## 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 12 mL contains 120 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

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.

Renal cell carcinoma (RCC)

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).

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.

Posology

*OPDIVO in combination with ipilimumab*

*Renal cell carcinoma*
The recommended dose is 3 mg/kg nivolumab in combination with 1 mg/kg ipilimumab administered intravenously every 3 weeks for the first 4 doses. This is then followed by a second phase in which nivolumab monotherapy is administered intravenously at either 240 mg every 2 weeks **or** at 480 mg every 4 weeks, as presented in Table 1. For the monotherapy phase, the first dose of nivolumab should be administered;

- 3 weeks after the last dose of the combination of nivolumab and ipilimumab if using 240 mg every 2 weeks; or
- 6 weeks after the last dose of the combination of nivolumab and ipilimumab if using 480 mg every 4 weeks.

**Table 1: Recommended doses and infusion times for intravenous administration of nivolumab in combination with ipilimumab for RCC**

| | **Combination phase, every 3 weeks for 4 dosing cycles** | **Monotherapy phase** |
|---|---|---|
| **Nivolumab** | 3 mg/kg over 30 minutes | 240 mg every 2 weeks over 30 minutes or<br>480 mg every 4 weeks over 60 minutes |
| **Ipilimumab** | 1 mg/kg over 30 minutes | - |

*OPDIVO in combination with ipilimumab and chemotherapy*

*Non-small cell lung cancer*
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes every 3 weeks in combination with 1 mg/kg ipilimumab administered intravenously over 30 minutes every 6 weeks, and platinum-based chemotherapy administered every 3 weeks. After completion of 2 cycles of chemotherapy, treatment is continued with 360 mg nivolumab administered intravenously every 3 weeks in combination with 1 mg/kg ipilimumab every 6 weeks. Treatment is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

*OPDIVO in combination with chemotherapy*

*Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma*
The recommended dose is 360 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 3 weeks **or** 240 mg nivolumab administered intravenously over 30 minutes in combination with fluoropyrimidine- and platinum-based chemotherapy administered every 2 weeks (see section 5.1). Treatment with nivolumab is recommended until disease progression, unacceptable toxicity, or up to 24 months in patients without disease progression.

*Duration of treatment*
Treatment with OPDIVO 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).

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 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 2. 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 product information (PI) of these other combination therapeutic agents regarding dosing.

**Table 2: Recommended treatment modifications for OPDIVO in combination**

| Immune-related adverse reaction | Severity | Treatment modification |
|---|---|---|
| Immune-related pneumonitis | Grade 2 pneumonitis | Withhold dose(s) until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete |
| | Grade 3 or 4 pneumonitis | Permanently discontinue treatment |
| Immune-related colitis | Grade 2 diarrhoea or colitis | Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete |
| | Grade 3 diarrhoea or colitis<br>OPDIVO monotherapy | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete |
| | - OPDIVO+ipilimumab[a] | Permanently discontinue treatment |
| | Grade 4 diarrhoea or colitis | Permanently discontinue treatment |
| Immune-related hepatitis | Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin | Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete |
| | Grade 3 or 4 elevation in AST, ALT, or total bilirubin | Permanently discontinue treatment |
| Immune-related nephritis and renal dysfunction | Grade 2 or 3 creatinine elevation | Withhold dose(s) until creatinine returns to baseline and management with corticosteroids is complete |
| | Grade 4 creatinine elevation | Permanently discontinue treatment |
| Immune-related endocrinopathies | Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis,<br>Grade 2 adrenal insufficiency<br>Grade 3 diabetes | 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 |
| | Grade 4 hypothyroidism<br>Grade 4 hyperthyroidism<br>Grade 4 hypophysitis<br>Grade 3 or 4 adrenal insufficiency<br>Grade 4 diabetes | Permanently discontinue treatment |
| Immune-related skin adverse reactions | Grade 3 rash | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete |
| | Grade 4 rash | Permanently discontinue treatment |

| | | |
|---|---|---|
| | Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) | Permanently discontinue treatment (see section 4.4) |

| Immune-related adverse reaction | Severity | Treatment modification |
|---|---|---|
| Immune-related myocarditis | Grade 2 myocarditis | Withhold dose(s) until symptoms resolve and management with corticosteroids is complete[c] |
| | Grade 3 or 4 myocarditis | Permanently discontinue treatment |
| Other immune-related adverse reactions | Grade 3 (first occurrence) | Withhold dose(s) |
| | Grade 4 or recurrent Grade 3; persistent Grade 2 or 3 despite treatment modification; inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day | 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.

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 PI 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.

*Special populations*

*Paediatric population*
The safety and efficacy of OPDIVO in children below 18 years of age have not been established. Currently available data of OPDIVO in combination with ipilimumab are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

*Elderly*
No dose adjustment is required for elderly patients (≥ 65 years) (see section 5.2).

*Renal impairment*
Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Data from patients with severe renal impairment are too limited to draw conclusions on this population.

*Hepatic impairment*
Based on the population PK results, no dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Data from patients with moderate or severe hepatic impairment are too limited to draw conclusions on these populations. OPDIVO must be administered with caution in patients with moderate (total bilirubin > 1.5 × to 3 × the upper limit of normal [ULN] and any AST) or severe (total bilirubin > 3 × ULN and any AST) hepatic impairment.

Method of administration

OPDIVO is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 or 60 minutes depending on the dose (see Tables 1, 2, 3 and 4). The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line filter with a pore size of 0.2-1.2 µm.

OPDIVO must not be administered as an intravenous push or bolus injection.

The total dose of OPDIVO required can be infused directly as a 10 mg/mL solution or can be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection (see section 6.6).

When administered in combination with ipilimumab 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.

## 4.4 Special warnings and precautions for use

Assessment of PD-L1 status
When assessing the PD-L1 status of the tumour, it is important that a well-validated and robust methodology is used.

Immune-related adverse reactions
When nivolumab is administered in combination, refer to the PI of the other combination therapy agents prior to initiation of treatment. Immune-related adverse reactions have occurred at higher frequencies when nivolumab was administered in combination with ipilimumab compared with nivolumab as monotherapy. Therefore, the guidance below for immune-related adverse reactions applies to the OPDIVO component of the combination, except where specifically noted. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see section 4.2).
Immune-related adverse reactions affecting more than one body system can occur simultaneously.

Cardiac and pulmonary adverse reactions including pulmonary embolism have also been reported with combination therapy. Patients should be monitored for cardiac and pulmonary adverse reactions continuously, as well as for clinical signs, symptoms, and laboratory abnormalities indicative of electrolyte disturbances and dehydration prior to and periodically during treatment. Nivolumab in combination with ipilimumab should be discontinued for life-threatening or recurrent severe cardiac and pulmonary adverse reactions (see section 4.2).

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

For suspected immune-related adverse reactions, adequate evaluation should be performed to confirm aetiology or exclude other causes. Based on the severity of the adverse reaction, nivolumab or nivolumab in combination with ipilimumab should be withheld and corticosteroids administered. If immunosuppression with corticosteroids is used to treat an adverse reaction, a taper of at least 1 month duration should be initiated upon improvement. Rapid tapering may lead to worsening or recurrence of

the adverse reaction. Non-corticosteroid immunosuppressive therapy should be added if there is worsening or no improvement despite corticosteroid use.

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

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

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

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

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

*Immune-related colitis*
Severe diarrhoea or colitis has been observed with nivolumab monotherapy or nivolumab in combination with ipilimumab (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus or blood in stool. Cytomegalovirus (CMV) infection/reactivation has been reported in patients with corticosteroid-refractory immune-related colitis. Infectious and other aetiologies of diarrhoea should be ruled out, therefore appropriate laboratory tests and additional examinations must be performed. If diagnosis of corticosteroid-refractory immune-related colitis is confirmed addition of an alternative immunosuppressive agent to the corticosteroid therapy, or replacement of the corticosteroid therapy, should be considered.

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

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

For Grade 2 diarrhoea or colitis, nivolumab or nivolumab in combination with ipilimumab should be withheld. Persistent diarrhoea or colitis should be managed with corticosteroids at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, nivolumab or nivolumab

in combination with ipilimumab may be resumed after corticosteroid taper, if needed. If worsening or no improvement occurs despite initiation of corticosteroids, corticosteroid dose should be increased to 1 to 2 mg/kg/day methylprednisolone equivalents and nivolumab or nivolumab in combination with ipilimumab must be permanently discontinued.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

*Other immune-related adverse reactions*
The following immune-related adverse reactions were reported in less than 1% of patients treated with nivolumab monotherapy or nivolumab in combination with ipilimumab in clinical trials across doses and tumour types: pancreatitis, uveitis, demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), Guillain-Barré syndrome, myasthenia gravis, myasthenic syndrome, aseptic meningitis, encephalitis, gastritis, sarcoidosis, duodenitis, myositis, myocarditis, and rhabdomyolysis. Cases of Vogt-Koyanagi-Harada syndrome, hypoparathyroidism, and cystitis noninfective have been reported post-marketing (see sections 4.2 and 4.8).

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

Cases of myotoxicity (myositis, myocarditis, and rhabdomyolysis), some with fatal outcome, have been reported with nivolumab or nivolumab in combination with ipilimumab. If a patient develops signs and symptoms of myotoxicity, close monitoring should be implemented, and the patient referred to a specialist for assessment and treatment without delay. Based on the severity of myotoxicity, nivolumab or nivolumab in combination with ipilimumab should be withheld or discontinued (see section 4.2), and appropriate treatment instituted.
The diagnosis of myocarditis requires a high index of suspicion. Patients with cardiac or cardio-pulmonary symptoms should be assessed for potential myocarditis. If myocarditis is suspected, prompt initiation of a high dose of steroids (prednisone 1 to 2 mg/kg/day or methylprednisolone 1 to 2 mg/kg/day) and prompt cardiology consultation with diagnostic workup according to current clinical guidelines should be initiated. Once a diagnosis of myocarditis is established, nivolumab or nivolumab in combination with ipilimumab should be withheld or permanently discontinued (see section 4.2).

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

Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy and nivolumab in combination with ipilimumab. Caution should be taken when nivolumab is administered as monotherapy or in combination with ipilimumab. If HLH is confirmed, administration of nivolumab or nivolumab in combination with ipilimumab should be discontinued and treatment for HLH initiated.

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

Disease-specific precautions

*Non-small cell lung cancer*
*First-line treatment of NSCLC*
Patients with active autoimmune disease, symptomatic interstitial lung disease, medical conditions requiring systemic immunosuppression, active (untreated) brain metastasis, who received prior systemic treatment for advanced disease, or who had sensitising EGFR mutations or ALK translocations were excluded from the pivotal trial in first-line treatment of NSCLC (see sections 4.5 and 5.1). Limited data are available in elderly patients (≥ 75 years) (see section 5.1). In these patients, nivolumab in combination with ipilimumab and chemotherapy should be used with caution after careful consideration of the potential benefit/risk on an individual basis.

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

*Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma*
Patients who had baseline ECOG performance score ≥ 2, untreated central nervous system metastases, active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the clinical study in gastric, GEJ or oesophageal adenocarcinoma (see sections 4.5 and 5.1). In the absence of data, nivolumab in combination with chemotherapy should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Study CA209649 excluded patients with known HER2-positive status. Patients with undetermined status were allowed in the study and represented 40.3% of patients (see section 5.1).

Patients on controlled sodium diet
Each mL of this medicinal product contains 0.1 mmol (or 2.5 mg) sodium. This medicinal product contains 10 mg sodium per 4 ml vial, 25 mg sodium per 10 ml vial, 30 mg sodium per 12 ml vial or 60 mg sodium per 24 ml vial, which is equivalent to 0.5%, 1.25%, 1.5% or 3% respectively, of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

Nivolumab is a human monoclonal antibody, as such pharmacokinetic interaction studies have not been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of nivolumab.

Other forms of interaction

*Systemic immunosuppression*
The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab to treat immune-related adverse reactions. The preliminary results show that systemic immunosuppression after starting nivolumab treatment does not appear to preclude the response on nivolumab.

## 4.6 Fertility, pregnancy and lactation

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

Breast-feeding
It is unknown whether nivolumab is secreted in human milk. Because many medicinal products, including antibodies, can be secreted in human milk, a risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue from

nivolumab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

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

## 4.7 Effects on ability to drive and use machines

Nivolumab or nivolumab in combination with ipilimumab may have a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as fatigue (see section 4.8), patients should be advised to use caution when driving or operating machinery until they are certain that nivolumab does not adversely affect them.

## 4.8 Undesirable effects

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 PI 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 = 2626) with minimum follow-up ranging from 6 to 47 months, the most frequent adverse reactions (≥ 10%) were fatigue (47%), rash (37%), diarrhoea (35%), nausea (27%), pruritus (29%), musculoskeletal pain (26%), pyrexia (23%), decreased appetite (22%), cough (21%), abdominal pain (18%), vomiting (18%), constipation (18%), arthralgia (18%), dyspnoea (17%), hypothyroidism (16%), headache (15%), upper respiratory tract infection (13%), oedema (13%), and dizziness (10%). The incidence of Grade 3-5 adverse reactions was 66% for nivolumab in combination with ipilimumab (with or without chemotherapy), with 1.0% 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, or OSCC, 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 and 4.34 months (95% CI: 4.04, 4.70) for chemotherapy for gastric, GEJ or oesophageal adenocarcinoma, or OSCC.

*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 = 2626) and nivolumab in combination with chemotherapy (n = 1572) are presented in Table 3. 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 3: Adverse reactions with nivolumab in combination with other therapeutic agents**

| | **Combination with ipilimumab (with or without chemotherapy)** | **Combination with chemotherapy** |
|---|---|---|
| **Infections and infestations** | | |
| Very common | upper respiratory tract infection | |
| Common | pneumonia, bronchitis, conjunctivitis | upper respiratory tract infection, pneumonia[a] |
| Rare | aseptic meningitis | |
| **Blood and lymphatic system disorders** | | |
| Very common | anaemia[b,j], thrombocytopaenia[b], leucopoenia[b], lymphopaenia[b], neutropaenia[b] | neutropaenia[b], anaemia[b,j], leucopoenia[b], lymphopaenia[b], thrombocytopaenia[b] |
| Common | eosinophilia | febrile neutropaenia[a] |
| Uncommon | febrile neutropaenia | eosinophilia |
| Not known | haemophagocytic lymphohistiocytosis | |
| **Immune system disorders** | | |
| Common | infusion related reaction (including cytokine release syndrome), hypersensitivity | hypersensitivity, infusion related reaction (including cytokine release syndrome) |
| Rare | sarcoidosis | |
| Not known | solid organ transplant rejection[g] | |
| **Endocrine disorders** | | |
| Very common | hypothyroidism | |
| Common | hyperthyroidism, thyroiditis, adrenal insufficiency, hypophysitis, hypopituitarism, diabetes mellitus | hypothyroidism, hyperthyroidism, diabetes mellitus |
| Uncommon | diabetic ketoacidosis | adrenal insufficiency, thyroiditis, hypopituitarism, hypophysitis |
| Rare | hypoparathyroidism | |
| **Metabolism and nutrition disorders** | | |
| Very common | decreased appetite, hyperglycaemia[b], hypoglycaemia[b] | decreased appetite, hypoalbuminaemia, hyperglycaemia[b], hypoglycaemia[b] |
| Common | dehydration, hypoalbuminaemia, hypophosphataemia, weight decreased | hypophosphataemia |
| Uncommon | metabolic acidosis | |
| Rare | | tumour lysis syndrome |
| Not known | tumour lysis syndrome[h] | |

| | Combination with ipilimumab (with or without chemotherapy) | Combination with chemotherapy |
|---|---|---|
| **Nervous system disorders** | | |
| Very common | headache | peripheral neuropathy |
| Common | dizziness, peripheral neuropathy | paraesthesia, dizziness, headache |
| 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), optic neuritis | Guillain-Barré syndrome, encephalitis |
| Not known | | myelitis (including transverse myelitis), optic neuritis |
| **Eye disorders** | | |
| Common | blurred vision, dry eye | dry eye, blurred vision |
| Uncommon | uveitis, episcleritis | uveitis |
| Rare | Vogt-Koyanagi-Harada syndrome | |
| **Cardiac disorders** | | |
| Common | tachycardia, atrial fibrillation | tachycardia, atrial fibrillation |
| Uncommon | myocarditis[a], arrhythmia (including ventricular arrhythmia)[a], bradycardia | myocarditis |
| Not known | pericardial disorders[i] | |
| **Vascular disorders** | | |
| Common | hypertension | thrombosis[a, k], hypertension, vasculitis |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Very common | cough, dyspnoea | cough |
| Common | pneumonitis[a], pulmonary embolism[a], pleural effusion | pneumonitis[a], dyspnoea |
| **Gastrointestinal disorders** | | |
| Very common | diarrhoea, vomiting, nausea, abdominal pain, constipation | diarrhoea[a], stomatitis, vomiting, nausea, abdominal pain, constipation |
| Common | colitis[a], pancreatitis, stomatitis, gastritis, dry mouth | colitis, dry mouth |
| Uncommon | duodenitis | pancreatitis |
| Rare | intestinal perforation[a], pancreatic exocrine insufficiency, coeliac disease | |
| Not known | | pancreatic exocrine insufficiency, coeliac disease |
| **Hepatobiliary disorders** | | |
| Common | hepatitis | |
| Uncommon | | hepatitis |

| | Combination with ipilimumab (with or without chemotherapy) | Combination with chemotherapy |
|---|---|---|
| **Skin and subcutaneous tissue disorders** | | |
| Very common | rash[c], pruritus | rash[c], pruritus |
| Common | alopecia, vitiligo, urticaria, dry skin, erythema, | palmar-plantar erythrodysaesthesia syndrome, skin hyperpigmentation, alopecia, dry skin, erythema |
| Uncommon | Stevens-Johnson syndrome, erythema multiforme, psoriasis, other lichen disorders[d] | |
| Rare | toxic epidermal necrolysis[a,c,] lichen sclerosus | |
| **Musculoskeletal and connective tissue disorders** | | |
| Very common | musculoskeletal pain[f], arthralgia | musculoskeletal pain[f] |
| Common | muscle spasms, muscular weakness, arthritis | arthralgia, muscular weakness |
| Uncommon | polymyalgia rheumatica, myopathy, myositis (including polymyositis)[a] | |
| Rare | spondyloarthropathy, Sjogren's syndrome, rhabdomyolysis[a] | |
| **Renal and urinary disorders** | | |
| Common | renal failure (including acute kidney injury)[a] | renal failure[a] |
| Uncommon | tubulointerstitial nephritis, nephritis | cystitis noninfective, nephritis |
| Rare | cystitis noninfective | |
| **General disorders and administration site conditions** | | |
| Very common | fatigue, pyrexia, oedema (including peripheral oedema) | fatigue, pyrexia, oedema (including peripheral oedema) |
| Common | chest pain, pain, chills | malaise |
| **Investigations** | | |
| 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] | 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], hypermagnesaemia[b], increased thyroid stimulating hormone, increased gamma-glutamyltransferase | hypernatraemia[b], hypercalcaemia[b], hypermagnesaemia[b] |

Adverse reaction frequencies presented in Table 3 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] Lichen disorders is a composite term which includes lichen keratosis and lichen planus.

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

[f] 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.

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

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

[i] Pericardial disorders is a composite term which includes pericarditis, pericardial effusion, cardiac tamponade, and Dressler's syndrome.

[j] 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.

[k] 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 with other agents than in those receiving nivolumab monotherapy. Table 4 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 4: 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) or nivolumab in combination with chemotherapy)**

| | Nivolumab in combination with ipilimumab (with or without chemotherapy) % | Nivolumab in combination with chemotherapy % |
|---|---|---|
| **Immune-related adverse reaction leading to permanent discontinuation** | | |
| Pneumonitis | 2.1 | 1.8 |
| Colitis | 6 | 1.8 |
| Hepatitis | 5 | 0.8 |
| Nephritis and renal dysfunction | 1.1 | 3.3 |
| Endocrinopathies | 2.2 | 0.6 |
| Skin | 1.0 | 1.0 |
| Hypersensitivity/Infusion reaction | 0.3 | 1.8 |
| **Immune-related adverse reaction requiring high-dose corticosteroids[a,b]** | | |
| Pneumonitis | 59 | 58 |
| Colitis | 32 | 8 |
| Hepatitis | 39 | 8 |
| Nephritis and renal dysfunction | 27 | 7 |
| Endocrinopathies | 18 | 5 |
| Skin | 8 | 6 |
| Hypersensitivity/Infusion reaction | 18 | 22 |

[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 in combination with ipilimumab (with or without chemotherapy), the incidence of pneumonitis including interstitial lung disease, was 6.0% (157/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 3.0% (78/2626), 1.0% (27/2626), and 0.3% (8/2626) 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 129 patients (82.2%) with a median time to resolution of 6.1 weeks (range: $0.1^{+}$-$149.3^{+}$).

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: $0.3^{+}$-$121.3^{+}$).

*Immune-related colitis*
In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of diarrhoea or colitis was 26.0% (682/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 8.1% (212/2626), 6.4% (167/2626), and 0.2% (4/2626), of patients, respectively. Two patient (<0.1%) had a fatal outcome. Median time to onset was 1.4 months (range: 0.0-48.9). Resolution occurred in 618 patients (91%) with a median time to resolution of 2.9 weeks (range: 0.1-$170.0^{+}$). 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-$212.3^{+}$).

*Immune-related hepatitis*
In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of liver function test abnormalities was 21.2% (556/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 5.0% (132/2626), 8.3% (218/2626), and 1.3% (34/2626) of patients, respectively. Seven patients (0.3%) had a fatal outcome. Median time to onset was 1.5 months (range: 0.0-36.6). Resolution occurred in 482 patients (87.0%) with a median time to resolution of 5.9 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-$240.0^{+}$).

*Immune-related nephritis and renal dysfunction*
In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of nephritis or renal dysfunction was 5.4% (141/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 2.0% (52/2626), 0.8% (21/2626), and 0.4% (11/2626) of patients, respectively. Two patients (< 0.1%) had a fatal outcome. Median time to onset was 2.6 months (range: 0.0-34.8). Resolution occurred in 110 patients (78.0%) with a median time to resolution of 5.9 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+).

*Immune-related endocrinopathies*
In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of thyroid disorders was 23.2% (608/2626). Grade 2 and Grade 3 thyroid disorders were reported in 12.7% (333/2626) and 1.0% (27/2626) of patients, respectively.
Grade 2 and Grade 3 hypophysitis (including lymphocytic hypophysitis) occurred in 1.9% (49/2626) and 1.5% (40/2626) of patients, respectively. Grade 2 and Grade 3 hypopituitarism occurred in 0.6% (16/2094) and 0.5% (13/2626)) of patients, respectively. Grade 2, Grade 3, and Grade 4 adrenal insufficiency (including secondary adrenocortical insufficiency, adrenocortical insufficiency acute, blood corticotrophin decreased and immune-mediated insufficiency) occurred in 2.7% (72/2626), 1.6% (43/2626) and 0.2% (4/2626) of patients, respectively. Grade 1, Grade 2, Grade 3, and Grade 4 diabetes mellitus (including Type 1 diabetes mellitus, and diabetic ketoacidosis) occurred in <0.1% (1/2626), 0.3% (8/2626), 0.3% (8/2626), and 0.2 (6/2626) of patients, respectively Median time to onset of these endocrinopathies was 2.1 months (range: 0.0-28.1). Resolution occurred in 297 patients (40.0%). 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 3,1 Grade 4) were reported. Median time to onset of these endocrinopathies was 14.7 weeks (range: 1.1-124.3). Resolution occurred in 81 patients (37..2%). Time to resolution ranged from 0.4 to 233.6+ weeks.

*Immune-related skin adverse reactions*
In patients treated with nivolumab in combination with ipilimumab (with or without chemotherapy), the incidence of rash was 46.1% (1210/2626). Grade 2, Grade 3, and Grade 4 cases were reported in 14.3% (375/2626), 4.6% (97/2094), and 0.1% (3/2626) of patients, respectively. Median time to onset was 0.7 months (range: 0.0-33.8). Resolution occurred in 843 patients (70%) with a median time to resolution of 12.1 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+).

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 in combination with ipilimumab (with or without chemotherapy), the incidence of hypersensitivity/infusion reactions was 4.5% (118/2626). Grade 1, Grade 2, Grade 3, and Grade 4 cases were reported in 1.9% (49/2626), 2.4% (62/2626), 0.2% (6/2626), and < 0.1% (1/2626) 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.

*Laboratory abnormalities*
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: 4.8% for anaemia, 1.8% for thrombocytopaenia, 2.2% for leucopoenia, 6.9% for lymphopaenia, 3.3% for neutropaenia, 2.7% for increased alkaline phosphatase, 9.8% for increased AST, 9.3% for increased ALT, 2.3% for increased total bilirubin, 1.8% for increased creatinine, 1.4% for hypoalbuminemia, 7.1% for hyperglycaemia, 0.7% for hypoglycaemia, 7.8% for increased amylase, 16.3% for increased lipase, 0.8% for hypocalcaemia, 0.2% for hypernatraemia, 0.8% for hypercalcaemia, 2.0% for hyperkalaemia, 0.8% for hypermagnesaemia, 0.4% for hypomagnesaemia, 3.0% for hypokalaemia, and 8.7% 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.

*Immunogenicity*
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. The incidence of neutralising antibodies against nivolumab was 0.8% with nivolumab 3 mg/kg and ipilimumab 1 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% and neutralising antibodies against ipilimumab ranged from 0%.

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.

Elderly
No overall differences in safety were reported between elderly (≥ 65 years) and younger patients (< 65 years).

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:

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor
Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

### 4.9 Overdose

No cases of overdose have been reported in clinical trials. In case of overdose, patients should be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted immediately.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, PD-1/PDL-1 (Programmed cell death protein 1/ death ligand 1) inhibitors. ATC code: L01FF01.

Mechanism of action
Nivolumab is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to PD-L1 and PD-L2 ligands. In syngeneic mouse models, blocking PD-1 activity resulted in decreased tumour growth.

Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in improved anti-tumour responses in metastatic melanoma. In murine syngeneic tumour models, dual blockade of PD-1 and CTLA-4 resulted in synergistic anti-tumour activity.

Clinical efficacy and safety

Based on modelling of dose/exposure efficacy and safety relationships, there are no clinically significant differences in efficacy and safety between a nivolumab dose of 240 mg every 2 weeks or 3 mg/kg every 2 weeks. Additionally, based on these relationships, there were no clinically significant differences between a nivolumab dose of 480 mg every 4 weeks or 3 mg/kg every 2 weeks in advanced RCC.

*Non-small cell lung cancer*

First-line treatment of NSCLC

*Randomised phase 3 study of nivolumab in combination with ipilimumab and 2 cycles of platinum-based chemotherapy vs. 4 cycles of platinum-based chemotherapy (CA2099LA)*

The safety and efficacy of nivolumab 360 mg every 3 weeks in combination with ipilimumab 1 mg/kg every 6 weeks and 2 cycles of platinum-based chemotherapy were evaluated in a phase 3, randomised, open-label study (CA2099LA). The study included patients (18 years or older) with histologically confirmed non-squamous or squamous Stage IV or recurrent NSCLC (per the 7th International Association for the Study of Lung Cancer classification), ECOG performance status 0 or 1, and no prior anticancer therapy (including EGFR and ALK inhibitors). Patients were enrolled regardless of their tumour PD-L1 status.

Patients with sensitising EGFR mutations or ALK translocations, active (untreated) brain metastases, carcinomatous meningitis, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients with treated brain metastases were eligible if neurologically returned to baseline at least 2 weeks prior to enrolment, and either off corticosteroids, or on a stable or decreasing dose of < 10 mg daily prednisone equivalents. Randomisation was stratified by histology (squamous vs non-squamous), tumour PD-L1 expression level (≥ 1% vs < 1%), and gender (male vs female).

A total of 719 patients were randomised to receive either nivolumab in combination with ipilimumab and platinum-based chemotherapy (n = 361) or platinum-based chemotherapy (n = 358). Patients in the nivolumab in combination with ipilimumab and platinum-based chemotherapy arm received nivolumab 360 mg administered intravenously over 30 minutes every 3 weeks in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 6 weeks and platinum-based chemotherapy administered every 3 weeks for 2 cycles. Patients in the chemotherapy arm received platinum-based chemotherapy administered every 3 weeks for 4 cycles; non-squamous patients could receive optional pemetrexed maintenance therapy.
Platinum-based chemotherapy consisted of carboplatin (AUC 5 or 6) and pemetrexed 500 mg/m$^2$; or cisplatin 75 mg/m$^2$ and pemetrexed 500 mg/m$^2$ for non-squamous NSCLC; or carboplatin (AUC 6) and paclitaxel 200 mg/m$^2$ for squamous NSCLC.

Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months. Treatment could continue beyond disease progression if the patient was clinically stable and was considered to be deriving clinical benefit by the investigator. Patients who discontinued combination therapy because of an adverse event attributed to ipilimumab were permitted to continue nivolumab monotherapy. Tumour assessments were performed every 6 weeks after first dose of study treatment for the first 12 months, then every 12 weeks until disease progression or study treatment was discontinued.

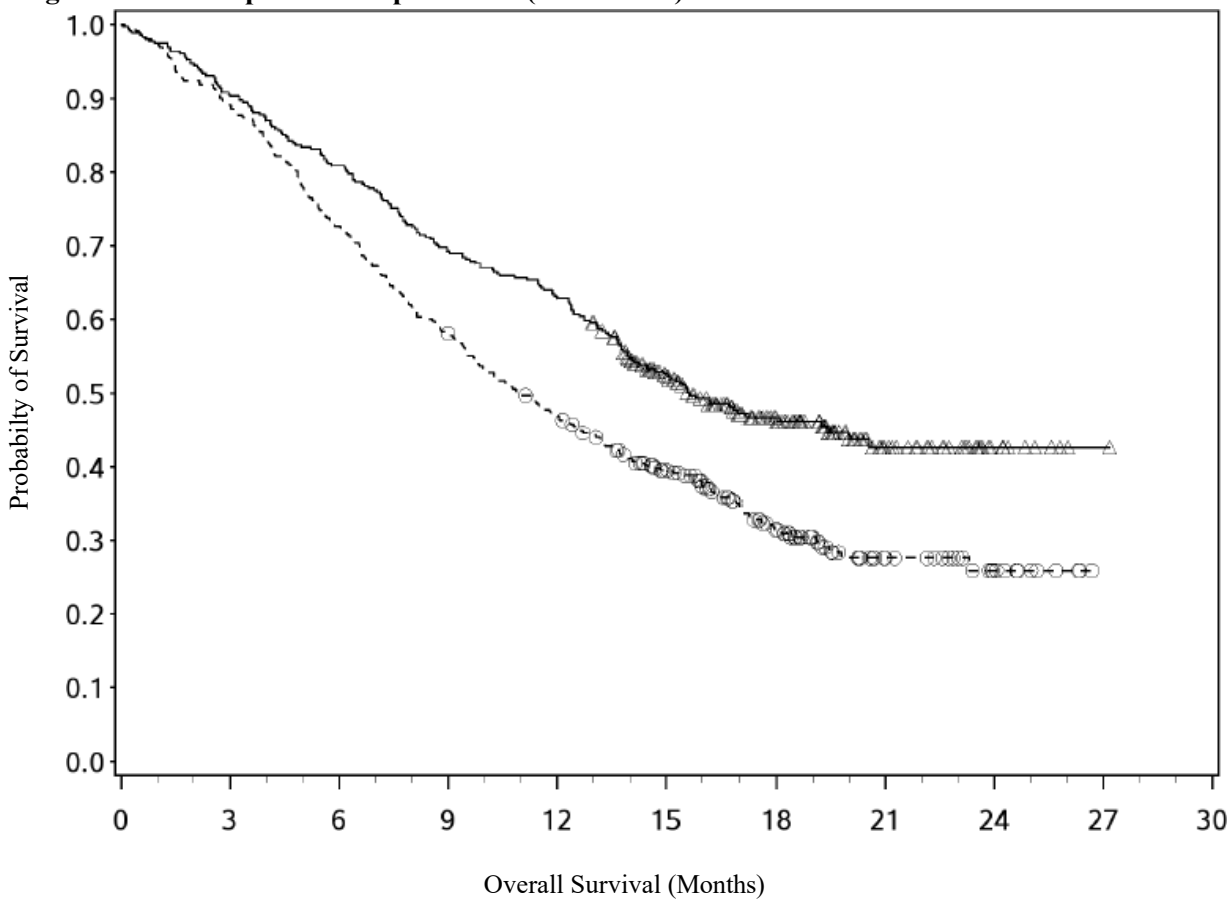
CA2099LA baseline characteristics were generally balanced across all treatment groups. The median age was 65 years (range: 26-86) with 51% ≥ 65 years of age and 10% ≥ 75 years of age. The majority of patients were white (89%) and male (70%). Baseline ECOG performance status was 0 (31%) or 1 (68%), 57% of patients with PD-L1 ≥ 1% and 37% with PD-L1 < 1%, 31% had squamous and 69% had non-squamous histology, 17% had brain metastases, and 86% were former/current smokers. No patients received prior immunotherapy.

CA2099LA primary efficacy outcome measure was OS. Additional efficacy endpoints were PFS, ORR, and duration of response as assessed by BICR.

The study demonstrated a statistically significant benefit in OS, PFS, and ORR for patients randomised to nivolumab in combination with ipilimumab and platinum-based chemotherapy as compared to platinum-based chemotherapy alone at the prespecified interim analysis when 351 events were observed (87% of the planned number of events for final analysis). Minimum follow-up for OS was 8.1 months.

Efficacy results are shown in Figure 1 (updated OS analysis with a minimum follow-up of 12.7 months) and Table 5 (primary analysis with a minimum follow-up of 8.1 months).
An updated efficacy analysis was performed when all patients had a minimum follow-up of 12.7 months (see Figure 1). At the time of this analysis, the hazard ratio for OS was 0.66 (95% CI: 0.55, 0.80) and the hazard ratio for PFS was 0.68 (95% CI: 0.57, 0.82).

**Figure 1: Kaplan-Meier plot of OS (CA2099LA)**




Number of subjects at risk

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + ipilimumab + chemotherapy | | | | | | | | | | |
| 361 | 326 | 292 | 250 | 227 | 153 | 86 | 33 | 10 | 1 | 0 |
| Chemotherapy | | | | | | | | | | |
| 358 | 319 | 260 | 208 | 166 | 116 | 67 | 26 | 11 | 0 | 0 |

—△—— Nivolumab + ipilimumab + chemotherapy (events: 190/361), median and 95% CI: 15.64 (13.93, 19.98)

- - -○- - - Chemotherapy (events: 242/358), median and 95% CI: 10.91 (9.46, 12.55)

**Table 5: Efficacy results (CA2099LA)**

| | **nivolumab + ipilimumab + chemotherapy (n = 361)** | | **chemotherapy (n = 358)** |
|---|---|---|---|
| **Overall survival** | | | |
| Events | 156 (43.2%) | | 195 (54.5%) |
| Hazard ratio (96.71% CI)[a] | | 0.69 (0.55, 0.87) | |
| Stratified log-rank p-value[b] | | 0.0006 | |
| Median (months) (95% CI) | 14.1 (13.24, 16.16) | | 10.7 (9.46, 12.45) |
| Rate (95% CI) at 6 months | 80.9 (76.4,84.6) | | 72.3 (67.4,76.7) |

| | nivolumab + ipilimumab + chemotherapy (n = 361) | | chemotherapy (n = 358) |
|---|---|---|---|
| **Progression-free survival** | | | |
| Events | 232 (64.3%) | | 249 (69.6%) |
| Hazard ratio (97.48% CI)[a] | | 0.70 (0.57, 0.86) | |
| Stratified log-rank p-value[c] | | 0.0001 | |
| Median (months)[d] (95% CI) | 6.83 (5.55, 7.66) | | 4.96 (4.27, 5.55) |
| Rate (95% CI) at 6 months | 51.7 (46.2, 56.8) | | 35.9 (30.5, 41.3) |
| **Overall response rate[e]** | 136 (37.7%) | | 90 (25.1%) |
| (95% CI) | (32.7, 42.9) | | (20.7, 30.0) |
| Stratified CMH test p-value[f] | | 0.0003 | |
| Complete response (CR) | 7 (1.9%) | | 3 (0.8%) |
| Partial response (PR) | 129 (35.7%) | | 87 (24.3%) |
| **Duration of response** | | | |
| Median (months) (95% CI)[d] | 10.02 (8.21, 13.01) | | 5.09 (4.34, 7.00) |
| % with duration ≥ 6 months[g] | 74 | | 41 |

[a] Based on a stratified Cox proportional hazard model.
[b] p-value is compared with the allocated alpha of 0.0329 for this interim analysis.
[c] p-value is compared with the allocated alpha of 0.0252 for this interim analysis.
[d] Kaplan-Meier estimate.
[e] Proportion with complete or partial response; CI based on the Clopper and Pearson Method.
[f] p-value is compared with the allocated alpha of 0.025 for this interim analysis.
[g] Based on Kaplan-Meier estimates of duration of response.
CMH = Cochran-Mantel-Haenszel

Subsequent systemic therapy was received by 28.8% and 41.1% of patients in the combination and chemotherapy arms, respectively. Subsequent immunotherapy (including anti-PD-1, anti-PD-L1, and anti-CTLA4) was received by 3.9% and 27.9% of patients in the combination and chemotherapy arms, respectively.

In study CA2099LA, subgroup descriptive analysis relative to chemotherapy, OS benefit was shown in patients treated with nivolumab in combination with ipilimumab and chemotherapy with squamous histology (HR [95% CI] 0.65 [0.46, 0.93], n = 227) and in patients with non-squamous histology (HR [95% CI] 0.72 [0.55, 0.93], n = 492).

Table 6 summarises efficacy results of OS, PFS, and ORR by tumour PD-L1 expression in pre-specified subgroup analyses.

**Table 6: Efficacy results by tumour PD-L1 expression (CA2099LA)**

| | nivolumab + ipilimumab + chemo-therapy | chemo-therapy | nivolumab + ipilimumab + chemo-therapy | chemo-therapy | nivolumab + ipilimumab + chemo-therapy | chemo-therapy | nivolumab + ipilimumab + chemo-therapy | chemo-therapy |
|---|---|---|---|---|---|---|---|---|
| | **PD-L1 < 1% (n = 264)** | | **PD-L1 ≥ 1% (n = 406)** | | **PD-L1 ≥ 1% to 49% (n = 233)** | | **PD-L1 ≥ 50% (n = 173)** | |
| **OS hazard ratio (95% CI)[a]** | 0.65 (0.46, 0.92) | | 0.67 (0.51, 0.89) | | 0.69 (0.48, 0.98) | | 0.64 (0.41, 1.02) | |
| **PFS hazard ratio (95% CI)[a]** | 0.77 (0.57, 1.03) | | 0.67 (0.53, 0.85) | | 0.71 (0.52, 0.97) | | 0.59 (0.40, 0.86) | |
| **ORR %** | 31.1 | 20.9 | 41.9 | 27.6 | 37.8 | 24.5 | 48.7 | 30.9 |

[a] Hazard ratio based on unstratified Cox proportional hazards model.

A total of 70 NSCLC patients aged ≥ 75 years were enrolled in study CA2099LA (37 patients in the nivolumab in combination with ipilimumab and chemotherapy arm and 33 patients in the chemotherapy arm). A HR of 1.36 (95% CI: 0.74, 2.52) in OS and a HR of 1.12 (95% CI: 0.64, 1.96) in PFS was observed for nivolumab in combination with ipilimumab and chemotherapy vs. chemotherapy within this study subgroup. ORR was 27.0% in the nivolumab in combination with ipilimumab and chemotherapy arm and 15.2% in the chemotherapy arm. Forty-three percent of patients aged ≥ 75 years discontinued treatment with nivolumab in combination with ipilimumab and chemotherapy. Efficacy and safety data of nivolumab in combination with ipilimumab and chemotherapy are limited in this patient population.

In a subgroup analysis, a reduced survival benefit for nivolumab in combination with ipilimumab and chemotherapy compared to chemotherapy was observed in patients who were never smokers. However, due to the small numbers of patients, no definitive conclusions can be drawn from these data.

*Renal cell carcinoma*

*Randomised phase 3 study of nivolumab in combination with ipilimumab vs. sunitinib (CA209214)*
The safety and efficacy of nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg for the treatment of advanced/metastatic RCC was evaluated in a phase 3, randomised, open-label study (CA209214). The study included patients (18 years or older) with previously untreated, advanced or metastatic renal cell carcinoma with a clear-cell component. The primary efficacy population included those intermediate/poor risk patients with at least 1 or more of 6 prognostic risk factors as per the International Metastatic RCC Database Consortium (IMDC) criteria (less than one year from time of initial renal cell carcinoma diagnosis to randomisation, Karnofsky performance status <80%, haemoglobin less than the lower limit of normal, corrected calcium of greater than 10 mg/dL, platelet count greater than the upper limit of normal, and absolute neutrophil count greater than the upper limit of normal). This study included patients regardless of their tumour PD-L1 status. Patients with Karnofsky performance status < 70% and patients with any history of or concurrent brain metastases, active autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. Patients were stratified by IMDC prognostic score and region.

A total of 1096 patients were randomised in the trial, of which 847 patients had intermediate/poor-risk RCC and received either nivolumab 3 mg/kg (n = 425) administered intravenously over 60 minutes in combination with ipilimumab 1 mg/kg administered intravenously over 30 minutes every 3 weeks for 4 doses followed by nivolumab monotherapy 3 mg/kg every 2 weeks or sunitinib (n = 422) 50 mg daily, administered orally for 4 weeks followed by 2 weeks off, every cycle. Treatment was continued as long as clinical benefit was observed or until treatment was no longer tolerated. The first tumour

assessments were conducted 12 weeks after randomisation and continued every 6 weeks thereafter for the first year and then every 12 weeks until progression or treatment discontinuation, whichever occurred later. Treatment beyond initial investigator-assessed RECIST, version 1.1-defined progression was permitted if the patient had a clinical benefit and was tolerating study drug as determined by the investigator. The primary efficacy outcome measures were OS, ORR and PFS as determined by a BICR in intermediate/poor risk patients.

Baseline characteristics were generally balanced between the two groups. The median age was 61 years (range: 21-85) with 38% ≥ 65 years of age and 8% ≥ 75 years of age. The majority of patients were male (73%) and white (87%), and 31% and 69% of patients had a baseline KPS of 70 to 80% and 90 to 100%, respectively. The median duration of time from initial diagnosis to randomisation was 0.4 years in both the nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg and sunitinib groups. The median duration of treatment was 7.9 months (range: 1 day-21.4+ months) in nivolumab with ipilimumab-treated patients and was 7.8 months (range: 1 days-20.2+ months) in sunitinib-treated patients. Nivolumab with ipilimumab was continued beyond progression in 29% of patients.

Efficacy results for the intermediate/poor risk patients are shown in Table 7 (primary analysis with a minimum follow-up of 17.5 months and with a minimum follow-up of 60 months) and in Figure 2 (minimum follow-up of 60 months).
OS results at an additional descriptive analysis undertaken at a minimum follow-up of 60 months show outcomes consistent with the original primary analysis.

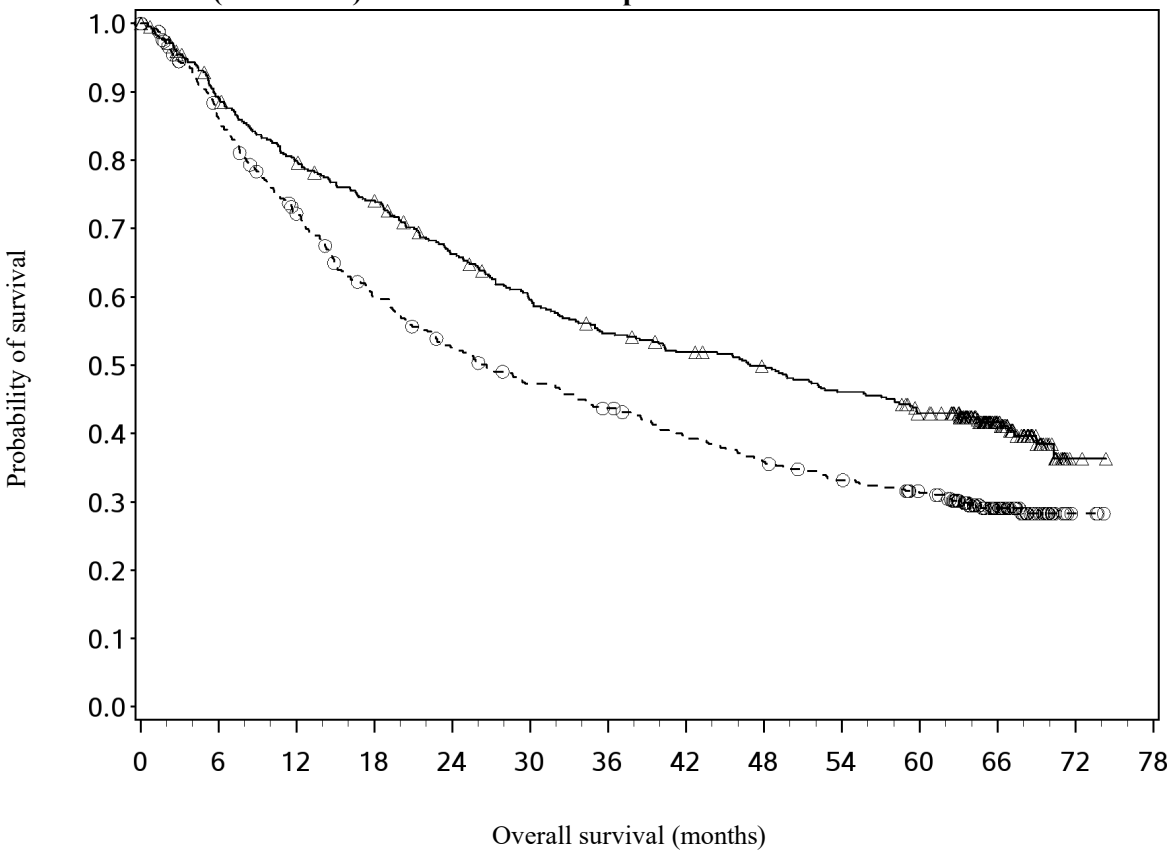
**Table 7: Efficacy results in intermediate/poor risk patients (CA209214)**

| | **nivolumab + ipilimumab (n = 425)** | | **sunitinib (n = 422)** |
|---|---|---|---|
| | **Primary analysis** minimum follow-up: 17.5 months | | |
| **Overall survival** | | | |
| Events | 140 (33%) | | 188 (45%) |
| Hazard ratio[a] | | 0.63 | |
| 99.8% CI | | (0.44, 0.89) | |
| p-value[b, c] | | < 0.0001 | |
| Median (95% CI) | NE (28.2, NE) | | 25.9 (22.1, NE) |
| Rate (95% CI) | | | |
| At 6 months | 89.5 (86.1, 92.1) | | 86.2 (82.4, 89.1) |
| At 12 months | 80.1 (75.9, 83.6) | | 72.1 (67.4, 76.2) |
| **Progression-free survival** | | | |
| Events | 228 (53.6%) | | 228 (54.0%) |
| Hazard ratio[a] | | 0.82 | |
| 99.1% CI | | (0.64, 1.05) | |
| p-value[b,h] | | 0.0331 | |
| Median (95% CI) | 11.6 (8.71, 15.51) | | 8.4 (7.03, 10.81) |
| **Confirmed objective response (BICR)** | 177 (41.6%) | | 112 (26.5%) |
| (95% CI) | (36.9, 46.5) | | (22.4, 31.0) |
| Difference in ORR (95% CI)[d] | | 16.0 (9.8, 22.2) | |
| p-value[e,f] | | < 0.0001 | |
| Complete response (CR) | 40 (9.4%) | | 5 (1.2%) |
| Partial response (PR) | 137 (32.2%) | | 107 (25.4%) |
| Stable disease (SD) | 133 (31.3%) | | 188 (44.5%) |

| | nivolumab + ipilimumab (n = 425) | | sunitinib (n = 422) |
|---|---|---|---|
| **Median duration of response[g]** | | | |
| Months (range) | NE (1.4+-25.5+) | | 18.17 (1.3+-23.6+) |
| **Median time to response** | | | |
| Months (range) | 2.8 (0.9-11.3) | | 3.0 (0.6-15.0) |
| | **Updated analysis*** minimum follow-up: 60 months | | |
| **Overall survival** | | | |
| Events | 242 (57%) | | 282 (67%) |
| Hazard ratio[a] | | 0.68 | |
| 95% CI | | (0.58, 0.81) | |
| Median (95% CI) | 46.95 (35.35, 57.43) | | 26.64 (22.08, 33.54) |
| Rate (95% CI) | | | |
| At 24 months | 66.3 (61.5, 70.6) | | 52.4 (47.4, 57.1) |
| At 36 months | 54.6 (49.7, 59.3) | | 43.7 (38.7, 48.5) |
| At 48 months | 49.9 (44.9, 54.6) | | 35.8 (31.1, 40.5) |
| At 60 months | 43.0 (38.1, 47.7) | | 31.3 (26.8, 35.9) |
| **Progression-free survival** | | | |
| Events | 245 (57.6%) | | 253 (60.0%) |
| Hazard ratio[a] | | 0.73 | |
| 95% CI | | (0.61, 0.87) | |
| Median (95% CI) | 11.6 (8.44, 16.63) | | 8.3 (7.03, 10.41) |
| **Confirmed objective response (BICR)** | 179 (42.1%) | | 113 (26.8%) |
| (95% CI) | (37.4, 47.0) | | (22.6, 31.3) |
| Difference in ORR (95% CI)[d,e] | | 16.2 (10.0, 22.5) | |
| Complete response (CR) | 48 (11.3%) | | 9 (2.1%) |
| Partial response (PR) | 131 (30.8%) | | 104 (24.6%) |
| Stable disease (SD) | 131 (30.8%) | | 187 (44.3%) |
| **Median duration of response[g]** | | | |
| Months (range) | NE (50.89-NE) | | 19.38 (15.38-25.10) |
| **Median time to response** | | | |
| Months (range) | 2.8 (0.9-35.0) | | 3.1 (0.6-23.6) |

[a] Based on a stratified proportional hazards model.
[b] Based on a stratified log-rank test.
[c] p-value is compared to alpha 0.002 in order to achieve statistical significance.
[d] Strata adjusted difference.
[e] Based on the stratified DerSimonian-Laird test.
[f] p-value is compared to alpha 0.001 in order to achieve statistical significance.
[g] Computed using Kaplan-Meier method.
[h] p-value is compared to alpha 0.009 in order to achieve statistical significance.
"+" denotes a censored observation.
NE = non-estimable
* Descriptive analysis based on data cut-off: 26-Feb-2021.

**Figure 2: Kaplan-Meier curves of OS in intermediate/poor risk patients (CA209214) - Minimum follow-up of 60 months**




Number of subjects at risk

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + ipilimumab | | | | | | | | | | | | | |
| 425 | 372 | 332 | 306 | 270 | 241 | 220 | 207 | 196 | 181 | 163 | 79 | 2 | 0 |
| Sunitinib | | | | | | | | | | | | | |
| 422 | 353 | 291 | 237 | 206 | 184 | 169 | 151 | 137 | 125 | 112 | 58 | 3 | 0 |

—△—— Nivolumab + ipilimumab (events: 242/425), median and 95.0% CI: 46.95 (35.35, 57.43)
- - -○- - - Sunitinib (events: 282/422), median and 95.0% CI: 26.64 (22.08, 33.54)

An updated descriptive OS analysis was performed when all patients had a minimum follow-up of 24 months. At the time of this analysis, the hazard ratio was 0.66 (99.8% CI 0.48-0.91) with 166/425 events in the combination arm and 209/422 events in the sunitinib arm. In intermediate/poor-risk patients, OS benefit was observed in the nivolumab in combination with ipilimumab arm vs. sunitinib regardless of tumour PD-L1 expression. Median OS for tumour PD-L1 expression ≥ 1% was not reached for nivolumab in combination with ipilimumab, and was 19.61 months in the sunitinib arm (HR = 0.52; 95% CI: 0.34, 0.78). For tumour PD-L1 expression < 1%, the median OS was 34.7 months for the nivolumab in combination with ipilimumab, and was 32.2 months in the sunitinib arm (HR = 0.70; 95% CI: 0.54, 0.92).

CA209214 also randomised 249 favourable risk patients as per IMDC criteria to nivolumab plus ipilimumab (n = 125) or to sunitinib (n = 124). These patients were not evaluated as part of the primary efficacy population. At a minimum of 24 months follow-up, OS in favourable risk patients receiving nivolumab plus ipilimumab compared to sunitinib had a hazard ratio of 1.13 (95% CI: 0.64, 1.99; p = 0.6710). With 60 months minimum follow-up, the HR for OS was 0.94 (95% CI: 0.65, 1.37).

There are no data on the use of nivolumab in combination with ipilimumab in patients with only a non clear-cell histology in first-line RCC.

Patients ≥ 75 years of age represented 8% of all intermediate/poor risk patients in CA209214, and the combination of nivolumab and ipilimumab showed numerically less effect on OS (HR 0.97, 95% CI: 0.48, 1.95) in this subgroup versus the overall population at a minimum follow-up of 17.5 months. Because of the small size of this subgroup, no definitive conclusions can be drawn from these data.

*Gastric, gastro-oesophageal junction or oesophageal adenocarcinoma*

The safety and efficacy of nivolumab 240 mg every 2 weeks or 360 mg every 3 weeks in combination with chemotherapy (dose and schedule of nivolumab selected depending on the chemotherapy regimen used, see below) was evaluated in a phase 3, randomised, open-label study (CA209649). The study included adult patients (18 years or older) with previously untreated advanced or metastatic gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma, no prior systemic treatment (including HER2 inhibitors), and ECOG performance status score 0 or 1. Patients were enrolled regardless of their tumour cell PD-L1 status, and tumour cell PD-L1 expression was determined using the PD-L1 IHC 28-8 pharmDx assay. A retrospective re-scoring of a patient's tumour PD-L1 status using CPS was conducted using the PD-L1-stained tumour specimens used for randomisation. Patients with known HER2-positive tumours, who had baseline ECOG performance score ≥ 2, untreated central nervous system metastases, or who had active, known, or suspected autoimmune disease, or medical conditions requiring systemic immunosuppression were excluded from the study. A total of 643 patients with HER2-undetermined status (40.3% of the study population) were included in the study. Randomisation was stratified by tumour cell PD-L1 status (≥ 1% vs. < 1% or indeterminate), region (Asia vs. US vs. rest of world), ECOG performance status (0 vs. 1), and chemotherapy regimen. Chemotherapy consisted of FOLFOX (fluorouracil, leucovorin and oxaliplatin) or CapeOX (capecitabine and oxaliplatin).

A total of 1581 patients were randomised to receive either nivolumab in combination with chemotherapy or chemotherapy. Of these, 955 patients had PD-L1 CPS ≥ 5; 473 in the nivolumab plus chemotherapy arm and 482 in the chemotherapy arm. Patients in the nivolumab plus chemotherapy arm received either nivolumab 240 mg by intravenous infusion over 30 minutes in combination with FOLFOX (oxaliplatin 85 mg/m$^2$, leucovorin 400 mg/m$^2$ and fluorouracil 400 mg/m$^2$ intravenously on day 1 and fluorouracil 1200 mg/m$^2$ intravenously by continuous infusion over 24 hours daily or per local standard on days 1 and 2) every 2 weeks, or nivolumab 360 mg by intravenous infusion over 30 minutes in combination with CapeOX (oxaliplatin 130 mg/m$^2$ intravenously on day 1 and capecitabine 1000 mg/m$^2$ orally twice daily on days 1-14) every 3 weeks. Treatment continued until disease progression, unacceptable toxicity, or for up to 24 months for nivolumab only. In patients who received nivolumab plus chemotherapy and in whom chemotherapy was discontinued, nivolumab monotherapy was allowed to be given at 240 mg every 2 weeks, 360 mg every 3 weeks or 480 mg every 4 weeks up to 24 months after treatment initiation. Tumour assessments were performed every 6 weeks up to and including week 48, then every 12 weeks thereafter.

Baseline characteristics were generally balanced across treatment groups. In patients with PD-L1 CPS ≥ 5, the median age was 62 years (range: 18-90), 11% were ≥ 75 years of age, 71% were male, 25% were Asian and 69% were white. Baseline ECOG performance status was 0 (42%) or 1 (58%). Tumour locations were distributed as gastric (70%), GEJ (18%) and oesophagus (12%).

Primary efficacy outcome measures were PFS (by BICR) and OS assessed in patients with PD-L1 CPS ≥ 5 based on the PD-L1 IHC 28-8 pharmDX. Secondary endpoints per the pre-specified hierarchical testing were OS in patients with PD-L1 CPS ≥ 1 and in all randomised patients; further endpoints included ORR (BICR) in PD-L1 CPS ≥ 5 and all randomised patients. At the primary pre-specified analysis, with a minimum follow-up of 12.1 months, the study demonstrated a statistically significant improvement in OS and PFS in patients with PD-L1 CPS ≥ 5. Median OS was 14.4 months (95% CI: 13.1, 16.2) for nivolumab in combination with chemotherapy vs. 11.1 months (95% CI: 10.0, 12.1) for chemotherapy (HR = 0.71; 98.4% CI: 0.59, 0.86; p-value <0.0001). Median PFS was 7.69 months (95% CI: 7.03, 9.17) for nivolumab in combination with chemotherapy vs. 6.05 months (95% CI: 5.55, 6.90) for chemotherapy (HR = 0.68; 98% CI: 0.56, 0.81; p-value <0.0001). The ORR was 60% (95% CI: 55, 65) for nivolumab in combination with chemotherapy vs. 45% (95% CI: 40, 50) for chemotherapy.

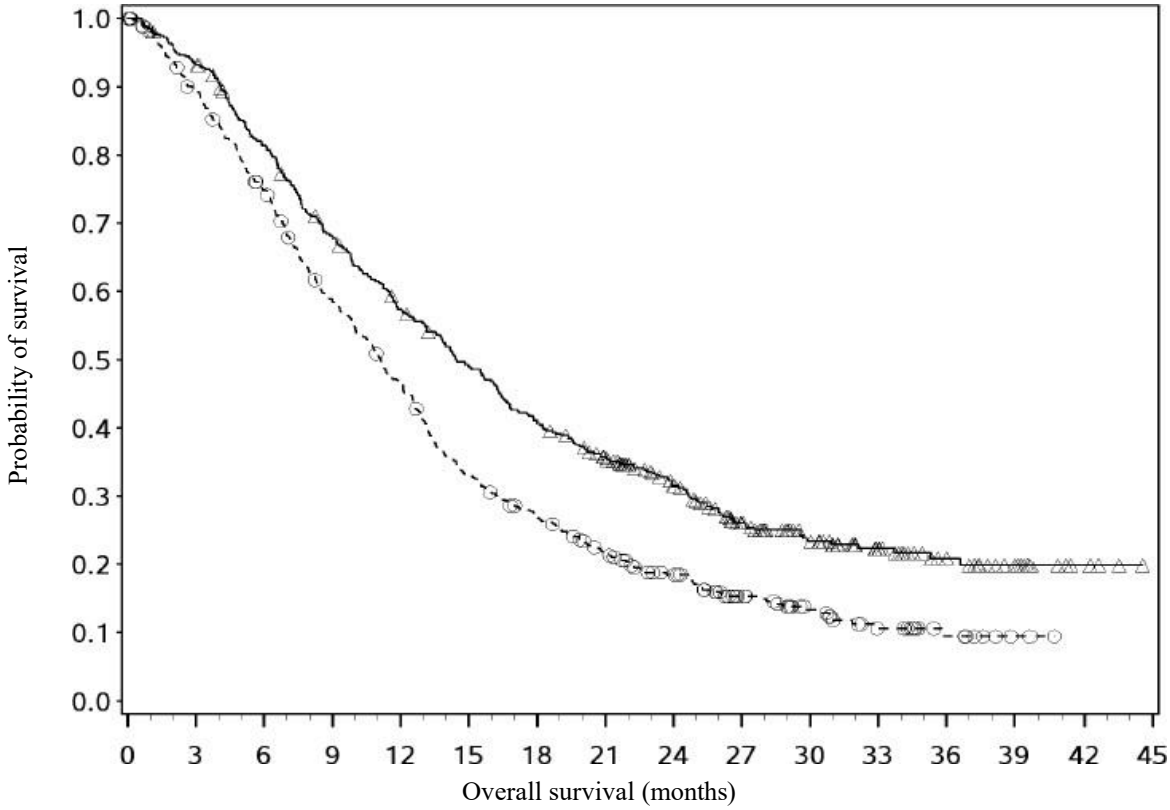
At an updated descriptive analysis with a minimum follow-up of 19.4 months, OS improvements were consistent with the primary analysis. Efficacy results are shown in Table 8, and Figures 3, and 4.

**Table 8: Efficacy results in patients with PD-L1 CPS ≥ 5 (CA209649)**

| | **nivolumab + chemotherapy (n = 473)** | **chemotherapy (n = 482)** |
|---|---|---|
| | Minimum follow-up 19.4 months[a] | |
| **Overall survival** | | |
| Events | 344 (73%) | 397 (82%) |
| Hazard ratio (95% CI)[b] | 0.69 (0.60, 0.81) | |
| Median (95% CI) (months)[c] | 14.4 (13.1, 16.3) | 11.1 (10.0, 12.1) |
| Rate (95% CI) at 12 months | 57.3 (52.6, 61.6) | 46.4 (41.8, 50.8) |
| **Progression-free survival[d]** | | |
| Events | 342 (72.3%) | 366 (75.9%) |
| Hazard ratio (95% CI)[b] | 0.68 (0.59, 0.79) | |
| Median (95% CI) (months)[c] | 8.31 (7.03, 9.26) | 6.05 (5.55, 6.90) |
| Rate (95% CI) at 12 months | 36.3 (31.7, 41.0) | 21.9 (17.8, 26.1) |
| **Objective response rate, n[d,e]** | 227/378 (60%) | 176/390 (45%) |
| (95% CI) | (54.9, 65.0) | (40.1, 50.2) |
| Complete response | 12.2% | 6.7% |
| Partial response | 47.9% | 38.5% |
| **Duration of response[d,e]** | | |
| Median (95% CI) (months)[c] | 9.69 (8.25, 12.22) | 6.97 (5.62, 7.85) |

[a] Descriptive analysis based on data cut-off: 04-Jan-2021.
[b] Based on stratified long Cox proportional hazard model.
[c] Kaplan-Meier estimate.
[d] Confirmed by BICR.
[e] Based on patients with measurable disease at baseline.

**Figure 3: Kaplan-Meier curves of OS in patients with PD-L1 CPS ≥ 5 (CA209649)**



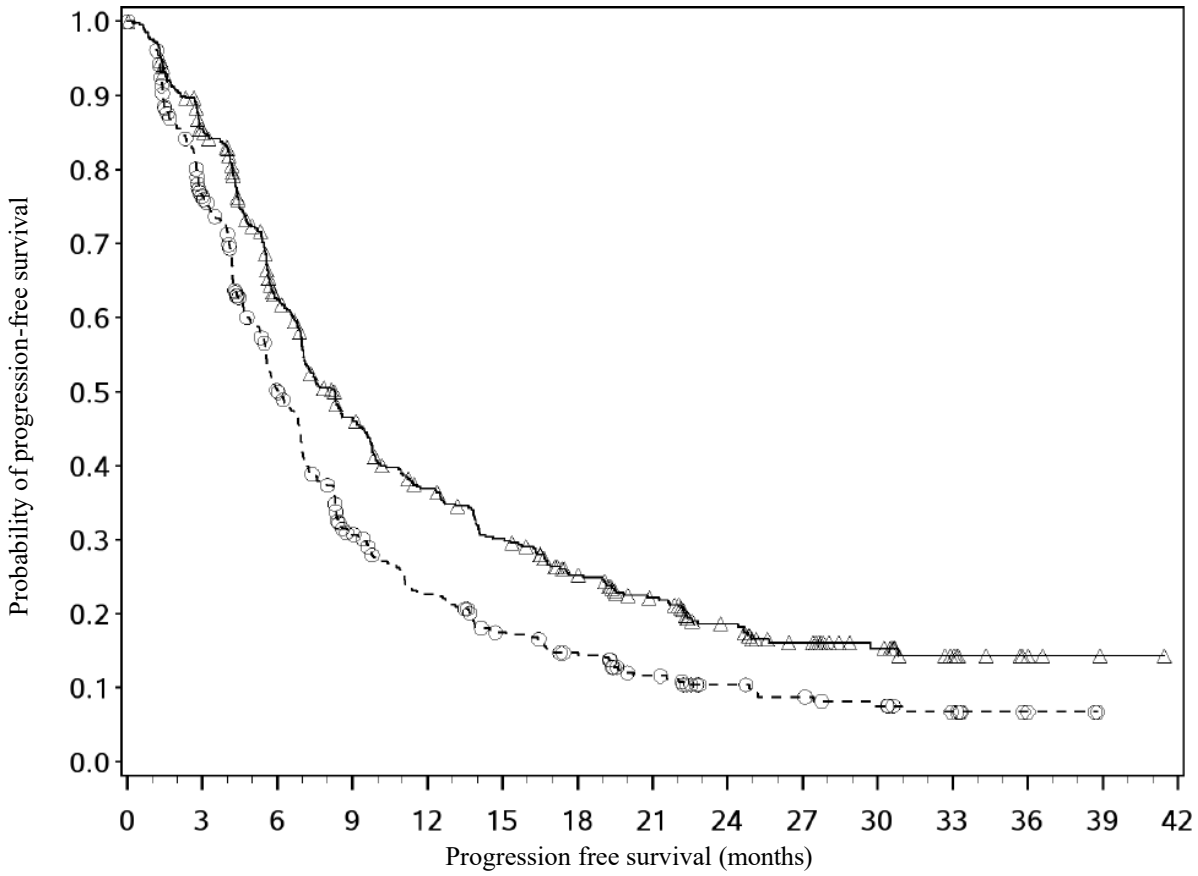

Number of subjects at risk

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + chemotherapy | | | | | | | | | | | | | | | |
| 473 | 439 | 378 | 314 | 263 | 223 | 187 | 155 | 118 | 78 | 56 | 37 | 23 | 13 | 4 | 0 |
| Chemotherapy | | | | | | | | | | | | | | | |
| 482 | 421 | 350 | 272 | 213 | 152 | 122 | 92 | 68 | 44 | 28 | 16 | 8 | 2 | 0 | 0 |

—△—— Nivolumab + chemotherapy (events: 344/473), median and 95% CI: 14.42 (13.14, 16.26)
- - -❍- - - Chemotherapy (events: 397/482), median and 95% CI: 11.10 (10.02, 12.09)

Minimum follow-up of 19.4 months

**Figure 4: Kaplan-Meier curves of PFS in patients with PD-L1 CPS ≥ 5 (CA209649)**




Number of subjects at risk

| | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Nivolumab + chemotherapy | | | | | | | | | | | | | | |
| 473 | 386 | 259 | 186 | 143 | 115 | 88 | 67 | 47 | 31 | 20 | 11 | 4 | 1 | 0 |
| Chemotherapy | | | | | | | | | | | | | | |
| 482 | 328 | 202 | 114 | 81 | 58 | 46 | 30 | 20 | 16 | 12 | 7 | 3 | 0 | 0 |

—△—— Nivolumab + chemotherapy (events: 342/473), median and 95% CI: 8.31 (7.03, 9.26)
- - -○- - - Chemotherapy (events: 397/482), median and 95% CI: 6.05 (5.55, 6.90)

Minimum follow-up of 19.4 months

Safety and efficacy in elderly patients

No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years).

## 5.2 Pharmacokinetic properties

Nivolumab in combination with ipilimumab

When nivolumab 3 mg/kg was administered in combination with ipilimumab 1 mg/kg, the CL of nivolumab was increased by 1% and the CL of ipilimumab was decreased by 1.5%, which were not considered clinically relevant.

When administered in combination with ipilimumab, the CL of nivolumab increased by 20% in the presence of anti-nivolumab antibodies and the CL of ipilimumab increased by 5.7% in the presence of anti-ipilimumab antibodies. These changes were not considered clinically relevant.

Nivolumab in combination with ipilimumab and chemotherapy

When nivolumab 360 mg every 3 weeks was administered in combination with ipilimumab 1 mg/kg every 6 weeks and with 2 cycles of chemotherapy, the CL of nivolumab decreased approximately 10%

and the CL of ipilimumab increased approximately 22%, which were not considered clinically relevant.

Special populations

A population PK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumour type, tumour size, and hepatic impairment. Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful.

*Renal impairment*
The effect of renal impairment on the CL of nivolumab was evaluated in patients with mild (GFR < 90 and ≥ 60 mL/min/1.73 $m^2$; n = 379), moderate (GFR < 60 and ≥ 30 mL/min/1.73 $m^2$; n = 179), or severe (GFR < 30 and ≥ 15 mL/min/1.73 $m^2$; n = 2) renal impairment compared to patients with normal renal function (GFR ≥ 90 mL/min/1.73 $m^2$; n = 342) in population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions on this population (see section 4.2).

*Hepatic impairment*
The effect of hepatic impairment on the CL of nivolumab was evaluated in patients with mild hepatic impairment (total bilirubin 1.0 × to 1.5 × ULN or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction; n = 92) compared to patients with normal hepatic function (total bilirubin and AST ≤ ULN; n = 804) in the population PK analyses. No clinically important differences in the CL of nivolumab were found between patients with mild hepatic impairment and normal hepatic function. Nivolumab has not been studied in patients with moderate (total bilirubin > 1.5 × to 3 × ULN and any AST) or severe hepatic impairment (total bilirubin > 3 × ULN and any AST) (see section 4.2).

## 5.3 Preclinical safety data

Blockade of PD-L1 signalling has been shown in murine models of pregnancy to disrupt tolerance to the foetus and to increase foetal loss. The effects of nivolumab on prenatal and postnatal development were evaluated in monkeys that received nivolumab twice weekly from the onset of organogenesis in the first trimester through delivery, at exposure levels either 8 or 35 times higher than those observed at the clinical dose of 3 mg/kg of nivolumab (based on AUC). There was a dose-dependent increase in foetal losses and increased neonatal mortality beginning in the third trimester.

The remaining offspring of nivolumab-treated females survived to scheduled termination, with no treatment-related clinical signs, alterations to normal development, organ-weight effects, or gross and microscopic pathology changes. Results for growth indices, as well as teratogenic, neurobehavioral, immunological, and clinical pathology parameters throughout the 6-month postnatal period were comparable to the control group. However, based on its mechanism of action, foetal exposure to nivolumab may increase the risk of developing immune-related disorders or altering the normal immune response and immune-related disorders have been reported in PD-1 knockout mice.

Fertility studies have not been performed with nivolumab.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

Sodium citrate dihydrate
Sodium chloride
Mannitol (E421)
Pentetic acid (diethylenetriaminepentaacetic acid)
Polysorbate 80 (E433)
Sodium hydroxide (for pH adjustment)
Hydrochloric acid (for pH adjustment)
Water for injections

### 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. OPDIVO should not be infused concomitantly in the same intravenous line with other medicinal products.

### 6.3 Shelf life

Unopened vial
3 years

After preparation of infusion
Chemical and physical in-use stability from the time of preparation has been demonstrated as follows (times are inclusive of the administration period):

| **Infusion preparation** | **Chemical and physical in-use stability** | |
|---|---|---|
| | **Storage at 2ºC to 8ºC protected from light** | **Storage at room temperature (≤ 25°C) and room light** |
| Undiluted or diluted with sodium chloride 9 mg/mL (0.9%) solution for injection. | 30 days | 24 hours<br>(of total 30 days storage) |
| Diluted with 50 mg/mL (5%) glucose solution for injection | 7 days | 8 hours<br>(of total 7 days storage) |

From a microbiological point of view the prepared solution for infusion, regardless of the diluent, should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 7 days at 2°C to 8°C or 8 hours (of the total 7 days of storage) at room temperature (≤ 25°C). Aseptic handling should be ensured during the preparation of infusion (see section 6.6).

### 6.4 Special precautions for storage

Store in a refrigerator (2°C-8°C).
Do not freeze.
Store in the original package in order to protect from light.
The unopened vial can be stored at controlled room temperature up to 25°C with room light for up to 48 hours.

For storage conditions after preparation of the infusion, see section 6.3.

### 6.5 Nature and contents of container

12 mL of concentrate in a 25 mL vial (Type I glass) with a stopper (coated butyl rubber) and a blue flip-off seal (aluminium). Pack size of 1 vial.

## 6.6 Special precautions for disposal and other handling

Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Preparation and administration

*Calculating the dose*

More than one vial of OPDIVO concentrate may be needed to give the total dose for the patient.

*Nivolumab in combination with ipilimumab*
The prescribed dose for the patient is given in mg/kg. Based on this prescribed dose, calculate the total dose to be given.

- The total nivolumab dose in mg = the patient's weight in kg × the prescribed dose in mg/kg.
- The volume of OPDIVO concentrate to prepare the dose (mL) = the total dose in mg, divided by 10 (the OPDIVO concentrate strength is 10 mg/mL).

*Nivolumab in combination with chemotherapy in gastric, GEJ or oesophageal adenocarcinoma*
The prescribed dose for the patient is 360 mg or 240 mg given regardless of body weight.

*Nivolumab in combination with ipilimumab and chemotherapy*
The prescribed dose for the patient is 360 mg given regardless of body weight.

*Preparing the infusion*
Take care to ensure aseptic handling when you prepare the infusion.

OPDIVO can be used for intravenous administration either:
- without dilution, after transfer to an infusion container using an appropriate sterile syringe; or
- after diluting according to the following instructions:
  - the final infusion concentration should range between 1 and 10 mg/mL.
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion must not exceed 4 mL per kilogram of patient weight.

OPDIVO concentrate may be diluted with either:
- sodium chloride 9 mg/mL (0.9%) solution for injection; or
- 50 mg/mL (5%) glucose solution for injection.

STEP 1
- Inspect the OPDIVO concentrate for particulate matter or discoloration. Do not shake the vial. OPDIVO concentrate is a clear to opalescent, colourless to pale yellow liquid. Discard the vial if the solution is cloudy, is discoloured, or contains particulate matter other than a few translucent-to-white particles.
- Withdraw the required volume of OPDIVO concentrate using an appropriate sterile syringe.

STEP 2
- Transfer the concentrate into a sterile, evacuated glass bottle or intravenous container (PVC or polyolefin).
- If applicable, dilute with the required volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection. For ease of preparation, the concentrate can also be transferred directly into a pre-filled bag containing the appropriate volume of sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.
- Gently mix the infusion by manual rotation. Do not shake.

*Administration*
OPDIVO infusion must not be administered as an intravenous push or bolus injection.

Administer the OPDIVO infusion intravenously over a period of 30 or 60 minutes depending on the dose.

OPDIVO infusion should not be infused at the same time in the same intravenous line with other agents. Use a separate infusion line for the infusion.

Use an infusion set and an in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm).

OPDIVO infusion is compatible with PVC and polyolefin containers, glass bottles, PVC infusion sets and in-line filters with polyethersulfone membranes with pore sizes of 0.2 µm to 1.2 µm.

After administration of the nivolumab dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

*Disposal*
Do not store any unused portion of the infusion solution for reuse. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

## 7. MANUFACTURER

Vetter Pharma-Fertigung GmbH & Co. KG
Mooswiesen 2
88214 Ravensburg Germany

## 8. BATCH RELEASER

Swords Laboratories Unlimited Company
t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road
Mulhuddart, Dublin 15,
Ireland

## 9. MARKETING AUTHORISATION HOLDER

PT Mecosin Indonesia
Bogor, Indonesia

## 10. MARKETING AUTHORISATION NUMBERS

Opdivo 120 mg/12mL Box @ 1 vial DKIXXXXXXXXXXXX

## 11. DATE OF APPROVAL

MMM YYYY

**HARUS DENGAN RESEP DOKTER**

**Leaflet Informasi untuk Pasien**

**OPDIVO 10 mg/mL Larutan Konsentrat untuk infus**

nivolumab

**Bacalah seluruh leaflet ini dengan seksama sebelum Anda diberikan obat ini karena mengandung informasi penting untuk Anda.**

- Simpan leaflet ini. Mungkin dibutuhkan untuk dibaca Kembali
- Jika Anda memiliki pertanyaan lebih lanjut, tanyakan kepada dokter.
- Jika Anda mendapatkan efek samping, bicarakan dengan dokter Anda. Ini termasuk kemungkinan efek samping yang tidak tercantum dalam selebaran ini. Lihat bagian 4.

**Apa yang ada pada leaflet ini**



## 1. Apa itu Opdivo dan kegunaannya

OPDIVO adalah obat yang digunakan untuk mengobati:

- kanker paru-paru non sel kecil stadium lanjut (sejenis kanker paru-paru) pada orang dewasa
- karsinoma sel ginjal stadium lanjut (kanker ginjal lanjut) pada orang dewasa
- lambung, persimpangan gastro esofagus atau adenokarsinoma esofagus stadium lanjut(kanker perut atau kerongkongan) pada orang dewasa.

Ini mengandung zat aktif nivolumab, yang merupakan antibodi monoklonal, sejenis protein yang dirancang untuk mengenali dan menempel pada zat target tertentu di dalam tubuh.

Nivolumab menempel pada protein target yang disebut reseptor kematian 1 terprogram (PD 1) yang dapat mematikan aktivitas sel T (sejenis sel darah putih yang membentuk bagian dari sistem kekebalan, pertahanan alami tubuh). Dengan menempel pada PD 1, nivolumab memblokir aksinya dan mencegahnya mematikan sel T Anda. Ini membantu meningkatkan aktivitas mereka melawan sel kanker, paru-paru, ginjal, lambung, esofagus atau gastro esofagus.

OPDIVO dapat diberikan dalam kombinasi dengan obat anti kanker lainnya. Penting agar Anda juga membaca leaflet untuk obat-obatan lain. Jika Anda memiliki pertanyaan tentang obat-obatan ini, silakan tanyakan kepada dokter Anda.

## 2. Apa yang perlu Anda ketahui sebelum menggunakan OPDIVO

### Anda tidak boleh diberi OPDIVO

- jika Anda **alergi** terhadap nivolumab atau bahan lain dari obat ini (tercantum di bagian 6 "Isi kemasan dan informasi lainnya"). **Bicaralah dengan dokter Anda** jika Anda tidak yakin.

### Peringatan dan pencegahan

Bicaralah dengan dokter Anda sebelum menggunakan OPDIVO karena dapat menyebabkan:

- **Masalah dengan jantung Anda** seperti perubahan ritme atau laju detak jantung atau ritme jantung yang tidak normal.
- **Masalah dengan paru-paru** Anda seperti kesulitan bernapas atau batuk. Ini mungkin tanda radang paru-paru(pneumonitis atau penyakit paru interstisial).
- **Diare (feses encer, encer atau lunak) atau gejala radang usus (kolitis)**, seperti sakit perut dan lendir atau darah dalam tinja.
- **Radang hati (hepatitis).** Tanda dan gejala hepatitis mungkin termasuk tes fungsi hati yang tidak normal, mata atau kulit menguning (sakit kuning), nyeri di sisi kanan area perut, atau kelelahan.
- **Peradangan atau masalah dengan ginjal Anda.** Tanda dan gejala mungkin termasuk tes fungsi ginjal yang abnormal, atau penurunan volume urin.

- **Masalah dengan kelenjar penghasil hormon Anda** (termasuk kelenjar hipofisis, tiroid, paratiroid, dan adrenal) yang dapat memengaruhi cara kerja kelenjar ini. Tanda dan gejala bahwa kelenjar ini tidak berfungsi dengan baik mungkin termasuk kelelahan (kelelahan ekstrim), perubahan berat badan atau sakit kepala, penurunan kadar kalsium darah dan gangguan penglihatan.
- **Diabetes termasuk masalah yang serius**, terkadang mengancam nyawa akibat asam dalam darah yang dihasilkan dari diabetes (diabetic ketoacidosis). Gejala mungkin termasuk merasa lebih lapar atau haus dari biasanya, ingin buang air kecil lebih sering, penurunan berat badan, merasa lelah atau sulit berpikir jernih, napas berbau manis atau buah, rasa manis atau logam di mulut, atau bau yang berbeda dengan Anda. urin atau keringat, merasa mual atau sakit, sakit perut, dan napas dalam atau cepat.
- **Peradangan kulit** yang dapat menyebabkan reaksi kulit yang parah (dikenal sebagai nekrolisis epidermal toksik dan sindrom Stevens Johnson). Tanda dan gejala reaksi kulit yang parah dapat berupa ruam, gatal, dan pengelupasan kulit (mungkin fatal).
- **Radang otot** seperti miokarditis (radang otot jantung), myositis (radang otot) dan rhabdomyolysis (kekakuan pada otot dan persendian, kejang otot). Tanda dan gejala

mungkin termasuk nyeri otot, kekakuan, kelemahan, nyeri dada, atau kelelahan yang parah.

- **Penolakan transplantasi organ padat.**
- **Graft versus host disease**
- **Limfohistiositosis hemofagositik.** Penyakit langka di mana sistem kekebalan kita membuat terlalu banyak sel penangkal infeksi normal yang disebut histiosit dan limfosit. Gejala mungkin termasuk pembesaran hati dan/atau limpa, ruam kulit, pembesaran kelenjar getah bening, masalah pernapasan, mudah memar, kelainan ginjal, dan masalah jantung.

**Beri tahu dokter Anda segera** jika Anda memiliki salah satu dari tanda atau gejala ini atau jika gejala tersebut memburuk. **Jangan mencoba mengobati gejala Anda sendiri dengan obat lain.** Dokter Anda mungkin

- memberi Anda obat-obatan lain untuk mencegah komplikasi dan mengurangi gejala Anda,
- menahan dosis OPDIVO berikutnya,
- atau hentikan perawatan Anda dengan OPDIVO sama sekali.

Harap perhatikan bahwa tanda dan gejala ini **terkadang tertunda**, dan dapat berkembang berminggu-minggu atau berbulan-bulan setelah dosis terakhir Anda. Sebelum perawatan, dokter Anda akan memeriksa kesehatan umum Anda. Anda juga akan menjalani tes darah selama perawatan.

**Tanyakan kepada dokter atau perawat Anda sebelum Anda diberikan OPDIVO jika:**

- Anda memiliki **penyakit autoimun** (suatu kondisi di mana tubuh menyerang selnya sendiri);
- Anda memiliki **melanoma mata;**
- Anda sebelumnya diberikan ipilimumab, obat lain untuk mengobati melanoma, dan mengalami **efek samping yang serius** karena obat tersebut;
- Anda telah diberitahu bahwa **kanker telah menyebar ke otak Anda;**
- Anda memiliki riwayat **radang paru-paru;**
- Anda telah minum **obat untuk menekan sistem kekebalan Anda.**

**OPDIVO bekerja pada sistem imun Anda. Obat ini dapat menyebabkan peradangan di beberapa bagian tubuh Anda. Risiko efek samping ini mungkin lebih tinggi jika Anda sudah memiliki penyakit autoimun (kondisi di mana tubuh menyerang sel-selnya sendiri). Anda mungkin juga mengalami kambuhnya penyakit autoimun secara berkala, yang dalam sebagian besar kasus bersifat ringan.**

**Komplikasi transplantasi sel punca yang menggunakan sel punca donor (alogenik) setelah pengobatan dengan OPDIVO.** Komplikasi ini bisa parah dan bisa menyebabkan kematian. Penyedia layanan kesehatan Anda akan memantau tanda-tanda komplikasi jika Anda memiliki transplantasi sel induk alogenik.

**Anak-anak dan remaja**

OPDIVO tidak boleh digunakan pada anak-anak dan remaja di bawah usia 18 tahun.

**Obat-obatan lain dan OPDIVO**

**Sebelum Anda diberikan OPDIVO, beri tahu dokter Anda** jika Anda sedang mengonsumsi obat apa pun yang menekan sistem kekebalan Anda, seperti kortikosteroid, karena obat ini dapat mengganggu efek OPDIVO. Namun, setelah Anda dirawat dengan OPDIVO, dokter Anda mungkin memberi Anda kortikosteroid untuk mengurangi kemungkinan efek samping yang mungkin Anda alami selama perawatan dan ini tidak akan memengaruhi efek obatnya.

**Beri tahu dokter Anda** jika Anda sedang mengonsumsi atau baru saja mengonsumsi obat lain. **Jangan minum obat lain** selama perawatan Anda tanpa berbicara dengan dokter Anda terlebih dahulu.

**Kehamilan dan menyusui**

**Beritahu dokter Anda** jika Anda sedang hamil atau berpikir Anda mungkin hamil, jika Anda berencana untuk hamil, atau jika Anda sedang menyusui.

**Jangan gunakan OPDIVO jika Anda sedang hamil** kecuali jika dokter Anda secara khusus memberi tahu Anda. Efek OPDIVO pada wanita hamil tidak diketahui, tetapi ada kemungkinan zat aktif nivolumab dapat membahayakan bayi yang belum

lahir.

- Anda harus menggunakan **kontrasepsi yang efektif** saat Anda sedang dirawat dengan OPDIVO dan setidaknya 5 bulan setelah dosis terakhir OPDIVO, jika Anda seorang wanita yang mungkin hamil.
- Jika Anda hamil saat menggunakan OPDIVO **beri tahu dokter Anda.**

Tidak diketahui apakah OPDIVO masuk ke ASI. Risiko terhadap bayi yang disusui tidak dapat dikesampingkan. **Tanyakan kepada dokter Anda** apakah Anda dapat menyusui selama atau setelah perawatan dengan OPDIVO.

**Mengemudi dan menggunakan mesin**

OPDIVO atau OPDIVO dalam kombinasi dengan ipilimumab mungkin memiliki sedikit pengaruh pada kemampuan mengemudi dan menggunakan mesin; namun, berhati-hatilah saat melakukan aktivitas ini hingga Anda yakin bahwa OPDIVO tidak berdampak buruk bagi Anda.

**OPDIVO mengandung natrium**

Beri tahu dokter jika Anda sedang menjalani diet rendah sodium (rendah garam) sebelum diberikan OPDIVO. Obat ini mengandung 2,5 mg sodium (komponen utama garam masak/meja) dalam setiap mL konsentrat. OPDIVO mengandung 10 mg sodium per 4 ml vial, 25 mg sodium per 10 ml vial, 30 mg sodium per 12 ml vial atau 60 mg sodium per 24 ml vial, yang masing-

masing setara dengan 0,5%, 1,25%, 1,5% atau 3%. , dari asupan natrium harian maksimum yang direkomendasikan untuk orang dewasa.

## 3. Cara menggunakan OPDIVO

### Berapa banyak OPDIVO yang diberikan

Ketika OPDIVO diberikan dalam kombinasi dengan ipilimumab untuk pengobatan kanker ginjal stadium lanjut, dosis OPDIVO yang dianjurkan adalah 3 mg nivolumab per kilogram berat badan Anda untuk 4 dosis pertama (fase kombinasi). Setelah itu, dosis OPDIVO yang dianjurkan adalah 240 mg diberikan setiap 2 minggu atau 480 mg diberikan setiap 4 minggu (fase agen tunggal).

Ketika OPDIVO diberikan dalam kombinasi dengan kemoterapi untuk pengobatan lambung lanjut, persimpangan gastro esofagus atau adenokarsinoma esofagus, dosis OPDIVO yang dianjurkan adalah 360 mg setiap 3 minggu atau 240 mg setiap 2 minggu.

Ketika OPDIVO diberikan dalam kombinasi dengan ipilimumab dan kemoterapi untuk pengobatan kanker paru non sel kecil stadium lanjut, dosis OPDIVO yang dianjurkan adalah 360 mg setiap 3 minggu. Setelah selesai 2 siklus kemoterapi, OPDIVO diberikan dalam kombinasi dengan ipilimumab, dosis OPDIVO yang dianjurkan adalah 360 mg setiap 3 minggu.

Bergantung pada dosis Anda, jumlah OPDIVO yang sesuai akan diencerkan dengan larutan natrium klorida 9 mg/mL (0,9%) untuk injeksi atau larutan glukosa 50 mg/mL (5%) untuk

injeksi sebelum digunakan. Lebih dari satu botol OPDIVO mungkin diperlukan untuk mendapatkan dosis yang dibutuhkan

**Bagaimana OPDIVO diberikan**

Anda akan menerima perawatan dengan OPDIVO di rumah sakit atau klinik, di bawah pengawasan dokter yang berpengalaman. OPDIVO akan diberikan kepada Anda sebagai infus (tetesan) ke pembuluh darah (intravena) selama 30 atau 60 menit, setiap 2 minggu atau 4 minggu, tergantung pada dosis yang Anda terima. Dokter Anda akan terus memberi Anda OPDIVO selama Anda terus mendapat manfaat darinya atau sampai Anda tidak lagi mentolerir pengobatannya.

Ketika OPDIVO diberikan dalam kombinasi dengan ipilimumab untuk pengobatan kanker ginjal stadium lanjut, Anda akan diberikan infus selama 30 menit, setiap 3 minggu untuk 4 dosis pertama (fase kombinasi). Setelah itu akan diberikan sebagai infus selama 30 atau 60 menit, setiap 2 minggu atau 4 minggu, tergantung pada dosis yang Anda terima (fase tunggal).

Ketika OPDIVO diberikan dalam kombinasi dengan kemoterapi untuk pengobatan lambung lanjut, persimpangan gastro esofagus atau adenokarsinoma esofagus, Anda akan diberikan infus selama 30 menit setiap 3 minggu atau setiap 2 minggu, tergantung pada dosis yang Anda terima.

Ketika OPDIVO diberikan dalam kombinasi dengan ipilimumab dan kemoterapi untuk pengobatan kanker paru-paru non sel kecil stadium lanjut, Anda akan diberikan infus selama 30

menit, setiap 3 minggu.

**Jika Anda melewatkan satu dosis OPDIVO**

Sangat penting bagi Anda untuk menepati semua janji Anda untuk menerima OPDIVO. Jika Anda melewatkan janji temu, tanyakan kepada dokter Anda kapan harus menjadwalkan dosis berikutnya.

**Jika Anda berhenti menggunakan OPDIVO**

Menghentikan pengobatan Anda dapat menghentikan efek obat. Jangan hentikan pengobatan dengan OPDIVO kecuali Anda telah membicarakan hal ini dengan dokter Anda.

Jika Anda memiliki pertanyaan lebih lanjut tentang perawatan Anda atau tentang penggunaan obat ini, tanyakan kepada dokter Anda.

Ketika OPDIVO diberikan dalam kombinasi dengan obat anti kanker lainnya, Anda akan diberikan OPDIVO terlebih dahulu diikuti dengan obat lainnya.

Silakan lihat brosur obat-obatan lain ini untuk memahami penggunaan obat-obatan ini. Jika Anda memiliki pertanyaan tentang mereka, silakan tanyakan kepada dokter Anda.

## 4. Kemungkinan efek samping

Seperti semua obat, obat ini bisa menimbulkan efek samping, meski tidak semua orang mendapatkannya. Dokter Anda akan membicarakan hal ini dengan Anda dan akan menjelaskan risiko dan manfaat pengobatan Anda.

**Waspadai gejala peradangan yang penting.** OPDIVO bekerja pada sistem kekebalan Anda dan dapat menyebabkan peradangan di beberapa bagian tubuh Anda. Peradangan dapat menyebabkan kerusakan serius pada tubuh Anda dan beberapa kondisi peradangan dapat mengancam nyawa dan memerlukan pengobatan atau penarikan OPDIVO.

Efek samping berikut telah dilaporkan **dengan OPDIVO dalam kombinasi dengan obat anti kanker lainnya** (frekuensi dan tingkat keparahan efek samping dapat bervariasi dengan kombinasi obat anti kanker yang diterima):

**Sangat umum (dapat mempengaruhi lebih dari 1 dari 10 orang)**

- Infeksi pada saluran pernapasan bagian atas
- Penurunan jumlah sel darah merah (yang membawa oksigen), sel darah putih (yang penting dalam melawan infeksi) atau trombosit (sel yang membantu pembekuan darah)
- Kelenjar tiroid yang kurang aktif (yang dapat menyebabkan kelelahan atau penambahan berat badan), kelenjar tiroid yang terlalu aktif (yang dapat menyebabkan detak jantung cepat, berkeringat, dan penurunan berat badan)
- Penurunan nafsu makan, penurunan berat badan, penurunan kadar albumin dalam darah, kadar gula tinggi (hiperglikemia) atau rendah (hipoglikemia) dalam darah
- Peradangan saraf (menyebabkan mati rasa, lemah, kesemutan atau nyeri terbakar pada lengan dan kaki), sakit kepala, pusing, perubahan indera perasa
- Tekanan darah tinggi (hipertensi)

- Sesak napas (dispnoea), batuk, suara bicara tidak normal (disfonia)
- Diare (tinja encer, encer atau lunak), sembelit, muntah, mual, sakit perut, sariawan dan luka dingin (stomatitis), gangguan pencernaan (dispepsia)
- Ruam kulit kadang disertai lepuh, gatal, nyeri pada tangan atau telapak kaki: ruam atau kemerahan pada kulit, kesemutan dan nyeri berkembang menjadi kemerahan simetris, bengkak dan nyeri terutama pada telapak tangan dan telapak kaki ( sindrom palmar plantar erythrodysaesthaesia)
- Nyeri pada persendian (arthralgia), nyeri pada otot dan tulang (nyeri muskuloskeletal), spasme otot
- Kelebihan protein dalam urin
- Merasa lelah atau lemah, demam, edema (bengkak)

**Umum (dapat mempengaruhi hingga 1 dari 10 orang)**

- Infeksi paru-paru serius (pneumonia), bronkitis, radang mata (konjungtivitis)
- Peningkatan beberapa sel darah putih, penurunan neutrofil dengan demam
- Reaksi alergi, reaksi yang berhubungan dengan infus obat
- Penurunan sekresi hormon yang dihasilkan oleh kelenjar adrenal (kelenjar yang terletak di atas ginjal), fungsi yang kurang aktif (hipopituitarisme) atau peradangan

(hipofisitis) kelenjar pituitari yang terletak di dasar otak, pembengkakan kelenjar tiroid, diabetes

- Dehidrasi, penurunan kadar fosfat dalam darah
- Sensasi seperti mati rasa dan kesemutan (parestesia)
- Mendengar suara terus-menerus di telinga Anda saat tidak ada suara (tinnitus)
- Penglihatan kabur, mata kering
- Denyut jantung cepat, irama jantung tidak normal, penyakit radang pembuluh darah
- Pembentukan bekuan darah di dalam pembuluh darah (trombosis)
- Radang paru-paru (pneumonitis, ditandai dengan batuk dan kesulitan bernapas), cairan di sekitar paru-paru, bekuan darah, mimisan
- Radang usus (kolitis), radang pankreas (pankreatitis), mulut kering, radang lambung (gastritis), nyeri mulut, wasir (wasir)
- Peradangan hati
- Perubahan warna kulit pada bercak (termasuk vitiligo), kemerahan pada kulit, kerontokan atau penipisan rambut yang tidak biasa, perubahan warna rambut, gatal-gatal (ruam gatal), perubahan warna atau penggelapan kulit yang tidak normal (hiperpigmentasi kulit), kulit kering
- Radang sendi (arthritis), kelemahan otot, nyeri otot
- Gagal ginjal (termasuk tiba-tiba kehilangan fungsi ginjal)

- Nyeri, nyeri dada, menggigil
- Merasa umumnya tidak enak badan (malaise)

**Jarang (dapat mempengaruhi hingga 1 dari 100 orang)**

- Asam dalam darah yang dihasilkan dari diabetes (diabetic ketoacidosis)
- Peningkatan kadar asam dalam darah
- Peradangan saraf sementara yang menyebabkan nyeri, kelemahan dan kelumpuhan pada ekstremitas (sindrom Guillain Barré); kerusakan saraf yang menyebabkan mati rasa dan kelemahan (polineuropati); foot drop (kelumpuhan saraf peroneal); radang saraf yang disebabkan oleh tubuh yang menyerang dirinya sendiri, menyebabkan mati rasa, lemas, kesemutan atau nyeri terbakar (neuropati autoimun); kelemahan otot dan kelelahan tanpa atrofi (miastenia gravis atau sindrom)
- Radang otak
- Radang mata (yang menyebabkan rasa sakit dan kemerahan)
- Perubahan ritme atau laju detak jantung, detak jantung lambat, radang otot jantung
- Perforasi usus, radang duodenum, sensasi terbakar atau nyeri di lidah (glossodynia)
- Pengelupasan kulit yang parah dan mungkin fatal (sindrom Stevens Johnson), penyakit kulit dengan bercak kulit merah yang menebal, seringkali dengan sisik keperakan (psoriasis), kondisi kulit yang parah yang menyebabkan

bintik merah, seringkali gatal, mirip dengan ruam kulit campak, yang dimulai pada anggota badan dan terkadang pada wajah dan bagian tubuh lainnya (erythema multiforme)

- Kelembutan atau kelemahan otot, bukan disebabkan oleh olahraga (miopati), radang otot (myositis), kekakuan pada otot dan persendian, radang otot yang menyebabkan nyeri atau kaku (polymyalgia rheumatica), kerusakan tulang pada rahang, pembukaan abnormal antara dua bagian tubuh, seperti organ atau pembuluh darah dan struktur lain (fistula)
- Radang ginjal, radang kandung kemih, tanda dan gejala mungkin termasuk sering dan / atau buang air kecil yang menyakitkan, dorongan untuk buang air kecil, darah dalam urin, nyeri atau tekanan di perut bagian bawah

**Sangat Jarang (dapat mempengaruhi hingga 1 dari 1000 orang)**

- Peradangan non-infeksi sementara dan reversibel pada selaput pelindung yang mengelilingi otak dan sumsum tulang belakang (meningitis aseptik)
- Penyakit kronis yang berhubungan dengan penumpukan sel inflamasi di berbagai organ dan jaringan, paling sering di paru-paru (sarkoidosis)
- Penurunan fungsi kelenjar paratiroid
- Sekelompok komplikasi metabolik yang terjadi setelah pengobatan kanker yang ditandai dengan kadar kalium dan

fosfat dalam darah yang tinggi, dan kadar kalsium dalam darah yang rendah (sindrom lisis tumor)

- Gangguan inflamasi (kemungkinan besar berasal dari autoimun) yang memengaruhi mata, kulit, dan selaput telinga, otak, dan sumsum tulang belakang (sindrom Vogt Koyanagi Harada)
- Peradangan saraf optik yang dapat menyebabkan hilangnya penglihatan sebagian atau seluruhnya (sindrom optik)
- Radang saraf
- Rasa nyeri, mati rasa, kesemutan, atau kelemahan pada lengan atau kaki; masalah kandung kemih atau usus termasuk kebutuhan untuk buang air kecil lebih sering, inkontinensia urin, kesulitan buang air kecil dan sembelit (mielitis/mielitis transversal.
- Pengelupasan kulit yang parah dan mungkin fatal (nekrolisis epidermal toksik), perubahan pada area kulit dan/atau area genital yang berhubungan dengan kekeringan, penipisan, gatal dan nyeri (lichen sclerosus)
- Penyakit sendi kronis (spondyloarthropathy), penyakit di mana sistem kekebalan menyerang kelenjar yang membuat kelembaban tubuh, seperti air mata dan air liur (sindrom Sjogren), kejang otot (rhabdomyolysis)
- Kekurangan atau pengurangan enzim pencernaan yang dibuat oleh pankreas (insufisiensi eksokrin pankreas.
- Penyakit celiac (ditandai dengan gejala seperti sakit perut, diare, dan kembung setelah mengonsumsi makanan

yang mengandung gluten.

**Efek samping lain yang telah dilaporkan dengan frekuensi tidak diketahui (tidak dapat diperkirakan dari data yang tersedia):**

- Suatu kondisi di mana sistem kekebalan membuat terlalu banyak sel penangkal infeksi yang disebut histiosit dan limfosit yang dapat menyebabkan berbagai gejala (disebut limfohistiositosis hemofagositik)
- Penolakan transplantasi organ padat
- Peradangan pada penutup jantung dan akumulasi cairan di sekitar jantung (gangguan perikardial)

**Beri tahu dokter Anda segera** jika Anda mendapatkan salah satu efek samping yang tercantum di atas. Jangan mencoba mengobati gejala Anda sendiri dengan obat lain.

**Pelaporan Efek Samping**

Pusat Farmakovigilans/MESO Nasional
Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika, Psikotropika, Prekursor, dan Zat Adiktif
Badan Pengawas Obat dan Makanan
Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Phone: +62-21-4244691 Ext.1079
Website: https://e-meso.pom.go.id/ADR

**Perubahan hasil tes**

OPDIVO sendiri atau dalam kombinasi dapat menyebabkan perubahan pada hasil tes yang dilakukan oleh dokter Anda. Ini termasuk:

- Tes fungsi hati yang tidak normal (peningkatan jumlah enzim hati aspartat aminotransferase, alanine aminotransferase, gamma glutamyltransferase, atau alkaline phosphatase dalam darah Anda, tingkat darah yang lebih tinggi dari produk limbah bilirubin)
- Tes fungsi ginjal yang tidak normal (peningkatan jumlah kreatinin dalam darah Anda)
- Peningkatan kadar enzim yang memecah lemak dan enzim yang memecah pati
- Peningkatan atau penurunan jumlah kalsium atau kalium
- Peningkatan atau penurunan kadar magnesium atau natrium dalam darah
- Peningkatan jumlah hormon perangsang tiroid
- Peningkatan kadar trigliserida darah dalam darah
- Peningkatan kadar kolesterol dalam darah

## 5. Bagaimana cara menyimpan OPDIVO

Jauhkan obat ini dari pandangan dan jangkauan anak-anak.
Jangan gunakan obat ini setelah tanggal kedaluwarsa yang tertera pada karton dan label vial setelah EXP. Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.
Simpan di kulkas (2°C hingga 8°C).
Jangan membeku.

Simpan dalam kemasan aslinya untuk melindungi dari cahaya. Botol yang belum dibuka dapat disimpan pada suhu ruangan terkontrol hingga 25°C dengan cahaya ruangan hingga 48 jam. Jangan menyimpan bagian larutan infus yang tidak terpakai untuk digunakan kembali. Setiap obat atau bahan limbah yang tidak terpakai harus dibuang sesuai dengan persyaratan setempat.

## 6. Isi kemasan dan informasi lainnya

### Apa isi OPDIVO

- Zat aktifnya adalah nivolumab.

  Setiap mL konsentrat untuk larutan infus mengandung 10 mg nivolumab.

  Setiap vial mengandung nivolumab 120 mg (dalam 12 mL).

- Bahan lainnya adalah natrium sitrat dihidrat, natrium klorida (lihat bagian 2 "OPDIVO mengandung natrium"), manitol (E421), asam pentatik, polisorbat 80 (E433), natrium hidroksida, asam klorida dan air untuk injeksi.

### Seperti apa OPDIVO dan isi paketnya

Konsentrat OPDIVO untuk larutan infus (konsentrat steril) adalah cairan bening hingga opalescent, tidak berwarna hingga kuning pucat yang mungkin mengandung sedikit partikel cahaya. Ini tersedia dalam kemasan 1 vial 12 mL.

**Informasi berikut hanya ditujukan untuk profesional kesehatan:**

**Persiapan dan administrasi OPDIVO**

Persiapan harus dilakukan oleh personel terlatih sesuai dengan aturan praktik yang baik, terutama yang berkaitan dengan asepsis.

**Menghitung dosis**

Lebih dari satu vial konsentrat OPDIVO mungkin diperlukan untuk memberikan dosis total bagi pasien.

Nivolumab dalam kombinasi dengan ipilimumab:

**Dosis yang ditentukan** untuk pasien diberikan dalam mg/kg. Berdasarkan dosis yang ditentukan ini, hitung dosis total yang akan diberikan.

- **Total dosis nivolumab** dalam mg = berat pasien dalam kg × dosis yang ditentukan dalam mg/kg.
- **Volume konsentrat OPDIVO** untuk menyiapkan dosis (mL) = dosis total dalam mg, dibagi 10 (kekuatan konsentrat OPDIVO adalah 10 mg/mL).

Nivolumab dalam kombinasi dengan kemoterapi di lambung, persimpangan gastro esofagus atau adenokarsinoma esofagus:

Dosis yang ditentukan untuk pasien adalah 360 mg atau 240 mg diberikan terlepas dari berat badan.

Nivolumab dalam kombinasi dengan ipilimumab dan kemoterapi:
Dosis yang diresepkan untuk pasien adalah 360 mg yang diberikan tanpa mempertimbangkan berat badan.

**Mempersiapkan infus**

**Berhati-hatilah untuk memastikan penanganan aseptik** saat Anda menyiapkan infus.

OPDIVO dapat digunakan untuk pemberian intravena baik:

- **tanpa pengenceran,** setelah dipindahkan ke wadah infus menggunakan spuit steril yang sesuai;

  atau

- **setelah diencerkan** sesuai petunjuk berikut:
  - konsentrasi infus akhir harus berkisar antara 1 dan 10 mg/mL.
  - total volume infus tidak boleh melebihi 160 mL. Untuk pasien dengan berat badan kurang dari 40 kg, total volume infus tidak boleh melebihi 4 mL per kilogram berat badan pasien.
- Konsentrat OPDIVO dapat diencerkan dengan:
  - larutan natrium klorida 9 mg/mL (0,9%) untuk injeksi; atau
  - 50 mg/mL (5%) larutan glukosa untuk injeksi.

**LANGKAH 1**

- Periksa konsentrat OPDIVO untuk partikulat atau perubahan warna. Jangan mengocok vial. Konsentrat OPDIVO adalah cairan bening hingga opalescent, tidak berwarna hingga kuning pucat. Buang vial jika larutannya keruh, berubah warna, atau mengandung bahan partikulat selain beberapa partikel tembus cahaya hingga putih.
- Keluarkan volume konsentrat OPDIVO yang dibutuhkan menggunakan spuit steril yang sesuai.

**LANGKAH 2**

- Pindahkan konsentrat ke dalam botol kaca steril yang dikosongkan atau wadah intravena (PVC atau poliolefin).
- Jika memungkinkan, encerkan larutan natrium klorida 9 mg/mL (0,9%) untuk injeksi dengan volume yang diperlukan atau larutan glukosa 50 mg/mL (5%) untuk injeksi. Untuk memudahkan penyiapan, konsentrat dapat dipindahkan langsung ke dalam kantong berisi larutan natrium klorida 9 mg/mL (0,9%) untuk injeksi atau larutan glukosa 50 mg/mL (5%) untuk injeksi.
- Campur infus dengan lembut dengan putaran manual. Jangan goyang.

**Penggunaan**

Infus OPDIVO tidak boleh diberikan sebagai injeksi intravena atau injeksi bolus.

Berikan infus OPDIVO **secara intravena selama 30 atau 60 menit tergantung pada dosisnya.**

Infus OPDIVO tidak boleh diinfuskan pada waktu yang sama di jalur intravena yang sama dengan agen lain. Gunakan jalur infus terpisah untuk infus.

Gunakan set infus dan filter segaris, steril, non pirogenik, pengikat protein rendah (ukuran pori 0,2 µm hingga 1,2 µm).

Infus OPDIVO kompatibel dengan:

- Wadah PVC
- Wadah poliolefin
- Botol kaca
- Set infus PVC
- Sejajar filter dengan membran polietersulfon dengan ukuran pori 0,2 µm hingga 1,2 µm.

Setelah pemberian dosis nivolumab, bilas saluran dengan larutan natrium klorida 9 mg/mL (0,9%) untuk injeksi atau larutan glukosa 50 mg/mL (5%) untuk injeksi.

**Kondisi penyimpanan dan umur simpan**

Botol yang belum dibuka

OPDIVO harus disimpan di lemari es (2°C hingga 8°C). Botol harus disimpan dalam kemasan aslinya untuk melindungi dari cahaya. OPDIVO tidak boleh dibekukan.

Botol yang belum dibuka dapat disimpan pada suhu ruangan terkontrol hingga 25°C dengan cahaya ruangan hingga 48 jam.

Jangan gunakan OPDIVO setelah tanggal kedaluwarsa yang tertera pada karton dan label vial setelah EXP. Tanggal kedaluwarsa mengacu pada hari terakhir bulan itu.

Setelah dibuka

Dari sudut pandang mikrobiologis, setelah dibuka, produk obat harus segera disiapkan untuk infus.

Infus OPDIVO

Stabilitas kimia dan fisika dalam penggunaan sejak waktu persiapan telah dibuktikan sebagai berikut (waktu tersebut sudah termasuk periode pemberian):

| **Persiapan infus** | **Stabilitas kimia dan fisik saat digunakan** | |
|---|---|---|
| | **Penyimpanan pada suhu 2°C hingga 8°C terlindungi dari cahaya** | **Penyimpanan pada suhu ruangan (≤ 25°C) dan cahaya ruangan** |
| Larutan injeksi yang tidak diencerkan atau diencerkan dengan natrium klorida 9 mg/mL (0,9%) | 30 hari | 24 jam (dari total penyimpanan 30 hari) |
| Diencerkan dengan larutan glukosa 50 mg/mL (5%) untuk injeksi | 7 hari | 8 jam (dari total pemyimpanan 7 hari) |

Dari sudut pandang mikrobiologi, larutan yang disiapkan untuk infus, apa pun pengencernya, harus segera digunakan. Jika tidak segera digunakan, waktu penyimpanan dan kondisi sebelum digunakan menjadi tanggung jawab pengguna dan biasanya tidak lebih dari 7 hari pada suhu 2°C hingga 8°C atau 8 jam (dari total 7 hari penyimpanan) pada suhu ruangan (≤ 25°C).

Penanganan aseptik harus dipastikan selama persiapan infus.

**Pembuangan**

Jangan menyimpan bagian larutan infus yang tidak terpakai untuk digunakan kembali. Setiap obat atau bahan limbah yang tidak terpakai harus dibuang sesuai dengan persyaratan setempat.

**Pemegang Izin Edar**

PT Mecosin Indonesia

Bogor, Indonesia

**Produsen**

Vetter Pharma-Fertigung GmbH & Co. KG

Mooswiesen 2

88214 Ravensburg Germany

**Releaser**

Swords Laboratories Unlimited Company

t/a Bristol-Myers Squibb Cruiserath Biologics

Cruiserath Road

Mulhuddart, Dublin 15,

Ireland

**Nomor Izin Edar**

Opdivo 120 mg/12mL  Box @ 1 vial  DKIXXXXXXXXXXXX

**Leaflet ini disetujui pada**

MMM YYYY

**HARUS DENGAN RESEP DOKTER**