma OPDIVO as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy. 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 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 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. *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 = 4122) with minimum follow-up ranging from 2.3 to 28 months, the most frequent adverse reactions (≥ 10%) were fatigue (45%), musculoskeletal pain (31%), diarrhoea (26%), cough (24%), rash (24%), nausea (23%), pruritus (19%), decreased appetite (18%), constipation (17%), dyspnoea (17%), abdominal pain (16%), upper respiratory tract infection (16%), arthralgia (14%), pyrexia (14%), vomiting (14%), headache (13%) and oedema (10%). 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 = 4122) 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,i], leucopoenia[b], neutropaenia[a,b], thrombocytopaenia[b] Uncommon eosinophilia Not known haemophagocytic lymphohistiocytosis Immune system disorders Common infusion related reaction, hypersensitivity (including anaphylactic reaction) Uncommon sarcoidosis Not known solid organ transplant rejection[f] Endocrine disorders Common hypothyroidism, hyperthyroidism, thyroiditis Uncommon adrenal insufficiency[j], hypopituitarism, hypophysitis, diabetes mellitus Rare diabetic ketoacidosis, hypoparathyroidism Metabolism and nutrition disorders Very common decreased appetite, hyperglycaemia[b], hypoglycaemia[b] Common dehydration, weight decreased 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] Eye disorders Common blurred vision, dry eye Uncommon uveitis Not known Vogt-Koyanagi-Harada syndrome[f] 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 Hepatobiliary disorders Uncommon hepatitis , cholestasis Skin and subcutaneous tissue disorders Very common rash[c], pruritus Common vitiligo, dry skin, erythema, alopecia, urticaria Uncommon psoriasis, rosacea, erythema multiforme 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, oedema[l] Common pain, chest pain 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 = 1092), with a minimum follow-up ranging from 12.1 to 20 months for gastric, GEJ or oesophageal adenocarcinoma, or OSCC, the most frequent adverse reactions (≥ 10%) were nausea (53%), peripheral neuropathy (43%), fatigue (41%), diarrhoea (37%), decreased appetite (35%), constipation (30%), vomiting (29%), stomatitis (25%), abdominal pain (23%), pyrexia (19%), rash (17%), musculoskeletal pain (17%), cough (14%), oedema (including peripheral oedema) (14%), hypoalbuminaemia (13%), headache (10%). Incidences of Grade 3-5 adverse reactions were 76% for nivolumab in combination with chemotherapy and 62% for chemotherapy alone, with 1.4% 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 and 4.34 months (95% CI: 4.04, 4.70) for chemotherapy for gastric, GEJ or oesophageal adenocarcinoma, or OSCC. 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%), dysguesia (23.8%), upper respiratory tract infection (20.6%), cough (20.6%), pruritus (20.6%), arthralgia (19.4%), vomiting (18.4%), dysphonia (17.8%), headache (16.3%), dyspepsia (15.9%), dizziness (14.1%), constipation (14.1%), pyrexia (14.1%), oedema (13.4%), muscle spasm (12.2%), dyspnoea (11.6%), proteinuria (10.9%) and hyperthyroidism (10.0%). The 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 = 1092), 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, hypersensitivity; Uncommon:; Rare: sarcoidosis; Not known: solid organ transplant rejection[f] *Combination with chemotherapy* Common: hypersensitivity, infusion related reaction; 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, adrenal insufficiency; Uncommon: hypopituitarism, diabetes mellitus; Rare: hypophysitis; *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[b], 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 *Combination with chemotherapy* Very common: peripheral neuropathy, headache; Common: paraesthesia, dizziness; Uncommon:; Rare: Guillain-Barré syndrome, encephalitis *Combination with cabozantinib* Very common: dysgeusia, dizziness, headache; Common: peripheral neuropathy; Uncommon: encephalitis autoimmune, Guillain-Barré syndrome, myasthenic syndrome; Rare: Ear and labyrinth disorders *Combination with ipilimumab (with or without chemotherapy)* Common: *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; 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 *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] *Combination with chemotherapy* Very common: diarrhoea[a], stomatitis, vomiting, nausea, abdominal pain, constipation; Common: colitis, dry mouth; Uncommon: pancreatitis; Rare: *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: 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]; Common: palmar-plantar erythrodysaesthesia syndrome, pruritus, 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; Rare: nephritis *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: *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 transaminases[b], hyponatraemia[b], increased amylase, hypomagnesaemia[b], increased alkaline phosphatase[b], hypokalaemia[b], increased creatinine[b], increased lipase, hyperkalaemia[b], increased total bilirubin[b], hypernatraemia[b]; Common: 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:1,5;2,5;2,4;2,5 Colitis:1,0;6;2,5;2,5 Hepatitis: 0,9;5;1,1;4,1 Nephritis and renal dysfunction:0,3;1,2;3,3;0,6 Endocrinopathies:0,3;2,0;0,5;1,3 Skin:0,6;1,0;1,0;2,2 Hypersensitivity/Infusion reaction: 0,1;0,3;2,5;0 Immune-related adverse reaction requiring high dose corticosteroids[a,b] Pneumonitis:65;59;59;56 Colitis:14;32;8;8 Hepatitis:20;37;8;23 Nephritis and renal dysfunction:22;27;10;9 Endocrinopathies:6;20;6;4,2 Skin:4;8;6;8 Hypersensitivity/Infusion reaction:18;16;24;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 3.6% (147/4122). The majority of cases were Grade 1 or 2 in severity reported in 0.9% (38/4122) and 1.8% (74/4122) of patients respectively. Grade 3 and 4 cases were reported in 0.8% (32/4122) and <0.1% (1/4122) of patients respectively. Six patients i (0.1%) had a fatal outcome. Median time to onset was 14.4 weeks (range: 0.7-85.1). Resolution occurred in 100 patients (68.0%) with a median time to resolution of 6.6 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 5.4% (59/1092). Grade 2, Grade 3, and Grade 4 cases were reported in 2.7% (29/1092), 1.2% (13/1092), and 0.3% (3/1092), of patients, respectively. Two patients (0.2%) had a fatal outcome. Median time to onset was 24.1 weeks (range: 1.6-96.9). Resolution occurred in 40 patients (67.8%) 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

15.3% (631/4122). The majority of cases were Grade 1 or 2 in severity reported in 9. 9% (409/4122) and 3. 9% (160/4122) of patients respectively. Grade 3 and 4 cases were reported in 1. 5% (61/4122) and <0.1% (1/4122) of patients respectively. Median time to onset was 7.9 weeks(range:0.1-115.6). Resolution occurred in 565 patients (90.5%) with a median time to resolution of 2.4 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: .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 29.8% (325/1092). Grade 2, Grade 3, and Grade 4 cases were reported in 9.4% (103/1092), 4.0% (44/1092), and 0.5% (6/1092) 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 284 patients (87.7%) with a median time to resolution of 1.6 weeks (range: 0.1-117.6+). 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 7.4% (306/4122). The majority of cases were Grade 1 or 2 in severity reported in 4.0% (165/4122) and 1.7% (70/4122) of patients respectively. Grade 3 and 4 cases were reported in 1.4% (59/4122) and 0.3% (12/4122) of patients, respectively. Median time to onset was 10.0 weeks(range:0.1-120.0). Resolution occurred in 240 patients (79.5%) 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 21.6% (236/1092). Grade 2, Grade 3 and Grade 4 cases were reported in 7.1% (77/1092), 3.2% (35/1092) and < 0.1% (1/1092) of patients, respectively. Median time to onset was 7.9 weeks (range: 0.1-84.1). Resolution occurred in 185 patients (79.7%) with a median time to resolution of 9.1 weeks (range: 0.4-150.6+). 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 2.7% (112/4122). The majority of cases were Grade 1 or 2 in severity reported in 1.6% (66/4122) and 0.7% (28/4122) of patients respectively. Grade 3 and 4 cases were reported in 0.4% (17/4122) and <0.1% (1/4122) of patients, respectively. Median time to onset was 11.3 weeks (range:0.1-79.1). Resolution occurred in 74 patients (69.2%) 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 9.1% (99/1092). Grade 2, Grade 3, and Grade 4 cases were reported in 3.7% (40/1092), 1.1% (12/1092), and 0.2% (2/1092) of patients, respectively. One patient (< 0.1%) had a fatal outcome. Median time to onset was 11.3 weeks (range: 0.7-60.7). Resolution occurred in 62 patients (62.6%) with a median time to resolution of11.7 weeks (range: 0.1-135.1+). 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 12.5%(516/4122). The majority of cases were Grade 1 or 2 in severity reported in 6.1% (253/4122) and 6.2% (256/4122)) of patients, respectively. Grade 3 thyroid disorders were reported in 0.2% (7/4122) of patients. Hypophysitis (3 Grade 1, 5 Grade 2, 7 Grade 3, and 1 Grade 4), hypopituitarism (5 Grade 2 and 1 Grade 3), adrenal insufficiency (including secondary adrenocortical insufficiency and adrenocortical insufficiency acute) (1 Grade 1, 17 Grade 2, and 8 Grade 3), diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) (1 Grade1, 4 Grade 2 and 5 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 278 patients (49.8%). Median time to resolution was 44.1 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 11.7% (128/1092). Grade 2 thyroid disorder was reported in 5.5% (60/1092) patients. Grade 3 hypophysitis occurred in < 0.1% (1/1092) of patients. Grade 2 and Grade 3 hypopituitarism occurred in 0.3% (3/1092) and 0.3% (3/1092) of patients, respectively. Grade 2, Grade 3 and Grade 4 adrenal insufficiency occurred in 0.7% (8/1092), 0.2% (2/1092) and <0.1% (1/1092) of patients, respectively. Diabetes mellitus including Type 1 diabetes mellitus and fulminant Type 1 diabetes mellitus (1 Grade 2, 2 Grade 3 and 1 Grade 4), and diabetic ketoacidosis (1 Grade 4) were reported. Median time to onset of these endocrinopathies was14.3 weeks (range: 2.0-124.3). Resolution occurred in 56 patients (38.9%). Time to resolution ranged from 0.4 to 155.7+ 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 29.5% (1215/4122). The majority of cases were Grade 1 in severity reported in 22.4% (924/4122) of patients. Grade 2 and Grade 3 cases were reported 5.7% (235/4122) and 1.4% (56/4122) of patients respectively. Median time to onset was 6.3 weeks (range:0.1-121.1). Resolution occurred in 779 patients (64.6%) with a median time to resolution of 18.1 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 24.5% (267/1092). Grade 2 and Grade 3 cases were reported in 6.4% (70/1092), and 2.5% (27/1092) of patients, respectively. Median time to onset was 9.1weeks (range: 0.1-97.4). Resolution occurred in 166 patients (62.2%) with a median time to resolution of19.1 weeks (range: 0.1-188.1+). 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 3.9% (160/4122), 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 10.6% (116/1092). Grade 2, Grade 3, and Grade 4 cases were reported in 6.5% (71/1092), 1.4% (15/1092) and 0.2% (2/1092) 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: 3.9% for anaemia (all Grade 3), 0.7% for thrombocytopaenia, 0.8% for leucopaenia, 9.6% for lymphopaenia, 1.0% for neutropaenia, 1.9% for increased alkaline phosphatase, 2.7% for increased AST, 2.4% for increased ALT, 0.9% for increased total bilirubin, 0.7% for increased creatinine, 2.7% for hyperglycaemia, 1.2% for hypoglycaemia, 4.2% for increased amylase, 7.4% for increased lipase, 5.2% for hyponatraemia, 1.7% for hyperkalaemia, 1.4% for hypokalaemia, 1.2% for hypercalcaemia, 0.7% for hypermagnesaemia, 0.4% for hypomagnesaemia, 0.7% for hypocalcaemia, 0.9% 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, 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: 16.3% for anaemia, 5.8% for thrombocytopaenia, 11.5% leukopaenia, 15.4% for lymphopaenia, 26.1% neutropaenia, 3.0% for increased alkaline phosphatase, 4.2% for increased AST, 3.1% for increased ALT, 2.3% for increased bilirubin, 1.4% for increased creatinine, 5.9% for increased amylase, 4.0% for increased lipase, 0.6% for hypernatraemia, 8.7% for hyponatraemia, 1.7% for hyperkalaemia, 7.4% for hypokalaemia, 1.0% for hypercalcaemia, 2.0% for hypocalcaemia, 1.5% for hypomagnesaemia, 3.1% for hyperglycaemia, and 0.6% 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. 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** 31 may 2023. Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu