swissmedic

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Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Opdualag

International non-proprietary name:	nivolumab, relatlimab
Pharmaceutical form:	concentrate for solution for infusion
Dosage strength(s):	240 mg nivolumab/80 mg relatlimab/ 20 ml
Route(s) of administration:	intravenous use
Marketing authorisation holder:	Bristol-Myers Squibb SA
Marketing authorisation no.:	68609
Decision and decision date:	extension of therapeutic indication approved on 20 April 2026

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

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1 Terms, definitions, abbreviations

AE	Adverse event
BRAF	Serine/threonin-protein kinase B-Raf
CI	Confidence interval
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DCO	Data cut-off
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
HR	Hazard ratio
ITT	Intention-to-treat
MAH	Marketing Authorisation Holder
Max	Maximum
MEK	Mitogen-activated protein kinase kinase
Min	Minimum
N/A	Not applicable
NCCN	National Comprehensive Cancer Network
ORR	Objective response rate
OS	Overall survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

2 Background information on the procedure

2.1 Applicant's request(s) and information regarding procedure

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved indication in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Opdualag is indicated for the first-line treatment of adults with unresectable or metastatic melanoma.

2.2.2 Approved indication

Opdualag is indicated for the first-line treatment of adults with unresectable or metastatic melanoma (see "Properties/Effects").

2.2.3 Requested dosage

No change to the dosage recommendation was requested with the application for extension of indication.

2.2.4 Approved dosage

(See appendix)

2.3 Regulatory history (milestones)

Application	31 October 2025
Formal control completed	12 November 2025
Preliminary decision	9 March 2026
Response to preliminary decision	25 March 2026
Final decision	20 April 2026
Decision	approval

3 Medical context

Cutaneous melanoma is the most common and lethal type of cutaneous neoplasia. Incidence of malignant melanoma in 2022 in Europe was 21.5 per 100,000 and mortality was 3.5 per 100,000 in both sexes (age standardised rate) (source: ECIS – European Cancer Information System).

The current first-line standard of care treatment options for unresectable stage III/IV melanoma recommended by international guidelines are PD-1 blockade, PD-1 blockade combined with CTLA-4 blockade, PD-1 blockade combined with lymphocyte activation gene-3 (LAG-3) blockade, and, for BRAF V600-mutated melanoma, BRAF inhibitors combined with MEK inhibitors.

The fixed dose combination relatlimab + nivolumab is approved in Switzerland for patients with PD-L1 tumour expression of <1%.

4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested extension of the indication. This was considered acceptable. Based on the ERA, the extension of the indication will not be associated with a significant risk for the environment.

5 Clinical aspects

5.1 Clinical pharmacology

No new data were provided.

5.2 Dose finding and dose recommendation

No new dose finding studies were provided.

5.3 Efficacy

The applicant submitted updated descriptive efficacy analyses and safety results with data cut-off (DCO) of 24 September 2024 from the RELATIVITY-047 study. This study also served as the pivotal study for initial authorisation in patients with locally advanced and metastatic melanoma with PD-L1 tumour expression of <1% (see SwissPAR Opdualag, dated 19 April 2023).

RELATIVITY-047 is a 1:1 randomised, active-controlled, double-blind, global, phase 2/3 study comparing relatlimab + nivolumab (Opdualag) to nivolumab monotherapy. For details regarding study design, patient population and treatment, please refer to the attached Information for healthcare professionals.

As at DCO September 2024, the hazard ratio (HR) for the primary endpoint of progression-free survival (PFS) in the ITT population (irrespective of PD-L1 expression) in patients treated with Opdualag compared to nivolumab monotherapy was 0.78 (95%CI 0.65, 0.93), and the median PFS was 10.2 months vs. 4.6 months. The key secondary endpoint of overall survival (OS) showed a HR of 0.77 (95%CI 0.64, 0.94) with a median OS of 53.3 months in the Opdualag arm compared to 33.2 months in the nivolumab arm.

Subgroup results based on the stratification factor of PD-L1 expression ≥/< 1% showed a PFS HR of 0.68 (95%CI 0.54, 0.85) in patients with PD-L1<1% tumour expression and 0.95 (95%CI 0.71, 1.28) in patients with PD-L1 ≥1%. This was consistent with the previous DCO of 7 September 2021 (PD-L1<1%: HR 0.68 [95%CI 0.53, 0.86]; PD- L1 ≥1%: HR 0.96 [95%CI 0.70, 1.31]). Regarding OS, the HR for the PD-L1 ≥1% subgroup was 0.76 (95%CI 0.55, 1.05) in the Opdualag arm compared to nivolumab alone and the Kaplan-Meier (KM) curves showed late separation, at around 30 months, in favour of Opdualag. No OS detriment was observed in subgroups with PD-L1 expression ≥5% and ≥10%. For details, please refer to the “Clinical efficacy” section of the attached Information for healthcare professionals.

5.4 Safety

The safety profile of Opdualag was consistent with data from previous data cut-offs. No new safety signals and no additional events of death due to study drug toxicity were reported. For details regarding safety, please refer to the attached Information for healthcare professionals.

5.5 Final clinical benefit risk assessment

Based on the updated OS data, the benefit risk assessment for the all-comer population is considered positive. However, uncertainty remains regarding the overall predictive value of PD-L1 in this setting and the chosen arbitrary cut-offs. Therefore, the applicant was requested, as a pre-authorisation requirement, to reflect the OS Kaplan-Meier curves of both the PD-L1 cut-off 1% and 10% in the “Clinical efficacy” section of the Information for healthcare professionals.

6 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

7 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Opdualag was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Opdualag®

Composition

Active substances

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

Excipients

Histidinum (produced from genetically modified sugar beets, corn, or soy), Histidini hydrochloridum monohydricum (produced from genetically modified sugar beets, corn, or soy), Saccharum (produced from genetically modified sugar beets), Acidum penteticum, Polysorbatum 80, Aqua ad iniectabilia.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (i.v.; sterile concentrate)
Clear to opalescent, colourless to slightly yellow liquid that may contain light (few) particles.
The solution has a pH of approximately 5.8 and an osmolarity of approximately 310 mOsm/kg.

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

Indications/Uses

Opdualag is indicated for the first-line treatment of adults with unresectable or metastatic melanoma (see “Properties/Effects”).

Dosage/Administration

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

Usual dosage

The recommended dose of Opdualag is:

- Adult patients: Opdualag (480 mg nivolumab and 160 mg relatlimab) every 4 weeks administered as an intravenous infusion over 30 minutes.

Duration of treatment

Treatment with Opdualag should be continued as long as clinical benefit is observed or until treatment is no longer tolerated by the patient.

Dose adjustment following undesirable effects/interactions

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 “Warnings and precautions”.

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	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	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

Table 1 Recommended treatment modifications for Opdualag

Immune-related adverse reaction	Severity	Treatment modification
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 "Warnings and precautions")
Immune-related myocarditis	Grade 2 myocarditis	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete. Retreatment may be considered after recovery.[b]
	Grade 3 or 4 myocarditis	Permanently discontinue treatment
Immune-related Myelitis	Any Grade	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 "Warnings and precautions".

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

Patients with hepatic disorders

Based on the population pharmacokinetic (PK) results, no dose adjustment is required in patients with mild or moderate hepatic impairment (see "Pharmacokinetics"). Data from patients with severe hepatic impairment are too limited to draw conclusion on this population. Opdualag must be administered with caution in patients with hepatic impairment.

Patients with renal disorders

Based on the population PK results, no dose adjustment is required in patients with mild or moderate renal impairment (see "Pharmacokinetics"). Data from patients with severe renal impairment are too limited to draw conclusion on this population. Opdualag must be administered with caution in patients with renal impairment.

Elderly patients

No dose adjustment is required for elderly patients (≥ 65 years) (see “Pharmacokinetics”).

Children and adolescents

The safety and efficacy of Opdualag in children and adolescents have not been established. No data are available.

Mode of administration

Opdualag is for intravenous use only. It is to be administered as an intravenous infusion over a period of approximately 30 minutes. The infusion must be administered through a sterile, non-pyrogenic, low protein binding in-line or add-on filter with a pore size of 0.2-1.2 µm.
Opdualag must not be administered as an intravenous push or bolus injection.
Opdualag may be diluted with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 50 mg/mL (5%) solution for injection (see “Other information”).
For instructions on the handling of the medicinal product before administration, see “Other information”.

Traceability

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in “Composition”.

Warnings and precautions

Immune-related adverse reactions

Immune-related adverse reactions can occur with nivolumab in combination with relatlimab. Most immune-related adverse reactions improved or resolved with appropriate management, including initiation of corticosteroids and treatment modifications (see “Dosage/Administration”). 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 should 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 “Undesirable effects”). 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, 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 “Undesirable effects”). 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 “Undesirable effects”). 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 “Undesirable effects”). 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 “Undesirable effects”).

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, Opdualag should be withheld, and thyroid hormone replacement should be initiated as needed. For symptomatic hyperthyroidism, Opdualag 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 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.

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.

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.

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 “Undesirable effects”). 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 “Dosage/Administration”).

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 (see “Undesirable effects”). 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 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 “Dosage/Administration”).

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 “Dosage/Administration”).

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, exocrine pancreatic insufficiency, Guillain-Barre syndrome, myositis/rhabdomyolysis, myasthenia gravis, encephalitis, haemolytic anaemia, Vogt Koyanagi-Harada syndrome (VKH), and coeliac disease (see “Undesirable effects”).

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), myasthenic syndrome, aseptic meningitis, gastritis, sarcoidosis, duodenitis, and hypoparathyroidism.

Cases of transverse myelitis and aplastic anaemia have been observed in patients treated with checkpoint inhibitors. Patients should be monitored for signs and symptoms suggestive of these immune-mediated adverse reactions.

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.

Patients with pre-existing autoimmune disease

In patients with pre-existing autoimmune disease (AID), data from observational studies indicate an increased risk of immune-mediated adverse effects following treatment with immune checkpoint inhibitors compared to patients without pre-existing AID. Additionally, flare-ups of the underlying AID were common but predominantly mild and easily treatable.

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 HSCT, rapid-onset and severe 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 trial of nivolumab in combination with relatlimab (see “Undesirable effects”). 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 use of premedication according to local treatment guidelines for prophylaxis of infusion reactions.

Patients excluded from pivotal unresectable or metastatic melanoma clinical study

Patients with active autoimmune disease, medical conditions requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medications, and active or untreated brain or leptomeningeal metastases were excluded from the study. In the absence of data, nivolumab in combination with relatlimab should be used with caution in these population after careful consideration of the potential benefit/risk on an individual basis.

Interactions

Relatlimab and nivolumab are both human monoclonal antibodies, as such no interaction studies have 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 or relatlimab.

Pharmacodynamic interactions

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.

Pregnancy, 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 are no data on 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 “Preclinical data”). 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 unless the clinical condition of the woman requires treatment with nivolumab/relatlimab.

Lactation

It is unknown whether nivolumab and/or relatlimab are 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 Opdualag 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 and/or relatlimab on fertility have not been performed. Thus, the effect of nivolumab and/or relatlimab on male and female fertility is unknown.

Effects on ability to drive and use machines

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

Patients should be advised not to drive or use machines if they experience fatigue or dizziness.

Undesirable effects

Summary of the safety profile

The safety of nivolumab in combination with relatlimab has been evaluated in 722 patients with unresectable or metastatic melanoma (study CA224047 and CA224020).

The frequencies included below and in Table 2 are based on all reported adverse drug reactions, regardless of the investigator assessment of causality. With a minimum follow-up of 0.03 months and a median follow-up of 20.34 months, the most common adverse reactions (≥ 10%) were fatigue (41%), musculoskeletal pain (30%), rash (23%), pruritus (22%), arthralgia (22%), nausea (22%), diarrhoea (22%), headache (17%), decreased appetite (14%), cough (14%), abdominal pain (14%), constipation (13%), hypothyroidism (13%), pyrexia (12%), dyspnoea (10%) and vomiting (10%). The

most common serious adverse reactions (≥ 1%) were anaemia (1.1%), pyrexia (1.1%), colitis (1.1%), abdominal pain (1.0%), diarrhoea (1.0%), and dyspnoea (1.0%). Incidences of Grade 3-5 adverse reactions in patients with unresectable or metastatic melanoma were 42% for nivolumab in combination with relatlimab and 38% for nivolumab treated patients.

List of adverse reactions

Adverse reactions reported in the dataset for patients treated with nivolumab in combination with relatlimab are presented in Table 2. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000), not known (cannot be estimated from available post marketing data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 2: Adverse reactions in clinical studies – all grades	
Infections and infestations	
Common	upper respiratory tract infection, folliculitis
Uncommon	encephalitis, c-reactive protein increased, red blood cell sedimentation rate increased
Blood and lymphatic system disorders	
Very common	anaemia (44.2%)[a], lymphopaenia (38.9%)[a], leucopaenia (13.6%)[a], neutropaenia (12.9%)[a]
Common	thrombocytopaenia[a], eosinophilia, blood lactate dehydrogenase increased
Uncommon	haemolytic anaemia
Endocrine disorders	
Very common	hypothyroidism (12.5%)
Common	adrenal insufficiency, hyperthyroidism, thyroiditis
Uncommon	hypophysitis, hypopituitarism, hypogonadism
Metabolism and nutrition disorders	
Very common	hyponatraemia (26.0%)[a], hyperkalaemia (17.0%)[a], hypocalcaemia (17.6%)[a], decreased appetite (14.0%), hypomagnesaemia (12.2%)[a]
Common	diabetes mellitus, weight decreased, hypercalcaemia[a], hypokalaemia[a], hypermagnesaemia[a], hypernatraemia[a], hypoglycaemia[a], hypoalbuminemia, dehydration, hyperuricaemia
Psychiatric disorders	
Common	confusional state
Nervous system disorders	
Very common	headache (17.2%)
Common	dizziness, peripheral neuropathy, dysgeusia
Uncommon	Guillain-Barre syndrome, optic neuritis, transverse myelitis, myasthenia gravis
Eye disorders	
Common	uveitis, visual impairment, dry eye
Uncommon	Vogt-Koyanagi-Harada disease, increased lacrimation, ocular hyperaemia
Cardiac disorders	
Common	troponin increased

Uncommon	myocarditis, pericardial effusion
Vascular disorders	
Uncommon	phlebitis
Respiratory, thoracic and mediastinal disorders	
Very common	cough (14.3%), dyspnoea (10.5%)
Common	pneumonitis[b], nasal congestion
Uncommon	asthma, pleural effusion
Gastrointestinal disorders	
Very common	nausea (21.5%), diarrhoea (22.0%), abdominal pain (14.4%), constipation (12.7%), vomiting (10.4)
Common	pancreatitis, colitis, gastritis, dry mouth, lipase increased, amylase increased, stomatitis, dysphagia
Uncommon	oesophagitis
Rare	exocrine pancreatic insufficiency
Not known	coeliac disease
Hepatobiliary disorders	
Very common	increased AST (29.2%)[a], increased ALT (25.0%)[a], increased alkaline phosphatase (22.3%)[a]
Common	hepatitis, increased bilirubin[a], gamma-glutamyltransferase increased
Uncommon	cholangitis
Skin and subcutaneous tissue disorders	
Very common	rash (23.4%), pruritus (22.0%)
Common	vitiligo, alopecia, dry skin, urticaria
Uncommon	pemphigoid, lichenoid keratosis, photosensitivity reaction, psoriasis
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain (29.9%), arthralgia (21.9%)
Common	arthritis, muscular weakness, muscle spasms
Uncommon	myositis, systemic lupus erythematosus, polymyalgia rheumatica, Sjogren's Syndrome, rheumatoid arthritis, bursitis
Renal and urinary disorders	
Very common	increased creatinine (20.3%)[a]
Common	renal failure, proteinuria
Uncommon	nephritis
Reproductive system and breast disorders	
Uncommon	azoospermia
General disorders and administration site conditions	
Very common	fatigue (41.1%), pyrexia (11.5%)
Common	oedema, influenza-like illness, chills
Rare	serositis
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 CA224047.

Description of specific adverse reactions and additional information

Nivolumab and/or relatlimab are associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolved in most cases. The management guidelines for these adverse reactions are described in "Warnings and precautions".

Immune-related pneumonitis

In patients treated with nivolumab in combination with relatlimab, pneumonitis, including interstitial lung disease and lung infiltration occurred in 3.7% (27/722) of patients. Incidences of Grade 3/4 events were 0.6% (4/722). Fatal events occurred in 0.3% (2/722) of patients. Median time to onset was 28.1 weeks (range: 3.6-170.0). Resolution occurred in 21/27 patients (77.8%) with a median time to resolution of 10 weeks (range: 0.6-133.0^{+}). Immune-related pneumonitis led to permanent discontinuation of nivolumab in combination with relatlimab in 1.0% 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 23.7% (171/722) of patients. Incidences of Grade 3/4 events were 3.5% (25/722). Median time to onset was 13.4 weeks (range: 0.1-271.3). Resolution occurred in 152/171 patients (88.9%) with a median time to resolution of 2.3 weeks (range: 0.1-289.1^{+}). Immune-related colitis 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 21.1% of patients with immune-related colitis.

Immune-related hepatitis

In patients treated with nivolumab in combination with relatlimab, liver function test abnormalities occurred in 19.0% (137/722) of patients. Incidences of Grade 3/4 events were 5.1% (37/722). Median time to onset was 8.1 weeks (range: 0.1-198.0). Resolution occurred in 95/134 patients (70.9%) with a median time to resolution of 9.1 weeks (range: 0.6-280.6^{+}). Permanent discontinuation of nivolumab in combination with relatlimab occurred in 1.8% of patients and high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) was required in 24.1% of patients.

Immune-related nephritis and renal dysfunction

In patients treated with nivolumab in combination with relatlimab, nephritis or renal dysfunction occurred in 7.5% (54/722) of patients. Incidences of Grade 3/4 events were 1.2% (9/722). Median time to onset was 20.4 weeks (range: 0.1-210.4). Resolution occurred in 39/52 patients (75.0%) with a median time to resolution of 8.0 weeks (range: 0.1-274.1^{+}). Immune-related nephritis and renal dysfunction led to permanent discontinuation of nivolumab in combination with relatlimab in 0.7% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 7.5% of patients with Immune-related nephritis and renal dysfunction.

Immune-related endocrinopathies

In patients treated with nivolumab in combination with relatlimab, thyroid disorders, including hypothyroidism or hyperthyroidism, occurred in 16.3% (118/722) of patients. There were no incidences of Grade 3/4 thyroid disorder. Incidences of Grade 3/4 events adrenal insufficiency occurred in 1.1% (8/722). Incidences of Grade 3/4 hypophysitis occurred in 0.6% (4/722). There were no incidences of Grade 3/4 hypopituitarism. Incidences of Grade 3/4 diabetes mellitus (including Type 1 diabetes mellitus) were in 0.4% (3/722). Median time to onset of these endocrinopathies was 15.9 weeks (range: 1.0-223.7). Resolution occurred in 39/151 patients (25.8%). Time to resolution ranged from 0.4-328.0+ weeks. Immune-related endocrinopathies led to permanent discontinuation of nivolumab in combination with relatlimab in 0.6% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 12.6% of patients with immune-related endocrinopathies.

Immune-related skin adverse reactions

In patients treated with nivolumab in combination with relatlimab, rash occurred in 41.4% (299/722) of patients. Incidences of Grade 3/4 events were 1.4% (10/722). Median time to onset was 5.9 weeks (range: 0.1-142.1). Resolution occurred in 144/297 patients (48.5%) with a median time to resolution of 93.4 weeks (range: 0.1-318.0+). Immune-related skin adverse reactions led to permanent discontinuation of nivolumab in combination with relatlimab in 0.4% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 4.3% of patients with immune-related skin adverse reactions.

Immune-related myocarditis

In patients treated with nivolumab in combination with relatlimab, myocarditis occurred in 0.8% (6/722) of patients. Incidences of Grade 3/4 events were 0.4% (3/722). Median time to onset was 5.1 weeks (range: 2.1-8.1). Resolution occurred in 6/6 patients (100%) with a median time to resolution of 3 weeks (range: 0.6-14.0). Myocarditis led to permanent discontinuation of nivolumab in combination with relatlimab in 0.8% of patients and required high dose corticosteroids (prednisone ≥ 40 mg per day or equivalent) in 100% of patients with immune-related myocarditis.

Infusion reactions

In patients treated with nivolumab in combination with relatlimab, hypersensitivity/infusion reactions occurred in 4.8% (35/722) of patients. Incidences of Grade 3/4 events were 0.3% (2/722).

Immunogenicity

The incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the test. In addition, the observed incidence of antibody positivity (including neutralizing antibodies) in

a test may be influenced by several factors, such as test methodology, specimen handling, timing of specimen collection, concomitant medications, and underlying disease. Therefore, comparing the incidence of antibodies against nivolumab or relatlimab with the incidence of antibodies against other drugs may be misleading.

In patients treated with nivolumab in combination with relatlimab in study CA224047 and CA224020 out of the evaluable patients for anti-drug antibodies, the incidence of treatment-emergent anti-relatlimab antibodies and neutralizing antibodies against relatlimab were 4.5% (26/577) and 0.2% (1/577), respectively. The incidence of treatment-emergent anti-nivolumab antibodies and neutralizing antibodies against nivolumab were 3.4% (20/588) and 0.3% (2/588), respectively, which were similar to that observed in the nivolumab group 5.9% (16/272) and 0.4% (1/272), respectively.

Paediatric population

The safety of Opdualag for unresectable or metastatic melanoma have not been established in children and adolescents (see “Posology/Administration”).

Elderly

Of the 355 patients treated with Opdualag, 47% were ≥ 65 years, 29% were 65-74 years, 17% were 75-84 years, 19% were ≥ 75 years, and 2% were ≥ 85 years of age. Overall, no differences in safety were reported between elderly (≥ 65 years) and younger patients (see “Properties/Effects”).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Properties/Effects

ATC code

L01FY02

Pharmacotherapeutic group: Antineoplastic agents, combinations of monoclonal antibodies and antibody drug conjugates.

Mechanism of action

Opdualag is a fixed-dose combination of nivolumab (anti-PD-1) and relatlimab (anti-LAG-3).

LAG-3 is a T cell receptor that binds to its ligands, such as major histocompatibility complex Class II, and regulates an inhibitory immune pathway that inhibits T cell proliferation, effector function, cytokine production, and the development of memory T cells. Relatlimab is a human IgG4 monoclonal antibody that binds to the LAG-3 receptor and releases the LAG-3 mediated inhibition of immune response by blocking its interaction with ligands. Relatlimab exhibits in vitro functional activity in restoring effector function of T cells and promoting cytokine signalling.

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 and blocks its interaction with PD-L1 and PD-L2, releasing 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.

LAG-3 and PD-1, two distinct inhibitory immune checkpoint pathways, act synergistically on effector T cells, leading to the development of T cell exhaustion and impaired cytotoxic function. Combined relatlimab (anti-LAG-3) and nivolumab (anti-PD-1) mediated inhibition enables T-cell activation and restores effector function of T cells, that is greater than the effects 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.

Pharmacodynamics

Pharmacodynamic Changes in Interferon-γ (IFNγ)

In study CA224047, the level of IFNγ in the blood increased following the administration of nivolumab in combination with relatlimab or nivolumab alone. The increase of IFNγ levels was greater in the nivolumab in combination with relatlimab arm (median increases of 105.6% and 108.0% at trough after the first and second dose, respectively) than in the nivolumab arm (median increases of 56.3% and 50.7% at trough after the first and second dose, respectively). These data are supportive of increased T-cell activation and IFNγ production by nivolumab in combination with relatlimab.

Clinical efficacy

This section is presenting the clinical experience from Opdualag fixed dose combination of nivolumab and relatlimab in patients with unresectable or metastatic melanoma.

Randomised phase 2/3 study of nivolumab in combination with relatlimab vs. nivolumab (CA224047)
The safety and efficacy of nivolumab in combination with relatlimab for the treatment of 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, medical conditions requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medications, uveal melanoma, and active or untreated brain or leptomeningeal metastases were excluded from the study.

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 (PFS) in the intention to treat (ITT) population determined by Blinded Independent Central Review (BICR). Overall survival (OS) in the ITT population was a secondary outcome measure.

Baseline characteristics in the ITT population were balanced between the two groups. The median age was 63 years (range: 20-94), 58% were men, and 97% were white. 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, 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.

At primary analysis in the ITT population, with median follow up of 13.2 months (range: 0-33.1 months), a statistically significant improvement in PFS was observed with a median PFS of 10.1 months in the nivolumab in combination with relatlimab group as compared with 4.6 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).

In a subsequent descriptive analysis with a median follow-up time of 34.9 months, the median PFS in the nivolumab + relatlimab group was 10.2 months (95% CI: 6.51, 15.74) and 4.6 months (95% CI: 3.48, 6.47) in the nivolumab group (HR = 0.78; 95% CI: 0.65, 0.93). Median OS was 53.3 months (95% CI: 34.04, NR) in the nivolumab + relatlimab group and 33.2 months (95% CI: 25.23, 45.77) in the nivolumab group (HR = 0.77; 95% CI: 0.64, 0.94).

Descriptive OS subgroup analyses are presented below according to PD-L1 expression, with cut-offs of 1% and 10%; the study was not powered to show statistical differences between treatments within the various PD-L1 cut-offs.

Figure 1: Kaplan-Meier curve of OS for baseline PD-L1 expression < 1%

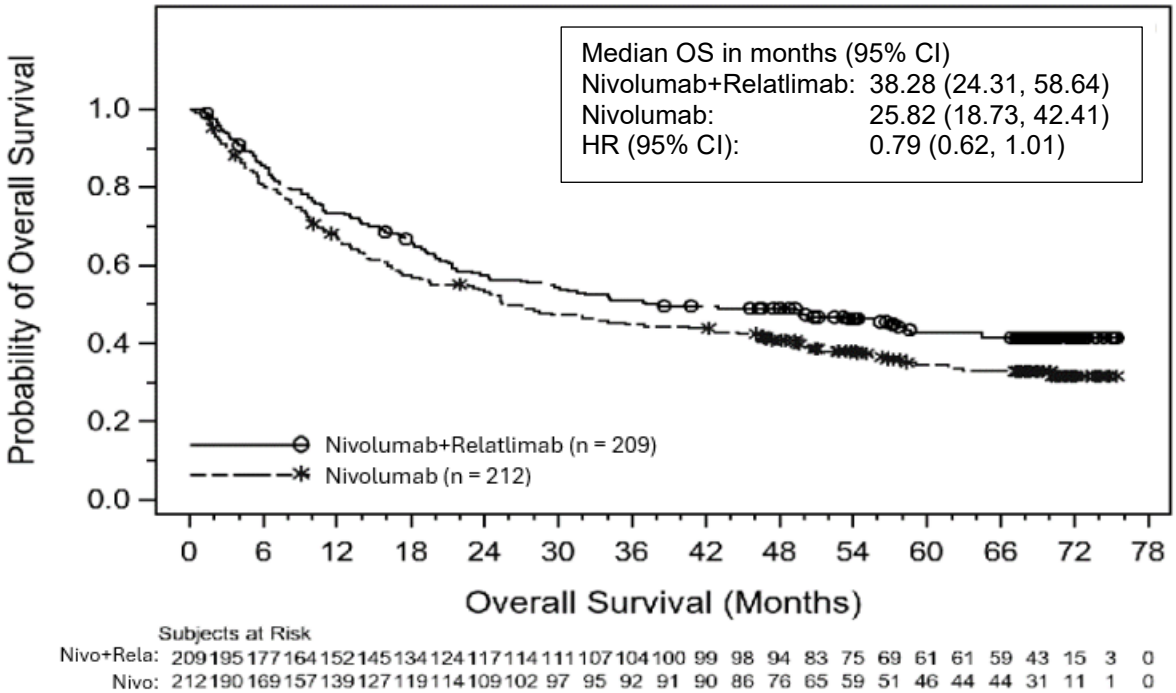


Figure 2: Kaplan-Meier curve of OS for baseline PD-L1 ≥ 1%

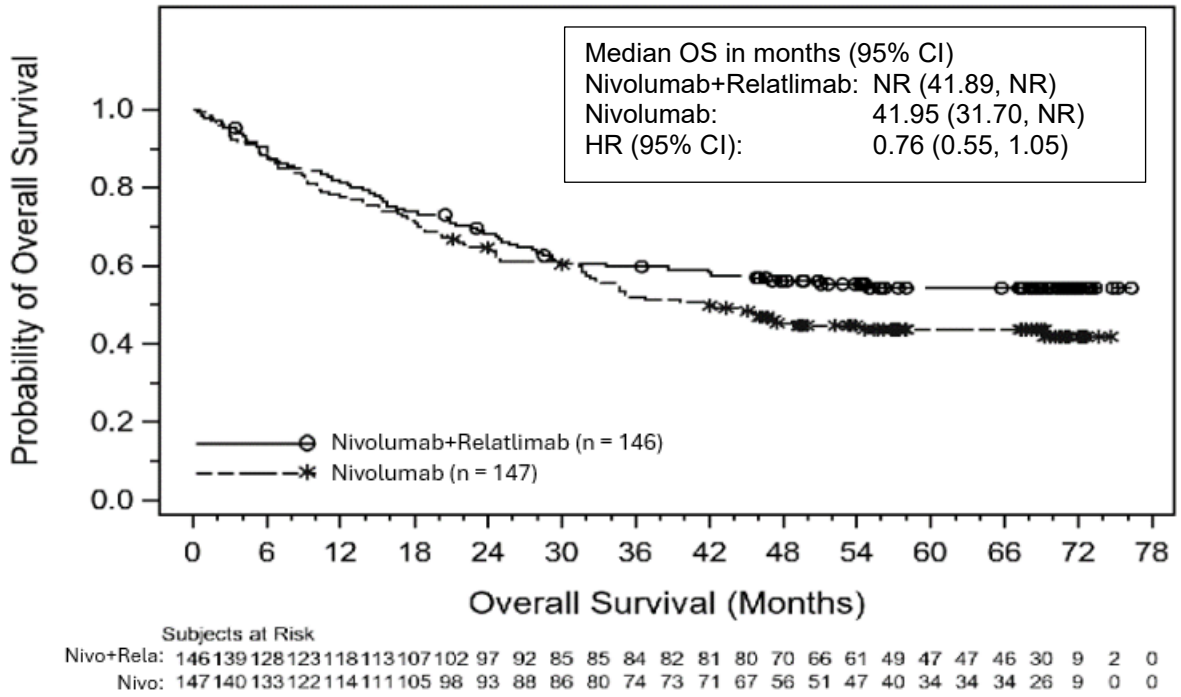


Figure 3: Kaplan-Meier curve of OS for baseline PD-L1 < 10%

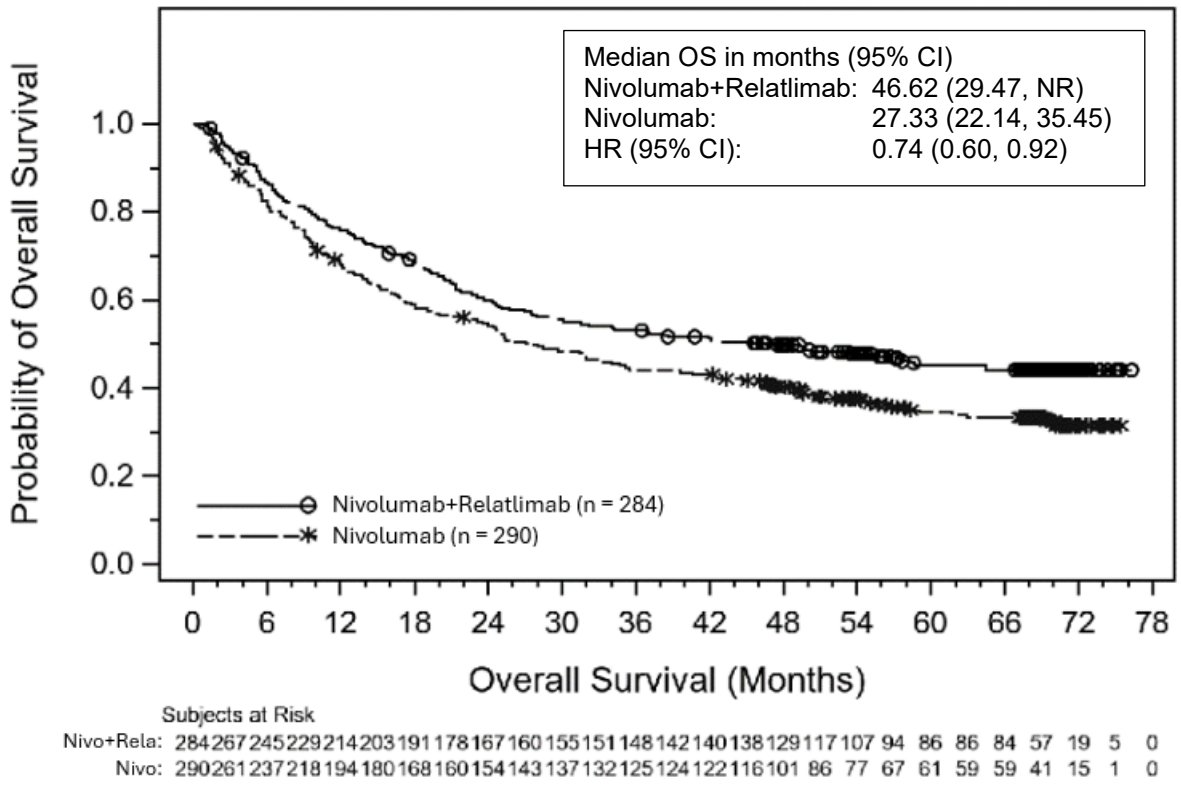
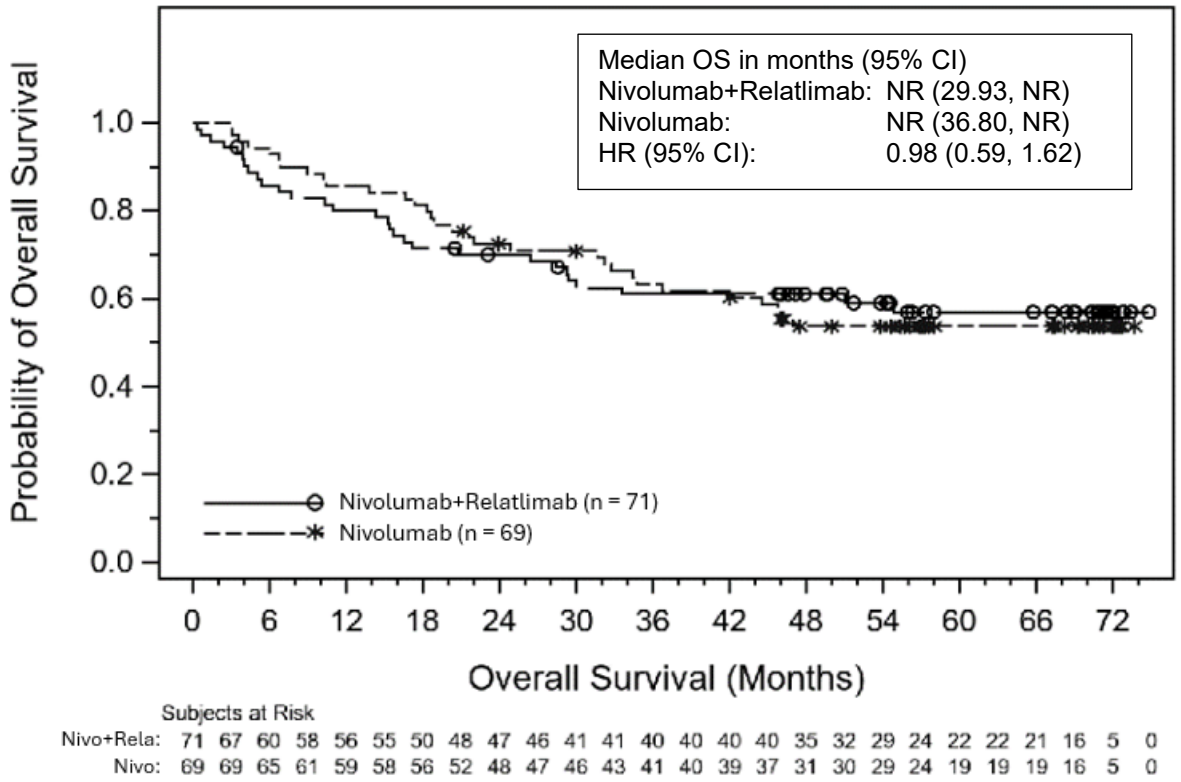


Figure 4: Kaplan-Meier curve of OS for baseline PD-L1 expression ≥ 10%



Pharmacokinetics

The pharmacokinetics (PK) of nivolumab and 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.
Following 480 mg nivolumab and 160 mg relatlimab fixed dose combination every 4 weeks, geometric mean (CV%) relatlimab steady state maximum concentration (C_{max}), minimum concentration (C_{min}) and C_{avg} were 62.2 µg/mL (30.1%), 15.3 µg/mL (64.3%) and 28.8 µg/mL (44.8%), respectively, and geometric mean (CV%) nivolumab steady state C_{max}, C_{min} and C_{avg} were 187 µg/mL (32.9%), 59.7 µg/mL (58.6%) and 94.4 µg/mL (43.3%), respectively.

The nivolumab geometric mean C_{min} with a geometric mean ratio of 0.931 (95% CI: 0.855-1.013) at steady state was similar when nivolumab was administered in combination with relatlimab as compared to the administration of nivolumab alone.

Absorption

Not applicable.

Distribution

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

Metabolism

The metabolic pathway of nivolumab and relatlimab have not been characterized. As a fully human IgG4 monoclonal antibody, nivolumab and relatlimab are expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

Relatlimab clearance (CL) 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 nivolumab 480 mg and relatlimab 160 mg administered every 4 weeks the mean (CV%) effective half-life of relatlimab is 26.2 days (37%).

Nivolumab clearance 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 mean (CV%) terminal half-life ($t_{1/2}$) is 26.5 days (36.4%).

Kinetics in specific patient groups

Based on a population PK analysis, the following factors had no clinically important effect on the CL of nivolumab and relatlimab: age (range: 17 to 92 years), sex, or race.

Hepatic impairment

The effect of hepatic impairment on the clearance of nivolumab and relatlimab was evaluated by population PK analysis in patients with mild or moderate hepatic impairment (as defined using the US National Cancer Institute criteria of hepatic dysfunction) compared to patients with normal hepatic

function. No clinically important differences in the clearance of nivolumab or relatlimab were found between patients with mild or moderate hepatic impairment and patients with normal hepatic function. Data from patients with severe hepatic impairment are too limited to draw conclusions in this population.

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 mild or moderate renal impairment and patients with normal renal function. Data from patients with severe renal impairment are too limited to draw conclusions in this population.

Preclinical data

Genotoxicity/cancerogenicity

Mutagenicity and carcinogenicity studies have not been performed with nivolumab or relatlimab. Since these are antibodies, no direct interaction with DNA is expected.

Reproductive toxicity

No dedicated reproductive toxicity studies were conducted with nivolumab in combination with relatlimab.

Relatlimab

There are no available animal data on the effect of relatlimab on pregnancy and reproduction. However, the effects of murine anti-LAG-3 antibodies were evaluated in mice using syngeneic and allogeneic breeding models. Anti-LAG-3 antibodies were well tolerated, when administered beginning on gestation day 6, with no maternal or developmental effects in either syngeneic or allogeneic breedings. 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.

Other information

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.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Shelf life after opening

After opening: From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately.

After preparation of infusion: The administration of the Opdualag infusion must be completed within 24 hours of preparation. If not used immediately, the solution may be stored under refrigeration conditions: 2°C-8°C and protected from light for up to 24 hours (a maximum of 8 hours of the total 24 hours can be at room temperature 15°C-25°C and room light - the maximum 8-hour period under room temperature and room light conditions should be inclusive of the product administration period).

Special precautions for storage

Store in the refrigerator (2-8°C).

Do not freeze.
Store in the original packaging.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.

The unopened vials can be stored at controlled room temperature up to 25°C with room light for up to 72 hours.

Instructions for handling

Opdualag is supplied as a single-dose vial and does not contain any preservatives. Aseptic techniques must be observed.

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 adult 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, is discoloured, or contains extraneous particulate matter other than a few translucent-to-white particles.
- 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 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).
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.

Authorisation number

68609 (Swissmedic).

Packs

Vial of 240 mg/80 mg pro 20 mL: 1 [A]

Marketing authorisation holder

Bristol-Myers Squibb SA, Steinhausen.

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March 2026