ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Opdualag 240 mg/80 mg concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of concentrate for solution for infusion contains 12 mg of nivolumab and 4 mg of relatlimab. One vial of 20 mL contains 240 mg of nivolumab and 80 mg of relatlimab.

Nivolumab and relatlimab are human immunoglobulin G4 (IgG4) monoclonal antibodies produced in Chinese Hamster Ovary cells by recombinant DNA technology.

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 slightly yellow liquid that is essentially free of particles.
The solution has a pH of approximately 5.8 and an osmolality of approximately 310 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Opdualag is indicated for the first-line treatment of advanced (unresectable or metastatic) melanoma in adults and adolescents 12 years of age and older with tumour cell PD-L1 expression < 1%.

4.2 Posology and method of administration

Treatment must be initiated and supervised by physicians experienced in the treatment of cancer.

Patients treated with Opdualag must be given the patient card and be informed about the risks of Opdualag (see also package leaflet).

PD-L1 testing
Patients should be selected for treatment with Opdualag based on the tumour expression of PD-L1 confirmed by a validated test (see sections 4.4 and 5.1).

Posology
The recommended dose for adults and adolescents 12 years of age and older is 480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as an intravenous infusion over 30 minutes. This dose is established for adolescent patients weighing at least 30 kg (see section 5.2).

Treatment with Opdualag should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient. Dose escalation or reduction is not recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Guidelines for permanent discontinuation or withholding of doses are described in Table 1. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4.

Table 1: Recommended treatment modifications for Opdualag

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 or 3 diarrhoea or colitis	Withhold dose(s) until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue treatment
Immune-related hepatitis	Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) increases to more than 3 and up to 5 times upper limit of normal (ULN) or Total bilirubin increases to more than 1.5 and up to 3 times ULN	Withhold dose(s) until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	AST or ALT increases to more than 5 times ULN regardless of baseline. or Total bilirubin increases to more than 3 times ULN or Concurrent AST or ALT increase to more than 3 times ULN and total bilirubin increase to more than 2 times ULN	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 Grade 2 adrenal insufficiency 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[a] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency 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
	Suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold dose(s)
	Grade 4 rash Confirmed SJS/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[b]
	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 5.0 (NCI-CTCAE v5).

[a] Recommendation for the use of hormone replacement therapy is provided in section 4.4.

[b] The safety of re-initiating Opdualag in patients previously experiencing immune-related myocarditis is not known.

Special populations

Paediatric population
The safety and efficacy of Opdualag in children below 12 years of age have not been established. No data are available (see section 5.2).

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

Renal impairment
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
No dose adjustment is required in patients with mild or moderate hepatic impairment (see section 5.2). Data from patients with severe hepatic impairment are too limited to draw conclusions on this population.

Method of administration

Opdualag is for intravenous use only. It is to be administered as an intravenous infusion over a period of 30 minutes.

Opdualag must not be administered as an intravenous push or bolus injection.
Opdualag can be used without dilution, or may 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).

For instructions on the preparation and handling of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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
Immune-related adverse reactions can occur with nivolumab in combination with relatlimab which require 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.

Patients should be monitored continuously (at least up to 5 months after the last dose) as an adverse reaction with Opdualag 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, Opdualag 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.

Opdualag should not be resumed while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive therapy. Prophylactic antibiotics may be used to prevent opportunistic infections in patients receiving immunosuppressive therapy.

Opdualag 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 a fatal case, has been observed with nivolumab in combination with relatlimab (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 infiltrates), dyspnoea, and hypoxia. Infectious and disease-related aetiologies should be ruled out.

For Grade 3 or 4 pneumonitis, Opdualag 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, Opdualag should be withheld and corticosteroids initiated at a dose of 1 mg/kg/day methylprednisolone equivalents. Upon improvement, Opdualag 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 Opdualag must be permanently discontinued.

Immune-related colitis
Severe diarrhoea or colitis has been observed with nivolumab in combination with relatlimab (see section 4.8). Patients should be monitored for diarrhoea and additional symptoms of colitis, such as abdominal pain and mucus and/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, Opdualag must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

Opdualag 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, Opdualag may be resumed after corticosteroid taper. If worsening or no improvement occurs despite initiation of corticosteroids, Opdualag must be permanently discontinued.

For Grade 2 diarrhoea or colitis, Opdualag 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, Opdualag 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 Opdualag must be permanently discontinued.

Immune-related hepatitis
Severe hepatitis has been observed with nivolumab in combination with relatlimab (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 AST or ALT increases to more than 5 times ULN regardless of baseline, total bilirubin increases to more than 3 times ULN, or concurrent AST or ALT increase to more than 3 times ULN and total bilirubin increase to more than 2 times ULN, Opdualag must be permanently discontinued, and corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents.

For AST/ALT increases to more than 3 and up to 5 times ULN, or total bilirubin increases to more than 1.5 and up to 3 times ULN, Opdualag 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, Opdualag 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 Opdualag must be permanently discontinued.

Immune-related nephritis and renal dysfunction
Severe nephritis and renal dysfunction have been observed with nivolumab in combination with relatlimab (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, Opdualag 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, Opdualag should be withheld, and corticosteroids should be initiated at a dose of 0.5 to 1 mg/kg/day methylprednisolone equivalents. Upon improvement, Opdualag 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 Opdualag must be permanently discontinued.

Immune-related endocrinopathies
Severe endocrinopathies, including hypothyroidism, hyperthyroidism, adrenal insufficiency (including secondary adrenocortical insufficiency), hypophysitis (including hypopituitarism), and diabetes mellitus have been observed with nivolumab in combination with relatlimab. Cases of diabetic ketoacidosis have been observed with nivolumab monotherapy and could potentially occur with nivolumab in combination with relatlimab (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.

Thyroid dysfunction
For symptomatic hypothyroidism, Opdualag should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, Opdualag should be withheld and antithyroid treatment 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, Opdualag may be resumed after corticosteroid taper, if needed. Monitoring of thyroid function should continue to ensure appropriate hormone replacement is utilised. Opdualag must be permanently discontinued for life-threatening (Grade 4) hyperthyroidism or hypothyroidism.

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

Hypophysitis
Opdualag must be permanently discontinued for life-threatening (Grade 4) hypophysitis. For symptomatic Grade 2 or 3 hypophysitis, Opdualag 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, Opdualag may be resumed after corticosteroid taper, if needed. Monitoring of pituitary function and hormone levels should continue to ensure appropriate hormone replacement is utilised.

Diabetes mellitus
For symptomatic diabetes, Opdualag should be withheld, and insulin replacement should be initiated as needed. Monitoring of blood sugar should continue to ensure appropriate insulin replacement is utilised. Opdualag must be permanently discontinued for life-threatening diabetes.

Immune-related skin adverse reactions
Severe rash has been observed with nivolumab in combination with relatlimab (see section 4.8). Opdualag 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 with nivolumab monotherapy and could potentially occur with nivolumab in combination with relatlimab. If symptoms or signs of SJS or TEN are suspected, Opdualag should be withheld and the patient referred to a specialised unit for assessment and treatment. If the patient has confirmed SJS or TEN with the use of Opdualag, permanent discontinuation of treatment is recommended (see section 4.2).

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

Immune-related myocarditis
Severe immune-related myocarditis has been observed with nivolumab in combination with relatlimab. 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, Opdualag should be withheld or permanently discontinued as described below.

For Grade 3 or 4 myocarditis, Opdualag must be permanently discontinued, and corticosteroids should be initiated at a dose of 2 to 4 mg/kg/day methylprednisolone equivalents (see section 4.2).

For Grade 2 myocarditis, Opdualag should be withheld and corticosteroids initiated at a dose of 1 to 2 mg/kg/day methylprednisolone equivalent. Upon improvement, resumption of Opdualag may be considered 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 Opdualag must be permanently discontinued (see section 4.2).

Other immune-related adverse reactions
The following clinically significant immune-related adverse reactions have been rarely reported in patient treated with nivolumab in combination with relatlimab: uveitis, pancreatitis, Guillain-Barré syndrome, myositis/rhabdomyolysis, encephalitis, haemolytic anaemia, Vogt-Koyanagi-Harada syndrome (VKH).

The following additional clinically significant immune-related adverse reactions have been rarely reported with nivolumab monotherapy or nivolumab in combination with other approved agents: demyelination, autoimmune neuropathy (including facial and abducens nerve paresis), myasthenia gravis, myasthenic syndrome, aseptic meningitis, gastritis, sarcoidosis, duodenitis, hypoparathyroidism, and cystitis noninfective.

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, Opdualag should be withheld and corticosteroids administered. Upon improvement, Opdualag may be resumed after corticosteroid taper. Opdualag must be permanently discontinued for any severe immune-related adverse reaction that recurs and for any life-threatening immune-related adverse reaction.

Other important warnings and precautions, including class effects
Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with nivolumab in combination with relatlimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with nivolumab in combination with relatlimab versus the risk of possible organ rejection should be considered in these patients.

Haemophagocytic lymphohistiocytosis (HLH) has been observed with nivolumab as monotherapy, nivolumab in combination with relatlimab and nivolumab in combination with other agents with a fatal event reported with nivolumab in combination with relatlimab. Caution should be taken when administering nivolumab in combination with relatlimab. If HLH is confirmed, administration of nivolumab in combination with relatlimab should be discontinued and treatment for HLH initiated.

In patients treated with nivolumab before or after allogeneic Haematopoietic Stem Cell Transplantation (HSCT), rapid-onset and severe graft-versus-host disease (GVHD), some with fatal outcome, have been reported. Treatment with nivolumab in combination with relatlimab may increase the risk of severe GVHD and death in patients who have had prior allogeneic HSCT, mainly in those with prior history of GVHD. The benefit of treatment with nivolumab in combination with relatlimab versus the possible risk should be considered in these patients.

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

Patients excluded from pivotal advanced melanoma clinical study
Patients with active autoimmune disease, medical conditions requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medicinal products, uveal melanoma, active or untreated brain, or leptomeningeal metastases, and those with a history of myocarditis,

elevated troponin levels > 2 times ULN or ECOG performance status score ≥ 2, were excluded from the pivotal clinical study of nivolumab in combination with relatlimab. In the absence of data, nivolumab in combination with relatlimab should be used with caution in these populations after careful consideration of the potential benefit/risk on an individual basis.

Patient card
The prescriber must discuss the risks of Opdualag therapy with the patient. The patient will be provided with the patient card and instructed to carry the card at all times.

4.5 Interaction with other medicinal products and other forms of interaction

Nivolumab and relatlimab are both human monoclonal antibodies and as such, no interaction studies have been conducted. As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other active substances metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of relatlimab or nivolumab.

Nivolumab and relatlimab are not expected to affect the pharmacokinetics of other active substances that are metabolised by CYP enzymes given the lack of significant modulation of cytokines by nivolumab and relatlimab and therefore lack of effect on expression of cytochrome P450 enzyme.

Systemic immunosuppression
The use of systemic corticosteroids and other immunosuppressants at baseline, before starting nivolumab in combination with relatlimab, should be avoided because of their potential interference with the pharmacodynamic activity. However, systemic corticosteroids and other immunosuppressants can be used after starting nivolumab in combination with relatlimab to treat immune-related adverse reactions.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception
Opdualag is not recommended 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 Opdualag.

Pregnancy
There is a limited amount of data from the use of nivolumab in combination with relatlimab in pregnant women. Based on its mechanism of action and data from animal studies, nivolumab in combination with relatlimab can cause foetal harm when administered to a pregnant woman. Studies in animals receiving nivolumab have shown embryofoetal toxicity (see section 5.3). Human IgG4 is known to cross the placental barrier and nivolumab and relatlimab are an IgG4; therefore, nivolumab and relatlimab have the potential to be transmitted from the mother to the developing foetus. Opdualag is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk.

Breast-feeding
It is unknown whether nivolumab and/or relatlimab are excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, Opdualag could be used during breast-feeding if clinically needed.

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

4.7 Effects on ability to drive and use machines

Opdualag has a minor influence on the ability to drive and use machines. Because of potential adverse reactions such as fatigue and dizziness (see section 4.8), patients should be advised to use caution when driving or operating machines until they are certain that Opdualag does not adversely affect them.

4.8 Undesirable effects

Summary of the safety profile
Nivolumab in combination with relatlimab is associated with immune-related adverse reactions (see "Description of selected adverse reactions" below). The management guidelines for these adverse reactions are described in section 4.4.

The most common adverse reactions are fatigue (41%), musculoskeletal pain (32%), rash (29%), arthralgia (26%), diarrhoea (26%), pruritus (26%), headache (20%), nausea (19%), cough (16%), decreased appetite (16%), hypothyroidism (16%), abdominal pain (14%), vitiligo (13%), pyrexia (12%), constipation (11%), urinary tract infection (11%), dyspnoea (10%), and vomiting (10%).

The most common serious adverse reactions are adrenal insufficiency (1.4%), anaemia (1.4%), back pain (1.1%), colitis (1.1%), diarrhoea (1.1%), myocarditis (1.1%), pneumonia (1.1%), and urinary tract infection (1.1%). Incidences of Grade 3-5 adverse reactions in patients with advanced (unresectable or metastatic) melanoma were 43% for nivolumab in combination with relatlimab and 35% for nivolumab treated patients.

Tabulated summary of adverse reactions
The safety of nivolumab in combination with relatlimab has been evaluated in 355 patients with advanced (unresectable or metastatic) melanoma (study CA224047). Adverse reactions reported in the dataset for patients treated with nivolumab in combination with relatlimab, with a median follow-up of 19.94 months, are presented in Table 2. The frequencies included above and in Table 2 are based on all-cause adverse event frequencies. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in clinical studies

Infections and infestations	
Very common	urinary tract infection
Common	upper respiratory tract infection
Uncommon	folliculitis
Blood and lymphatic system disorders	
Very common	anaemia[a], lymphopaenia[a], neutropaenia[a], leucopaenia[a]
Common	thrombocytopaenia[a], eosinophilia
Uncommon	haemolytic anaemia
Endocrine disorders	
Very common	hypothyroidism
Common	adrenal insufficiency, hypophysitis, hyperthyroidism, thyroiditis
Uncommon	hypopituitarism, hypogonadism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	diabetes mellitus, hypoglycaemia[a], weight decreased, hyperuricaemia, hypoalbuminaemia, dehydration
Psychiatric disorders	
Common	confusional state

Nervous system disorders	
Very common	headache
Common	peripheral neuropathy, dizziness, dysgeusia
Uncommon	encephalitis, Guillain-Barré syndrome, optic neuritis
Eye disorders	
Common	uveitis, visual impairment, dry eye, increased lacrimation
Uncommon	Vogt-Koyanagi-Harada disease, ocular hyperaemia
Cardiac disorders	
Common	myocarditis
Uncommon	pericardial effusion
Vascular disorders	
Common	phlebitis
Respiratory, thoracic and mediastinal disorders	
Very common	dyspnoea, cough
Common	pneumonitis[b], nasal congestion
Uncommon	asthma
Gastrointestinal disorders	
Very common	diarrhoea, vomiting, nausea, abdominal pain, constipation
Common	colitis, pancreatitis, gastritis, dysphagia, stomatitis, dry mouth
Uncommon	oesophagitis
Hepatobiliary disorders	
Common	hepatitis
Uncommon	cholangitis
Skin and subcutaneous tissue disorders	
Very common	rash, vitiligo, pruritus
Common	alopecia, lichenoid keratosis, photosensitivity reaction, dry skin
Uncommon	pemphigoid, psoriasis, urticaria
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain, arthralgia
Common	arthritis, muscle spasms, muscular weakness
Uncommon	myositis, Sjogren's Syndrome, polymyalgia rheumatica, rheumatoid arthritis, systemic lupus erythematosus
Renal and urinary disorders	
Common	renal failure, proteinuria
Uncommon	nephritis
Reproductive system and breast disorders	
Uncommon	azoospermia
General disorders and administration site conditions	
Very common	fatigue, pyrexia
Common	oedema, influenza-like illness, chills
Investigations	
Very common	increased AST[a], increased ALT[a], hyponatraemia[a], increased creatinine[a], increased alkaline phosphatase[a], hyperkalaemia[a], hypocalcaemia[a], hypomagnesaemia[a], hypercalcaemia[a], hypokalaemia[a]
Common	increased bilirubin[a], hypernatraemia[a], hypermagnesaemia[a], troponin increased, gamma-glutamyl transferase increased, blood lactate dehydrogenase increased, lipase increased, amylase increased
Uncommon	c-reactive protein increased, red blood cell sedimentation rate increased
Injury, poisoning and procedural complications	
Common	infusion-related reaction

[a] Frequencies of laboratory terms reflect the proportion of patients who experienced a worsening from baseline in laboratory measurements.

[b] Fatal case has been reported in the clinical study.

Description of selected adverse reactions

Immune-related pneumonitis
In patients treated with nivolumab in combination with relatlimab, pneumonitis, including interstitial lung disease and lung infiltration occurred in 5.1% of patients. Incidences of Grade 3/4 events were 0.8%. Fatal events occurred in 0.28% of patients. Median time to onset was 28 weeks (range: 3.6-94.4). Resolution occurred in 83.3% patients with a median time to resolution of 12.0 weeks (range: 2.1-29.7^{+}). Immune-related pneumonitis led to permanent discontinuation of nivolumab in combination with relatlimab in 1.7% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 55.6% of patients with immune-related pneumonitis.

Immune-related colitis
In patients treated with nivolumab in combination with relatlimab, diarrhoea, colitis, or frequent bowel movements occurred in 15.8% of patients. Incidences of Grade 3/4 events were 2.0%. Median time to onset was 14 weeks (range: 0.1-95.6). Resolution occurred in 92.7% patients with a median time to resolution of 3.9 weeks (range: 0.1-136.9^{+}). Immune-related colitis led to permanent discontinuation of nivolumab in combination with relatlimab in 2.0% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 33.9% of patients with immune-related colitis.

Immune-related hepatitis
In patients treated with nivolumab in combination with relatlimab, liver function test abnormalities occurred in 13.2% of patients. Incidences of Grade 3/4 events were 3.9%. Median time to onset was 11 weeks (range: 2.0-144.9). Resolution occurred in 78.7% patients with a median time to resolution of 6.1 weeks (range: 1.0-88.1^{+}). Immune-related hepatitis led to permanent discontinuation of nivolumab in combination with relatlimab in 2.0% of patients and required high dose corticosteroids in 38.3% of patients with immune-related hepatitis.

Immune-related nephritis and renal dysfunction
In patients treated with nivolumab in combination with relatlimab, nephritis or renal dysfunction occurred in 4.5% of patients. Incidences of Grade 3/4 events were 1.4%. Median time to onset was 21 weeks (range: 1.9-127.9). Resolution occurred in 81.3% patients with a median time to resolution of 8.1 weeks (range: 0.9-91.6^{+}). Immune-related nephritis and renal dysfunction led to permanent discontinuation of nivolumab in combination with relatlimab in 1.1% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 25.0% of patients with immune-related nephritis and renal dysfunction.

Immune-related endocrinopathies
In patients treated with nivolumab in combination with relatlimab, endocrinopathies occurred in 26% of patients.
Thyroid disorders, including hypothyroidism or hyperthyroidism, occurred in 20.8% of patients. There were no incidences of Grade 3/4 thyroid disorder. Adrenal insufficiency (including adrenocortical insufficiency acute) occurred in 4.8% of patients. Incidences of Grade 3/4 events adrenal insufficiency occurred in 1.4%. There were no incidences of Grade 3/4 hypopituitarism. Hypophysitis occurred in 1.1% of patients. Incidence of Grade 3/4 hypophysitis were 0.3%. Diabetes mellitus (including Type 1 diabetes mellitus) occurred in 0.3% of patients. Incidences of Grade 3/4 diabetes mellitus were in 0.3%.
Median time to onset of these endocrinopathies was 13 weeks (range: 1.0-73.0). Resolution occurred in 27.7% patients. Time to resolution ranged from 0.4 to 176.0^{+} weeks. Immune-related endocrinopathies led to permanent discontinuation of nivolumab in combination with relatlimab in 1.1% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 7.4% of patients with immune-related endocrinopathies.

Immune-related skin adverse reactions
In patients treated with nivolumab in combination with relatlimab, rash, including pruritis and vitiligo occurred in 45.1% of patients. Incidences of Grade 3/4 events were 1.4%. Median time to onset was

8 weeks (range: 0.1-116.4). Resolution occurred in 47.5% patients. Time to resolution ranged from 0.1-166.9+ weeks. Immune-related skin adverse reactions led to permanent discontinuation of nivolumab in combination with relatlimab in 0.3% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 3.8% of patients with immune-related skin adverse reactions.

Immune-related myocarditis
In patients treated with nivolumab in combination with relatlimab, myocarditis occurred in 1.4% of patients. Incidences of Grade 3/4 events were 0.6%. Median time to onset was 4.14 weeks (range: 2.1-6.3). Resolution occurred in 100% of patients with a median time to resolution of 3 weeks (1.9-14.0). Myocarditis led to permanent discontinuation of nivolumab in combination with relatlimab in 1.4% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 100% of patients with immune-related myocarditis.

Infusion-related reactions
In patients treated with nivolumab in combination with relatlimab, hypersensitivity/infusion reactions occurred in 6.8% of patients. All incidents were Grade 1/2.

Laboratory abnormalities
In patients treated with nivolumab in combination with relatlimab, the proportion of patients who experienced a shift from baseline to a Grade 3 or 4 laboratory abnormality was as follows: 3.6% for anaemia, 5.2% for lymphopaenia, 0.3% for neutropaenia, 0.6% for increased alkaline phosphatase, 2.9% for increased AST, 3.5% for increased ALT, 0.3% for increased total bilirubin, 0.9% for increased creatinine, 1.5% for hyponatraemia, 1.8% for hyperkalaemia, 0.3% for hypokalaemia, 0.9% for hypercalcaemia, 0.6% for hypocalcaemia, 0.9% for hypermagnesaemia, and 0.6% for hypomagnesaemia.

Immunogenicity
In study CA224047, out of the evaluable patients for anti-drug antibodies, the incidence of treatment-emergent anti-relatlimab antibodies and neutralizing antibodies against relatlimab in the Opdualag group were 5.6% (17/301) and 0.3% (1/301), respectively. The incidence of treatment-emergent anti-nivolumab antibodies and neutralizing antibodies against nivolumab in the Opdualag group were 4.0% (12/299) and 0.3% (1/299), respectively, which were similar to that observed in the nivolumab group 6.7% (19/283) and 0.4% (1/283), respectively. There was no evidence of an altered PK, efficacy, or safety profile with anti-nivolumab or anti-relatlimab antibody development.

Special populations

Elderly
Overall, no differences in safety were reported between elderly (≥ 65 years) and younger patients (see section 5.1).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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, ATC code: L01XY03.

Mechanism of action
Opdualag is a fixed-dose combination (FDC) of nivolumab, a programmed death-1 inhibitor (anti-PD-1) and relatlimab, a lymphocyte-activation gene-3 inhibitor (anti-LAG-3).

Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumours, and signalling through this pathway can contribute to inhibition of active T cell immune surveillance of tumours. Nivolumab is a human IgG4 monoclonal antibody that binds to the PD-1 receptor, blocks interaction with its ligands PD-L1 and PD-L2 and reduces PD-1 pathway-mediated inhibition of the immune response, including the anti-tumour immune response. In syngeneic mouse tumour models, blocking PD-1 activity resulted in decreased tumour growth.

Relatlimab is a human IgG4 monoclonal antibody that binds to the LAG-3 receptor, blocks its interaction with ligands, including MHC II, and reduces LAG-3 pathway-mediated inhibition of the immune response. Antagonism of this pathway promotes T cell proliferation and cytokine secretion.

The combination of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3) results in increased T-cell activation compared to the activity of either antibody alone. In murine syngeneic tumour models, LAG-3 blockade potentiates the anti-tumour activity of PD-1 blockage, inhibiting tumour growth and promoting tumour regression.

Clinical efficacy and safety

Randomised phase 2/3 study of nivolumab in combination with relatlimab vs. nivolumab in patients with previously untreated metastatic or unresectable melanoma (CA224047)
The safety and efficacy of nivolumab in combination with relatlimab for the treatment of patients with previously untreated metastatic or unresectable melanoma were evaluated in a phase 2/3, randomised, double-blinded study (CA224047). The study included patients with ECOG performance status score 0 or 1, and histologically confirmed stage III (unresectable) or stage IV melanoma per American Joint Committee on Cancer (AJCC) version 8. Patients were allowed to have received prior adjuvant or neoadjuvant melanoma therapy (anti-PD-1, anti-CTLA-4, or BRAF-MEK therapy was allowed as long as there was at least 6 months between the last dose of therapy and date of recurrence; interferon therapy was allowed as long as the last dose was at least 6 weeks prior to randomisation). Patients with active autoimmune disease, a history of myocarditis, elevated troponin levels > 2 times ULN, or ECOG performance status score ≥ 2, medical conditions requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medicinal products, uveal melanoma, and active or untreated brain or leptomeningeal metastases were excluded from the study (see section 4.4).

A total of 714 patients were randomised to receive either nivolumab in combination with relatlimab (n = 355), or nivolumab (n = 359). Patients in the combination arm received 480 mg nivolumab/160 mg relatlimab over 60 minutes every 4 weeks. Patients in the nivolumab arm received nivolumab 480 mg every 4 weeks. Randomisation was stratified by tumour PD-L1 (≥ 1% vs. < 1) using PD-L1 IHC 28-8 pharmDx test, and LAG-3 expression (≥ 1% vs. < 1) as determined by an analytically validated LAG-3 IHC assay, BRAF V600 mutation status, and M stage per the AJCC version 8 staging system (M0/M1any[0] vs. M1any[1]). Patients were treated until disease progression or unacceptable toxicity. Tumour assessments, according to the Response Evaluation Criteria in Solid Tumours (RECIST), version 1.1, were conducted 12 weeks after randomisation and continued every 8 weeks up to 52 weeks and then every 12 weeks until disease progression or treatment discontinuation, whichever occurred later. The primary efficacy outcome measure was progression-free survival determined by Blinded Independent Central Review (BICR). The secondary efficacy outcome measures were overall survival (OS), and overall response rate (ORR) by BICR. The

hierarchical statistical testing order was PFS followed by OS and then ORR. The primary and secondary outcome measures were evaluated in the intention to treat (ITT) population. No formal testing of ORR was conducted since the formal comparison of OS was not statistically significant.

Baseline characteristics in the ITT population were balanced between the two groups. The median age was 63 years (range: 20-94) with 47% ≥ 65 years of age and 19% ≥ 75 years of age. The majority of patients were white (97%) and male (58%). Baseline ECOG performance status was 0 (67%) or 1 (33%). The majority of the patients had AJCC Stage IV disease (92%); 38.9% had M1c, 2.4% had M1d disease, 8.7% had prior systemic therapies, 36% had a baseline LDH level greater than ULN at study entry. Thirty nine percent of patients had BRAF mutation-positive melanoma, 75% had LAG-3 ≥ 1% and 41% of patients had PD-L1 ≥ 1% tumour cell membrane expression. Among patients with quantifiable tumour PD-L1 expression, the distribution of patients was balanced across the two treatment groups. The demographics and baseline disease characteristics in patients with PD-L1 expression < 1% were generally balanced between the treatment arms.

At primary analysis in the ITT population, with median follow-up of 13.21 months (range: 0-33.1 months), a statistically significant improvement in PFS was observed with a median PFS of 10.12 months in the nivolumab in combination with relatlimab group as compared with 4.63 months in the nivolumab group (HR = 0.75, 95% CI: 0.62, 0.92; p = 0.0055). At the time of the pre-specified final OS analysis in the ITT population, with median follow up of 19.3 months, OS was not statistically significant (HR = 0.80, 95% CI: 0.64, 1.01).

Pre-specified subgroup analysis by PD-L1 expression < 1%

The key efficacy results for the subgroup of patients with tumour PD-L1 expression < 1% from an exploratory analysis with median follow-up of 17.78 months (range: 0.26-40.64 months) are summarised in Table 3.

Table 3: Efficacy results in patients with PD-L1 < 1% tumour cell expression (CA224047)

	nivolumab + relatlimab (n = 209)	**nivolumab (n = 212)**
Progression-free survival		
Hazard ratio (95% CI)[a]	0.68 (0.53, 0.86)	
Median in months	6.7	3.0
(95% CI)	(4.7, 12.0)	(2.8, 4.5)
Rate (95% CI) at 12 months	42.3	26.9
	(35.1, 49.4)	(20.9, 33.3)
Overall survival[b]		
Hazard ratio (95% CI)[a]	0.78 (0.59, 1.04)	
Median in months	NR	27.0
(95% CI)	(27.4, NR)	(17.1, NR)
Rate (95% CI) at 12 months	73.9	67.4
	(67.4, 79.4)	(60.6, 73.3)
Rate (95% CI) at 24 months	59.6	53.1
	(52.2, 66.2)	(45.8, 59.9)
Overall response rate (%)	36.4	24.1
(95% CI)	(29.8, 43.3)	(18.5, 30.4)
Complete response rate (%)	25 (12.0)	20 (9.4)
Partial response rate (%)	51 (24.4)	31 (14.6)
Stable disease rate (%)	41 (19.6)	31 (14.6)

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

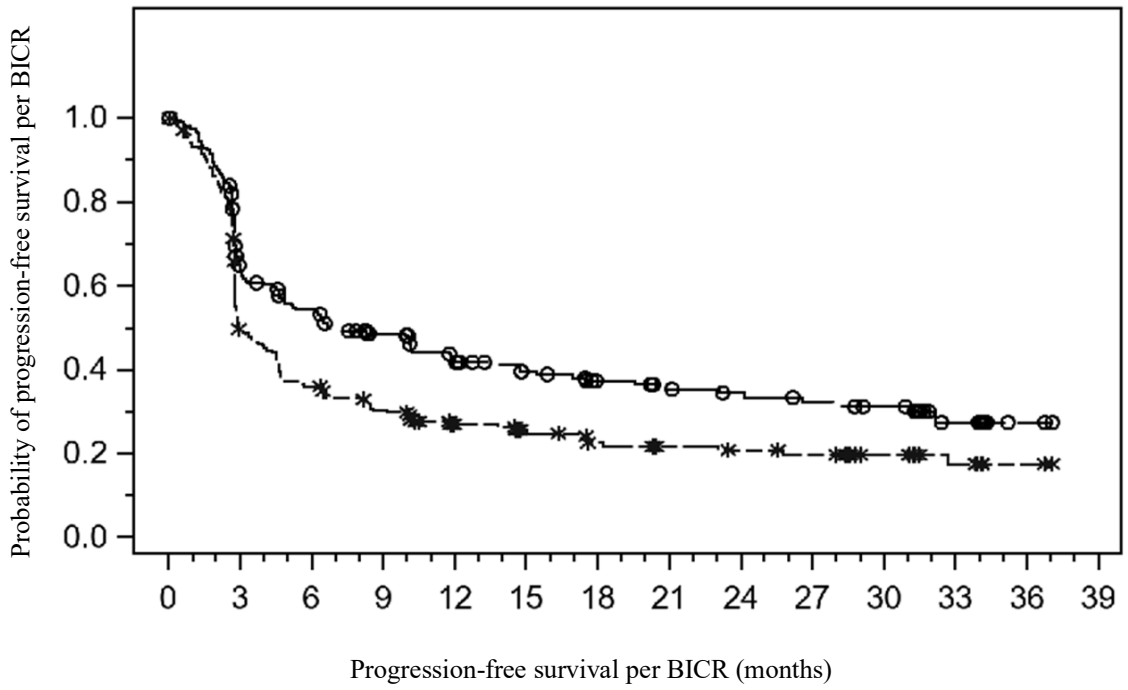
[b] OS results are not yet mature.

Median extent of follow-up: 17.78 months.

NR = not reached.

The Kaplan-Meier curves for PFS and OS in patients with tumour cell PD-L1 expression < 1% are presented in Figures 1 and 2, respectively.

Figure 1: Kaplan-Meier curves of PFS in patients with PD-L1 < 1% tumour cell expression (CA224047)

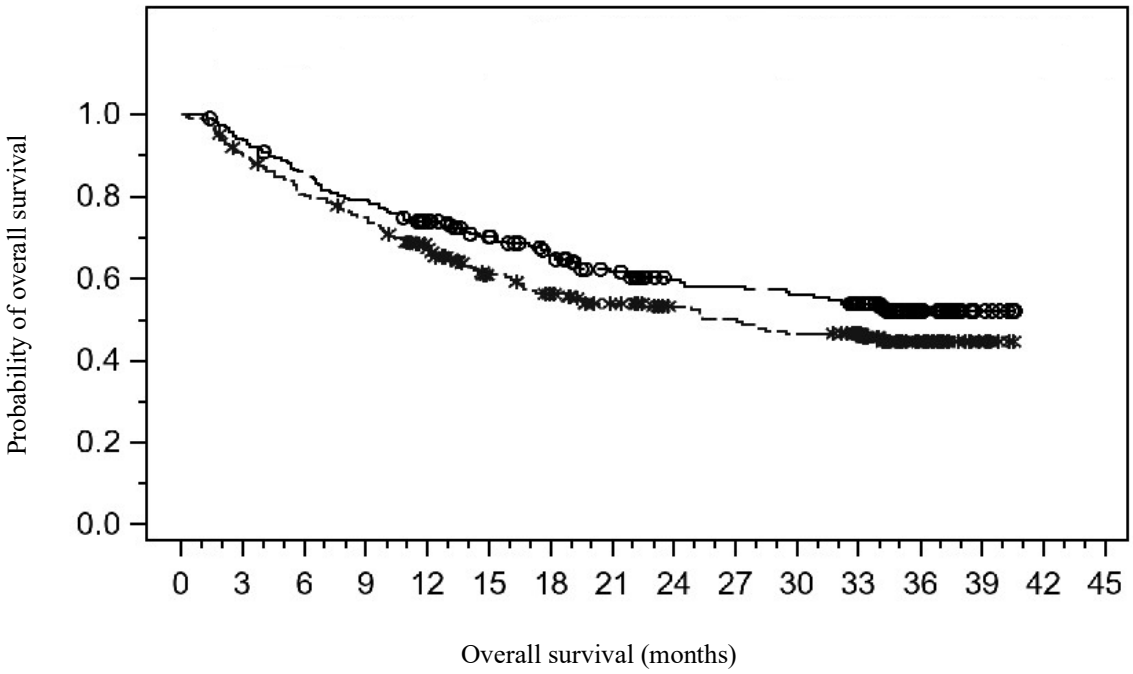


Number of subjects at risk

Nivolumab/relatlimab												
209	122	99	80	65	53	44	36	33	30	27	9	2	0
Nivolumab												
212	98	71	57	41	34	27	24	22	20	14	8	2	0

----❍---- Nivolumab/relatlimab (events: 124/209), median (95% CI): 6.67 months (4.67, 11.99)
- - -✳- - - Nivolumab (events: 155/212), median (95% CI): 2.96 months (2.79, 4.50)

Figure 2: Kaplan-Meier curves of OS in patients with PD-L1 < 1% tumour cell expression (CA224047)



Number of subjects at risk

Nivolumab/relatlimab														
209	195	177	164	147	128	114	98	85	83	80	68	29	6	0
Nivolumab														
212	189	168	155	132	106	94	82	72	68	63	56	27	6	0

----❍---- Nivolumab/relatlimab (events: 89/209), median (95% CI): N.A. (27.43, N.A.)
- - -✳- - - Nivolumab (events: 104/212), median (95% CI): 27.04 months (17.12, N.A.)

5.2 Pharmacokinetic properties

The pharmacokinetics (PK) of relatlimab following the administration of nivolumab in combination with relatlimab was characterised in patients with various cancers who received relatlimab doses of 20 to 800 mg every 2 weeks and 160 to 1440 mg every 4 weeks either as a monotherapy or in combination with nivolumab doses of 80 or 240 mg every 2 weeks or 480 mg every 4 weeks.

Steady-state concentrations of relatlimab were reached by 16 weeks with an every 4-week regimen and the systemic accumulation was 1.9-fold. The average concentration (C_{avg}) of relatlimab after the first dose increased dose proportionally at doses ≥ 160 mg every 4 weeks.

Table 4: Geometric mean (CV%) of nivolumab and relatlimab steady-state exposures following 480 mg nivolumab and 160 mg relatlimab fixed-dose combination every 4 weeks

	C_{max} (µg/mL)	**C_{min} (µg/mL)**	**C_{avg} (µg/mL)**
Relatlimab	62.2 (30.1)	15.3 (64.3)	28.8 (44.8)
Nivolumab	187 (32.9)	59.7 (58.6)	94.4 (43.3)

Based on population PK analyses, the nivolumab and relatlimab FDC infusion duration of 30 min and 60 min were predicted to produce similar (< 1% different) exposures of nivolumab and relatlimab.

In CA224047, the nivolumab geometric mean C_{min} at steady state in the nivolumab in combination with relatlimab arm was similar to the nivolumab arm with a geometric mean ratio of 0.931 (95% CI: 0.855-1.013).

Distribution
The geometric mean value (CV%) for nivolumab volume of distribution at steady state is 6.65 L (19.2%) and relatlimab is 6.65 L (19.8%).

Biotransformation
Nivolumab and relatlimab are therapeutic mAb IgG4 that are expected to be catabolised into small peptides, amino acids, and small carbohydrates by lysosome or receptor-mediated endocytosis.

Elimination
Nivolumab clearance is 21.1% lower [geometric mean (CV%), 7.57 mL/h (40.1%)] at steady state than that after the first dose [9.59 mL/h (40.3%)] and the terminal half-life (t1/2) is 26.5 days (36.4%).

Relatlimab clearance is 9.7% lower [geometric mean (CV%), 5.48 mL/h (41.3%)] at steady state than that after the first dose [6.06 mL/h (38.9%)]. Following administration of relatlimab 160 mg and nivolumab 480 mg administered every 4 weeks, the geometric mean (CV%) effective half-life (t1/2) of relatlimab is 26.2 days (37%).

Special populations
A population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab and relatlimab: age (range: 17 to 92 years), sex, [male (1056) and female (657)], or race [Caucasian (1655), African American (167) and Asian (41)]. The body weight (range: 37 to 170 kg) was a significant covariate on the nivolumab and relatlimab PK, however, there is no clinically relevant impact based on exposure-response analysis.

Paediatric population
Limited data suggest that nivolumab clearance and volume of distribution in adolescent subjects with solid tumours were 36% and 16% lower, respectively, than those of adult reference patients. It is unknown if the same holds for melanoma patients and if relatlimab clearance and volume of distribution are also lower in adolescents than adults. However, based on population PK simulations, the exposure of nivolumab and relatlimab in adolescents weighing at least 30 kg are expected to result in similar safety and efficacy to that of adults of the same weight, at the same recommended dose.

Renal impairment
The effect of renal impairment on the clearance of nivolumab and relatlimab was evaluated by a population PK analysis in patients with mild or moderate renal impairment compared to patients with normal renal function. No clinically important differences in the clearance of nivolumab or relatlimab were found between patients with renal impairment and patients with normal renal function.

Hepatic impairment
The effect of hepatic impairment on the clearance of nivolumab and relatlimab was evaluated by population PK analysis in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to upper limit of normal [ULN] and AST greater than ULN or TB greater than 1 to 1.5 times ULN and any AST) or moderate hepatic impairment (TB greater than 1.5 to 3 times ULN and any AST) compared to patients with normal hepatic function. No clinically important differences in the clearance of nivolumab or relatlimab were found between patients with hepatic impairment and patients with normal hepatic function.

Immunogenicity
The observed low incidence rate of treatment emergent anti-nivolumab antibody and treatment emergent anti-relatlimab antibody had no effects on PK of nivolumab and relatlimab.

5.3 Preclinical safety data

Nivolumab in combination with relatlimab
No animal studies were conducted with nivolumab in combination with relatlimab to evaluate potential carcinogenicity, genotoxicity or reproductive and developmental toxicity.

In a 1-month study in monkeys dosed with nivolumab and relatlimab, inflammation within the central nervous system (choroid plexus, vasculature, meninges, spinal cord) and the reproductive tract (epididymis, seminal vesicles and testes) was observed. Although safety margins were not established for these effects with the combination, they ocurred at doses that suppose exposure levels significantly higher (13 folds for nivolumab and 97 folds for relatlimab) than those reached in patients.

Relatlimab
There are no available animal data on effect of relatlimab on pregnancy and reproduction. In a embryo-foetal toxicity study in mice using murine anti-LAG-3 antibodies, no maternal or developmental effects were observed. The effects of relatlimab on prenatal and postnatal development have not been evaluated; however, based on the mechanism of action, blockade of LAG-3 with relatlimab can have a similar negative effect as nivolumab on pregnancy. There were no fertility studies performed with relatlimab.

Nivolumab
Blockade of the PD-1/PD-L1 pathway 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 their mechanism of action, foetal exposure to nivolumab, and, similarly, relatlimab, 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 and PD-1/LAG-3 knockout mice. Fertility studies have not been performed with nivolumab.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine hydrochloride monohydrate
Sucrose
Pentetic acid (diethylenetriaminepentaacetic acid)
Polysorbate 80 (E433)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. Opdualag 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 2 °C to 8 °C 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 (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	24 hours (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 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions (see section 6.6).

6.4 Special precautions for storage

Store in a refrigerator (2 °C-8 °C).
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
The unopened vials can be stored at controlled room temperature (up to 25 °C) for up to 72 hours.
For storage conditions after preparation of the infusion, see section 6.3.

6.5 Nature and contents of container

Pack of one 25 mL vial (Type I glass), with a stopper (coated butyl rubber) and a yellow flip-off aluminium seal. Each vial is filled with 21.3 mL of solution, which includes an overfill of 1.3 mL.

6.6 Special precautions for disposal and other handling

Opdualag is supplied as a single-dose vial and does not contain any preservatives. Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Opdualag 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 3 mg/mL of nivolumab and 1 mg/mL of relatlimab to 12 mg/mL of nivolumab and 4 mg/mL of relatlimab
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion should not exceed 4 mL per kilogram of patient weight.

Opdualag 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.

Preparing the infusion
- Inspect the Opdualag concentrate for particulate matter or discolouration. Do not shake the vial. Opdualag is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured, or contains extraneous particulate matter.

- Withdraw the required volume of Opdualag concentrate using an appropriate sterile syringe and transfer the concentrate into a sterile, intravenous container (ethylvinyl acetate (EVA), polyvinyl chloride [PVC], or polyolefin).
- If applicable, dilute Opdualag solution 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
Opdualag infusion must not be administered as an intravenous push or bolus injection.

Administer the Opdualag infusion intravenously over a period of 30 minutes.
Use of an infusion set and an in-line or add-on, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm) is recommended.

Opdualag infusion is compatible with EVA, PVC and polyolefin containers, PVC infusion sets and in-line filters with polyethersulfone (PES), nylon, and polyvinylidene fluoride (PVDF) membranes with pore sizes of 0.2 µm to 1.2 µm.
Do not co-administer other medicinal products through the same infusion line.
After administration of the Opdualag 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. MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1679/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substances

Bristol-Myers Squibb Co.
38 Jackson Road
Devens, MA 01434
USA

Name and address of the manufacturer responsible for batch release

Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH shall ensure that in each Member State where Opdualag is marketed, all healthcare professionals and patients/caregivers who are expected to prescribe and use Opdualag have access to/are provided with the patient card.

The Patient Card shall contain the following key messages:

- That Opdualag treatment may increase the risk of:
  - Immune-related pneumonitis
  - Immune-related colitis
  - Immune-related hepatitis
  - Immune-related endocrinopathies
  - Immune-related nephritis and renal dysfunction
  - Immune-related skin ARs
  - Immune-related myocarditis
  - Other immune-related ARs
- Signs or symptoms of the safety concern and when to seek attention from a HCP
- Contact details of the Opdualag prescriber

The MAH shall agree about the format and content of the above educational material with the National Competent Authority prior to launch of Opdualag in each Member State.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Opdualag 240 mg/80 mg concentrate for solution for infusion
nivolumab/relatlimab

2. STATEMENT OF ACTIVE SUBSTANCES

Each mL of concentrate contains 12 mg of nivolumab and 4 mg of relatlimab.
One vial of 20 mL contains 240 mg of nivolumab and 80 mg of relatlimab.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
Intravenous use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1679/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT

Opdualag 240 mg/80 mg sterile concentrate
nivolumab/relatlimab

2. STATEMENT OF ACTIVE SUBSTANCES

Each mL of concentrate contains 12 mg of nivolumab and 4 mg of relatlimab.
One vial of 20 mL contains 240 mg of nivolumab and 80 mg of relatlimab.

3. LIST OF EXCIPIENTS

Excipients: histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Sterile concentrate
20 mL

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
IV use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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B. PACKAGE LEAFLET

Package leaflet: Information for the user

Opdualag 240 mg/80 mg concentrate for solution for infusion
nivolumab/relatlimab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- It is important that you keep the patient card with you at all times.
- If you have any further questions, ask your doctor.
- If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Opdualag is and what it is used for

Opdualag is a cancer medicine used to treat advanced melanoma (a type of skin cancer that can spread elsewhere in the body). It can be used in adults and in adolescents 12 years of age and older.

Opdualag contains two active substances: nivolumab and relatlimab. Both active substances are monoclonal antibodies, proteins designed to recognise and attach to a specific target substance in the body. Nivolumab attaches to a target protein called PD 1. Relatlimab attaches to a target protein called LAG-3.

PD 1 and LAG-3 can switch off the activity of T cells (a type of white blood cell that forms part of the immune system, the body's natural defences). By attaching to the two proteins, nivolumab and relatlimab block their actions and prevent them from switching off your T cells. This helps increase the T cell activity against the melanoma cancer cells.

2. What you need to know before you are given Opdualag

You should not be given Opdualag
- if you are allergic to nivolumab, relatlimab or any of the other ingredients of this medicine (listed in section 6). Talk to your doctor if you are not sure.

Warnings and precautions

Talk to your doctor before you get Opdualag as it may cause:
- Problems with your lungs such as breathing difficulties or cough. These may be signs of inflammation of the lungs (pneumonitis or interstitial lung disease).
- Diarrhoea (watery, loose or soft stools) or inflammation of the intestines (colitis) with symptoms such as stomach pain and mucus or blood in stool.

- Inflammation of the liver (hepatitis). Signs and symptoms of hepatitis may include abnormal liver function tests, eye or skin yellowing (jaundice), pain in the right side of your stomach area, or tiredness.
- Inflammation of or problems with your kidneys. Signs and symptoms may include abnormal kidney function tests, or decrease in amount of urine.
- Problems with your hormone producing glands (including the pituitary, thyroid and adrenal glands), which may affect how these glands work. Signs and symptoms that these glands are not working properly may include fatigue (extreme tiredness), weight change or headache and visual disturbances.
- Diabetes including a serious, sometimes life-threatening problem due to acid in the blood produced from diabetes (diabetic ketoacidosis). Symptoms may include feeling more hungry or thirsty than usual, need to urinate more often, weight loss, feeling tired or having difficulty thinking clearly, breath that smells sweet or fruity, a sweet or metallic taste in your mouth, or a different odour to your urine or sweat, feeling sick or being sick, stomach pain, and deep or fast breathing.
- Inflammation of the skin that can lead to severe skin reaction (known as toxic epidermal necrolysis and Stevens-Johnson syndrome). Signs and symptoms of severe skin reaction may include rash, itching, and peeling of the skin (possibly fatal).
- Inflammation of the heart muscle (myocarditis). Signs and symptoms may include chest pain, irregular and/or rapid heartbeat, fatigue, swelling in the ankles or shortness of breath.
- Haemophagocytic lymphohistiocytosis. A rare disease in which your immune system makes too many otherwise normal infection-fighting cells called histiocytes and lymphocytes. Symptoms may include enlarged liver and/or spleen, skin rash, swollen lymph glands, breathing problems, easy bruising, kidney abnormalities, and heart problems.
- Solid organ transplant rejection.
- Graft-versus-host disease after stem cell transplantation (where the transplanted cells from a donor attack your own cells). If you have received one of these transplants, your doctor will consider whether you should receive treatment with Opdualag. Graft-versus-host disease can be severe and can lead to death.
- Infusion reactions, which may include shortness of breath, itching or rash, dizziness or fever.

Tell your doctor immediately if you have any of these signs or symptoms or if they get worse. Do not try to treat your symptoms with other medicines on your own. Your doctor may
- give you other medicines to prevent complications and reduce your symptoms,
- skip your next dose of Opdualag,
- or stop your treatment with Opdualag altogether.

Please note that these signs and symptoms are sometimes delayed and may develop weeks or months after your last dose. Before treatment, your doctor will check your general health. You will also have blood tests during your treatment.

Check with your doctor or nurse before you are given Opdualag if:
- you have an active autoimmune disease (a condition where the body attacks its own cells);
- you have melanoma of the eye;
- you have been told that your cancer has spread to your brain;
- you have been taking medicines to suppress your immune system.

Children and adolescents
Opdualag should not be used in children below 12 years of age.

Other medicines and Opdualag
Before you are given Opdualag, tell your doctor if you are taking any medicines that suppress your immune system, such as corticosteroids, since these medicines may interfere with the effect of Opdualag. However, once you are treated with Opdualag, your doctor may give you corticosteroids to reduce any possible side effects that you may have during your treatment.
Tell your doctor if you are taking, have recently taken or are planning to take any other medicines. Do not take any other medicines during your treatment without talking to your doctor first.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Do not use Opdualag if you are pregnant unless your doctor specifically tells you to. The effects of Opdualag in pregnant women are not known, but it is possible that the active substances, nivolumab and relatlimab, could harm an unborn baby.
- You must use effective contraception while you are being treated with Opdualag and for at least 5 months following the last dose of Opdualag, if you are a woman who could become pregnant.
- If you become pregnant while using Opdualag tell your doctor.

It is not known whether Opdualag can pass into breast milk and affect a baby that is breast-fed. Talk to your doctor about the benefits and risks before breast-feeding during or after treatment with Opdualag.

Driving and using machines
Opdualag has a minor influence on the ability to drive and use machines; however, use caution when performing these activities until you are sure that Opdualag does not adversely affect you.

Patient card
You will also find key messages from this package leaflet on the patient card you have been given by your doctor. It is important that you keep this patient card at all times and show it to your partner or caregivers.

3. How to use Opdualag

How much Opdualag is given
The recommended dose by infusion in adults and adolescents 12 years of age and older is 480 mg nivolumab and 160 mg relatlimab every 4 weeks. This dose is established for adolescent patients weighing at least 30 kg.

Depending on your dose, the appropriate amount of Opdualag may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection before use. Opdualag may also be used undiluted.

How Opdualag is given
You will receive treatment with Opdualag in a hospital or clinic, under the supervision of an experienced doctor.

Opdualag will be given to you as an infusion (a drip) into a vein, every 4 weeks. Each infusion takes about 30 minutes to give.

Your doctor will continue treating you with Opdualag for as long as you keep benefitting from it or until side effects become too severe.

If you miss a dose of Opdualag
It is very important for you to keep all your appointments to receive Opdualag. If you miss an appointment, ask your doctor when to schedule your next dose.

If you stop using Opdualag
Stopping your treatment may stop the effect of the medicine. Do not stop treatment with Opdualag unless you have discussed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. Your doctor will discuss these with you and will explain the risks and benefits of your treatment.

Be aware of important symptoms of inflammation (described in section 2 under 'warnings and precautions'). Opdualag acts on your immune system and may cause inflammation in parts of your body. Inflammation may cause serious damage to your body and some inflammatory conditions may be life-threatening and need treatment or withdrawal of Opdualag.

The following side effects have been reported with Opdualag:

Very common (may affect more than 1 in 10 people)
- infection of the urinary tract (the parts of the body that collect and pass out urine)
- decreased number of red blood cells (which carry oxygen) and white blood cells (lymphocytes, neutrophils, leucocytes; which are important in fighting infection)
- underactive thyroid gland (which can cause tiredness or weight gain)
- decreased appetite
- headache
- difficulty breathing, cough
- diarrhoea (watery, loose or soft stools), vomiting; nausea; stomach pain; constipation
- skin rash (sometimes with blisters), skin colour change in patches (vitiligo), itching
- pain in the muscles, bones and joints
- feeling tired or weak, fever.

Changes in the results of tests carried out by your doctor may show:
- abnormal liver function (increased amounts of the liver enzymes alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase in your blood)
- abnormal kidney function (increased amounts of creatinine in your blood)
- decrease of sodium and magnesium, and decrease or increase of calcium and potassium.

Common (may affect up to 1 in 10 people)
- infections of the upper respiratory tract (nose and upper airways)
- decreased number of platelets (cells which help the blood to clot), increase in some white blood cells
- decreased secretion of hormones produced by adrenal glands (glands situated above the kidneys), inflammation of the pituitary gland situated at the base of the brain, overactive thyroid gland, inflammation of the thyroid gland
- diabetes, low sugar levels in the blood; weight loss, high levels of the waste product uric acid in the blood, decreased levels of the protein albumin in the blood, dehydration
- state of confusion
- inflammation of the nerves (causing numbness, weakness, tingling or burning pain of the arms and legs), dizziness, changes in the sense of taste
- inflammation of the eye (which causes pain and redness, vision problems or blurry vision), vision problems, dry eyes, excessive tear production
- inflammation of the heart muscle
- inflammation of a vein, which can cause redness, tenderness and swelling
- inflammation of the lungs (pneumonitis), characterised by coughing and difficulty breathing; nasal congestion (blocked nose)
- inflammation of the intestines (colitis), inflammation of the pancreas, inflammation of the stomach (gastritis), difficulty swallowing, mouth ulcers and cold sores; dry mouth
- inflammation of the liver (hepatitis)
- unusual hair loss or thinning (alopecia), isolated area of skin growth that becomes red and itchy (lichenoid keratosis), sensitivity to light, dry skin
- painful joints (arthritis), muscle spasms, muscle weakness
- kidney failure (changes in amount or colour of urine, blood in urine, swelling ankles, loss of appetite), high levels of proteins in the urine

- oedema (swelling), flu-like symptoms, chills
- reactions related to the administration of the medicine.

Changes in the results of tests carried out by your doctor may show:
- abnormal liver function (higher blood levels of the waste product bilirubin, higher blood levels of the liver enzyme gamma-glutamyl transferase)
- increase in sodium and magnesium
- increased level of troponin (a protein released into the blood when the heart is damaged)
- increased level of the enzyme that breaks down glucose (sugar) (lactate dehydrogenase), the enzyme that breaks down fats (lipase), the enzyme that breaks down starch (amylase)

Uncommon (may affect up to 1 in 100 people)
- inflammation and infection in the hair follicles
- disorder in which red blood cells are destroyed faster than they can be made (haemolytic anaemia)
- underactive function of the pituitary gland situated at the base of the brain; underactive function of the glands producing sex hormones
- inflammation of the brain, which may include confusion, fever, memory problems or seizures (encephalitis), a temporary inflammation of the nerves that causes pain, weakness, and paralysis in the extremities (Guillain-Barré syndrome), inflammation of the optic nerve that may cause a complete or partial loss of vision
- an inflammatory disorder affecting the eyes, skin and the membranes of the ears, brain and spinal cord (Vogt-Koyanagi-Harada disease), red eye
- fluid around the heart
- asthma
- inflammation of the oesophagus (passage between throat and stomach)
- inflammation of the bile duct
- skin rashes and blistering on the legs, arms, and abdomen (pemphigoid), skin disease with thickened patches of red skin, often with silvery scales (psoriasis), hives (itchy, bumpy rash)
- inflammation of the muscles causing weakness, swelling, and pain, disease in which the immune system attacks the glands that make moisture for the body, such as tears and saliva (Sjogren's syndrome), inflammation of muscles causing pain or stiffness, inflammation of the joints (painful joint disease), disease in which the immune system attacks its own tissues, causing widespread inflammation and tissue damage in the affected organs, such as joints, skin, brain, lungs, kidneys, and blood vessels (systemic lupus erythematosus)
- inflammation of the kidney
- absence of sperm in the semen.

Changes in the results of tests carried out by your doctor may show:
- increase in level of c-reactive protein
- red blood cell sedimentation rate increased.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Opdualag

Opdualag will be given to you in a hospital or clinic and the healthcare professionals will be responsible for its storage.

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 °C - 8 °C).

Do not freeze.
Keep the vial in the outer carton in order to protect from light.
The unopened vial can be stored at controlled room temperature (up to 25 °C) for up to 72 hours.

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

6. Contents of the pack and other information

What Opdualag contains

- The active substances are nivolumab and relatlimab.
  Each mL of concentrate for solution for infusion contains 12 mg of nivolumab and 4 mg of relatlimab.
  One vial of 20 mL concentrate contains 240 mg nivolumab and 80 mg relatlimab.

- The other ingredients are histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid, polysorbate 80 (E433) and water for injections.

What Opdualag looks like and contents of the pack
Opdualag concentrate for solution for infusion (sterile concentrate) is a clear to opalescent, colourless to slightly yellow liquid that is essentially free of particles.
It is available in cartons containing one glass vial.

Marketing Authorisation Holder
Bristol-Myers Squibb Pharma EEIG
Plaza 254
Blanchardstown Corporate Park 2
Dublin 15, D15 T867
Ireland

Manufacturer
Swords Laboratories Unlimited Company t/a Bristol-Myers Squibb Cruiserath Biologics
Cruiserath Road, Mulhuddart
Dublin 15, D15 H6EF
Ireland

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

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The following information is intended for healthcare professionals only:

Opdualag is supplied as a single-dose vial and does not contain any preservatives. Preparation should be performed by trained personnel in accordance with good practices rules, especially with respect to asepsis.

Opdualag 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 3 mg/mL nivolumab and 1 mg/mL relatlimab to 12 mg/mL nivolumab and 4 mg/mL relatlimab.
  - the total volume of infusion must not exceed 160 mL. For patients weighing less than 40 kg, the total volume of infusion should not exceed 4 mL per kilogram of patient weight.

Opdualag 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.

Preparing the infusion
- Inspect the Opdualag concentrate for particulate matter or discolouration. Do not shake the vial. Opdualag is a clear to opalescent, colourless to slightly yellow solution. Discard the vial if the solution is cloudy, discoloured, or contains extraneous particulate matter.
- Withdraw the required volume of Opdualag concentrate using an appropriate sterile syringe and transfer the concentrate into a sterile, intravenous container (ethylvinyl acetate (EVA), polyvinyl chloride (PVC), or polyolefin). Each vial is filled with 21.3 mL of solution, which includes an overfill of 1.3 mL.
- If applicable, dilute Opdualag solution 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
Opdualag infusion must not be administered as an intravenous push or bolus injection.

Administer the Opdualag infusion intravenously over a period of 30 minutes.
Use of an infusion set and an in-line or add-on filter, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm to 1.2 µm) is recommended.

Opdualag infusion is compatible with EVA, PVC and polyolefin containers, PVC infusion sets and in-line filters with polyethersulfone (PES), nylon, and polyvinylidene fluoride (PVDF) membranes with pore sizes of 0.2 µm to 1.2 µm.

Do not co-administer other medicinal products through the same infusion line.
After administration of the Opdualag dose, flush the line with sodium chloride 9 mg/mL (0.9%) solution for injection or 50 mg/mL (5%) glucose solution for injection.

Storage conditions and shelf life

Unopened vial
Opdualag must be **stored in a refrigerator** (2 °C to 8 °C). The vials must be kept in the original package in order to protect from light. Opdualag should not be frozen.
The unopened vial can be stored at controlled room temperature (up to 25 °C) for up to 72 hours.

Do not use Opdualag after the expiry date which is stated on the carton and the vial label after EXP. The expiry date refers to the last day of that month.

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 2 °C to 8 °C 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 (of total 30 days storage)
Diluted with 50 mg/mL (5%) glucose solution for injection	7 days	24 hours (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 24 hours at 2 °C to 8 °C, unless preparation has taken place in controlled and validated aseptic conditions.

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.