Summary Report of Benefit-Risk Assessment

OPDUALAG CONCENTRATE FOR SOLUTION FOR INFUSION 240MG/80MG

NEW DRUG APPLICATION

Active Ingredient(s)	Nivolumab, relatlimab
Product Registrant	Bristol-Myers Squibb (Singapore) Pte. Ltd.
Product Registration Number	SIN16852P
Application Route	Abridged evaluation
Date of Approval	31 August 2023

Table of Contents

A INTRODUCTION

Opdualag is indicated for the first-line treatment of unresectable or metastatic melanoma in adults with tumour cell PD-L1 expression < 1%.

Opdualag is a fixed dose combination (FDC) of relatlimab and nivolumab. Relatlimab is an anti-lymphocyte-activation gene 3 (LAG-3) human Immunoglobulin G4 (IgG4) monoclonal antibody, which binds selectively to LAG-3 and blocks ligand binding, thereby stimulating antigen-specific T cell responses and cytokine signalling, thus promoting anti-tumour immunity. Nivolumab is an anti-PD-1 human IgG4 monoclonal antibody which binds selectively to PD-1 and blocks binding to PD-L1 and PD-L2, thereby inhibiting PD-1 pathway-mediated suppression of anti-tumour immunity.

Opdualag is available as a 20ml concentrate for solution for infusion containing 240mg of nivolumab and 80mg of relatlimab. Other ingredients in the vial are histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid (diethylenetriaminepentaacetic acid), polysorbate 80 (E433), and water for injection.

B ASSESSMENT OF PRODUCT QUALITY

The drug substances, nivolumab and relatlimab, are both manufactured at Bristol-Myers Squibb Company, Massachusetts, USA. The drug product, Opdualag, is manufactured at Catalent Indiana LLC, Indiana, USA.

Drug substance: Nivolumab and Relatlimab

Adequate controls have been presented for the cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation was conducted on three consecutive production-scale batches.

The characterisation of both drug substances and their impurities has been appropriately performed. Potential and actual impurities are adequately controlled in manufacturing process.

The drug substance specifications were established in accordance with ICH Q6B, and the impurity limits have been appropriately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data presented was adequate to support the storage of the drug substances at -60^{o}C with a shelf life of 48 months. The packaging consists of 12-L single-use, pre-sterilized ethylene vinyl acetate copolymer (EVA) bioprocess containers with integral high-density polyethylene (HDPE) protective shell.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered to be a standard manufacturing process.

The manufacturing site is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications have been established in accordance with ICH Q6B, and impurity limits were adequately qualified. The analytical methods used were adequately described and non-compendial methods have been validated in accordance with ICH guidelines, with information on the reference standards used for identity, assay and impurities testing presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months at 2-8ºC, with protection from light. The in-use period after reconstitution is up to 24 hours at 2-8ºC, when protected from light. The container closure system is a 25R Type I clear tubing glass vial, stoppered with a 20-mm FluroTec film-laminated chlorobutyl rubber stopper, and yellow flip-off seal containing 20mL of the drug product.

C ASSESSMENT OF CLINICAL EFFICACY

The efficacy of Opdualag for the treatment of unresectable or metastatic melanoma was based primarily on one pivotal study CA224047. This was a seamless Phase 2/3, randomised, double-blind study of relatlimab+nivolumab (rela+nivo) FDC compared with nivolumab monotherapy in patients with previously untreated metastatic or unresectable melanoma.

Patients in the study were randomised in a 1:1 ratio to receive rela+nivo 160/480 mg FDC via intravenous (IV) infusion every four weeks (Q4W) or nivolumab 480 mg IV Q4W. Patients received study treatment until unacceptable toxicity, disease progression, withdrawal of consent, or end of study. Dose reductions were not allowed for both treatment arms. The use of nivolumab as the comparator was considered acceptable as it is considered a standard of care for the proposed patient population.

The primary efficacy endpoint was progression-free survival (PFS) by Blinded Independent Central Review (BICR), defined as time from the date of randomisation to the first date of documented progression per RECIST v1.1 or death due to any cause, whichever occurred first. Key secondary efficacy endpoints were overall survival (OS) and objective response rate (ORR) as determined by BICR using RECIST v1.1. Tumour assessments were performed at 12 weeks from randomisation and continued every 8 weeks up to Week 52, and every 12 weeks thereafter until BICR-confirmed disease progression or treatment discontinuation, whichever occurred later.

The intention to treat (ITT) population comprising all randomised patients was analysed for the primary and secondary efficacy endpoints. Hazard ratios (HRs) of rela+nivo FDC over nivolumab and corresponding 2-sided 95% confidence interval (CI) were estimated using a Cox proportional hazards model, stratified by factors including LAG-3 expression (≥1% vs <1%), PD-L1 status (≥1% vs <1%), BRAF status, and American Joint Committee on Cancer (AJCC) M Stage.

A total of 714 patients were randomised in the study: 355 patients in the rela+nivo FDC arm and 359 patients in the nivolumab arm. The median age was 63 years (range 20 to 94 years), majority of subjects were male (58.3%) and White (96.6%). While the study permitted adolescents 12 years of age and older to enter, no adolescents were randomised. Majority

(91.7%) of subjects had Stage IV disease per the 8th edition of the AJCC staging system. The median duration of therapy at the time of primary analysis was 5.55 months in the rela+nivo FDC arm and 4.86 months in the nivolumab arm.

The primary analysis of PFS demonstrated a statistically significant improvement for patients in the rela+nivo FDC arm compared to the nivolumab arm (HR 0.75; 95% CI 0.62, 0.92; p=0.0055). The median duration of PFS was 10.12 months (95% CI: 6.37, 15.74) in the rela+nivo FDC arm and 4.63 months (95% CI: 3.38, 5.62) in the nivolumab arm. The PFS results were consistent in various sensitivity analyses, demonstrating robustness of the data.

OS analysis was performed with updated data at database lock (DBL) as of 28 Oct 2021. While the OS analysis was not statistically significant (HR 0.80; 95% CI 0.64, 1.01; p=0.0593), median OS demonstrated a trend favouring the rela+nivo FDC arm (not reached [95% CI: 34.2, NR]) compared to nivolumab (34.1 months [95% CI: 25.2, NR]). A clear separation was observed in the Kaplan-Meier (KM) curves in favour of rela+nivo FDC arm and this separation was maintained throughout the follow-up period (median follow-up: 19 months).

The ORR based on BICR was 43.1% (95% CI: 37.9, 48.4) for rela+nivo FDC and 32.6% (95% CI: 27.8, 37.7) for nivolumab. Statistical significance was not formally tested for ORR since the previous level of statistical testing hierarchy (i.e., OS) was not statistically significant.

Summary of key efficacy results

	Rela+nivo FDC (N=355)	**Nivolumab (N=359)**
Primary endpoint		
PFS per BICR		
PFS events, n (%)	180 (50.7%)	211 (58.8%)
Median PFS (months) (95% CI)	10.12 (6.37, 15.74)	4.63 (3.38, 5.62)
Stratified HR (95% CI)	0.75 (0.62, 0.92)	
Stratified log-rank p-value	0.0055[a]	
Key secondary endpoints		
OS (DBL of 28 Oct 2021)		
OS events, n (%)	137 (38.6%)	160 (44.6%)
Median OS (months) (95% CI)	NR (34.20, NR)	34.10 (25.23, NR)
Stratified HR (95% CI)	0.80 (0.64, 1.01)	
Stratified log-rank p-value	0.0593[b]	
ORR per BICR (DBL of 28 Oct 2021)		
Confirmed ORR, % (95% CI)	43.1 (37.9, 48.4)	32.6 (27.8, 37.7)

[a] Statistically significant after adjustment for multiplicity. The threshold for statistical significance is 0.049.
[b] Statistically not significant after adjustment for multiplicity. The threshold for statistical significance is 0.04302.
NR = not reached

As per the primary analysis, the combination therapy demonstrated PFS benefit regardless of LAG-3 expression. The HR for PFS was 0.78 (95% CI: 0.54, 1.15) in patients with LAG-3 expression <1% and 0.75 (95% CI: 0.59, 0.95) in patients with LAG-3 expression ≥1% favouring the dual therapy. Improvements in median PFS were observed with rela+nivo FDC compared to nivolumab alone, in both LAG-3 expression <1% (4.83 [95% CI: 2.86, 10.05] months vs 2.79 [95% CI: 2.79, 4.63] months) and ≥1% (12.58 [95% CI: 6.67, 23.10] months vs 4.76 [95% CI: 4.47, 8.61] months) subgroups. It was noted that the median PFS was observed to be substantially longer in the LAG-3 expression ≥1% subgroup compared to the <1% subgroup, suggesting that the former might be more likely to benefit from the rela+nivo FDC.

When stratified based on PD-L1 expression, the incremental benefit of adding relatlimab to nivolumab was not demonstrated in patients with PD-L1 expression ≥1% (which constituted 41% of the study population). The subgroup analysis, based on the updated data at DBL as of

28 Oct 2021, showed that the HR with respect to PFS was 0.96 (95% CI: 0.70, 1.31) with the rela+nivo FDC compared to nivolumab monotherapy. The point estimate was close to 1 and the upper bound of the 95% exceeded 1, suggesting no treatment difference. Similarly, no clinically meaningful difference was observed in terms of median PFS (median PFS: 15.7 months with rela+nivo FDC vs 14.7 months with nivolumab alone).

Furthermore, in the subgroups with PD-L1 expression ≥5% or ≥10%, there was a trend suggesting diminishing PFS benefit with increasing PD-L1 expression (HR 0.94 [95% CI: 0.60, 1.48] and HR 1.23 [95% CI: 0.74, 2.04], respectively). The OS results demonstrated similar negative trends with worsening HR as PD-L1 expression increased: PD-L1 ≥5% (HR 1.08 [95% CI: 0.65, 1.81]) and PD-L1 ≥10% (HR 1.43 [95% CI: 0.79, 2.60]). It was observed that the point estimates exceeded 1, hence a potential detrimental effect could not be excluded.

Conversely, in patients with low PD-L1 expression (PD-L1 <1%), consistent improvements with rela+nivo FDC was demonstrated for PFS (HR 0.68 [95% CI: 0.53, 0.86]) and OS (HR 0.78 [95% CI: 0.59, 1.04]). The median PFS with rela+nivo FDC (median PFS: 6.67 [95% CI: 4.67, 11.99] months) was observed to be longer compared to nivolumab alone (median PFS: 2.96 [95% CI: 2.79, 4.50] months). While the median OS was not reached (95% CI: 27.43, NR) in the rela+nivo FDC arm, the trend favoured the combination therapy when compared to 27.04 months (95% CI: 17.12, NR) in the nivolumab arm. Taken together, the data suggested that the addition of relatlimab did not potentiate the efficacy of nivolumab in patients with high PD-L1 expression, while those with low PD-L1 expression demonstrated consistent benefit from the combined checkpoint inhibition of LAG-3 and PD-1.

Based on the data presented, the results supported the efficacy of Opdualag for the treatment of unresectable or metastatic melanoma in the subset of adult patients with PD-L1 expression <1%.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of Opdualag was based primarily on safety data derived from the pivotal study CA224047, comprising a total of 714 patients who received at least one dose of study treatment: 335 patients in the rela+nivo FDC arm and 359 patients in the nivolumab arm. The median treatment duration was 5.6 months for rela+nivo FDC and 4.9 months for nivolumab at the time of submission.

Overview of safety profile

AE	Rela+nivo FDC (N=355)	Nivolumab (N=359)
Any AE	345 (97.2%)	339 (94.4%)
Treatment-related AE	288 (81.1%)	251 (69.9%)
SAE	121 (34.1%)	105 (29.2%)
Treatment-related SAE	50 (14.1%)	28 (7.8%)
Discontinuations due to AE	69 (19.4%)	41 (11.4%)
Deaths due to treatment-related AE	3 (0.8%)	2 (0.6%)

There were numerically higher incidences of adverse events (AEs) reported in patients receiving rela+nivo FDC than nivolumab (97.2% vs 94.4%), which was expected for a combination therapy. Majority of AEs were Grade 1-2 (56.9% in the rela+nivo FDC arm and 61.0% in the nivolumab arm). The most frequently reported AEs (rela+nivo FDC vs nivolumab) were fatigue (28.7% vs 20.1%), pruritus (24.8% vs 17.3%), arthralgia (23.7% vs 14.8%), diarrhoea (22.8% vs 16.7%), headache (17.5% vs 11.7%), nausea (16.9% vs 14.5%), rash

(16.6% vs 13.4%), hypothyroidism (15.2% vs 12.0%), decreased appetite (14.6% vs 7.2%), anaemia (13.5% vs 9.5%), cough (13.5% vs 10.3%), back pain (13.2% vs 8.1%), asthenia (12.4% vs 8.9%), pyrexia (11.0% vs 8.9%), vitiligo (11.0% vs 10.0%), constipation (10.7% vs 6.1%), and urinary tract infection (10.4% vs 8.1%).

The overall incidence of serious adverse events (SAEs) was higher in the rela+nivo FDC arm compared with the nivolumab arm (34.1% vs 29.2%). There was no SAE which was reported with a frequency > 2% in either arm except malignant neoplasm progression (3.7% in the rela+nivo FDC arm vs 5.3% in the nivolumab arm). Deaths were reported in 30.4% and 33.1% patients receiving rela+nivo FDC and nivolumab, respectively. Disease progression was the most common cause of death in both arms (25.4% in the rela+nivo FDC arm vs 27.6% in the nivolumab). Deaths due to treatment-related AEs were low and comparable between arms (0.8% in the rela+nivo FDC arm vs 0.6% in the nivolumab arm).

The AEs of special interest (including select AEs[1] and immune-mediated adverse events [IMAEs]) were reported at higher incidences in the rela+nivo FDC arm compared to the nivolumab arm, majority were low grade events which could be managed using established management algorithms. The most frequently reported select AEs in the rela+nivo FDC arm were pruritus (24.8%), diarrhoea (22.8%), rash (16.6%), hypothyroidism (15.2%), vitiligo (11.0%), AST increased (9.9%), ALT increased (9.3%), and hyperthyroidism (6.2%). The most frequently reported IMAEs were hypothyroidism (16.6%), rash (9.3%), diarrhoea/colitis (6.8%), hyperthyroidism (6.2%), and hepatitis (5.6%). The AEs of special interest have been adequately described under warnings and precautions in the product label.

The incidences of relatlimab and nivolumab treatment emergent anti-drug antibodies (ADAs) and neutralising antibodies (NAbs) were low. Incidences of ADA positive were 5.6% (to relatlimab) and 3.8% (to nivolumab) in the rela+nivo FDC arm, and 5.9% (to nivolumab) in the nivolumab arm. A total of 3 patients were tested positive for NAbs: 2 (1 to relatlimab and 1 to nivolumab) in the rela+nivo FDC arm and 1 in the nivolumab arm. No ADA-related effect on PK, efficacy and safety were identified.

Overall, the safety profile of Opdualag was adequately characterised and the AEs were expected for dual checkpoint inhibitor therapy.

E ASSESSMENT OF BENEFIT-RISK PROFILE

Melanoma remains a leading cause of cancer-related mortality in adults and adolescents worldwide. The current treatment options for patients with metastatic or unresectable disease include combination checkpoint blockade and anti-PD-1 monotherapy, as well as BRAF/MEK combination therapies for patients with BRAF mutated melanoma.

The pivotal study CA224047 demonstrated statistically significant improvement in PFS (HR 0.75; 95% CI; 0.62, 0.92; p=0.0055) and a favourable trend in OS (HR 0.80; 95% CI: 0.64, 1.01; p=0.0593) with the dual checkpoint inhibition (relatlimab and nivolumab) compared to nivolumab alone. The improvement in PFS of 5.5 months for rela+nivo FDC compared to nivolumab was considered clinically relevant. While the OS was not statistically significant, the results favoured the rela+nivo FDC regimen. Analysis by baseline PD-L1 expression levels suggested a trend of diminishing survival benefits with increasing PD-L1 expression and no survival benefit in patients with high PD-L1 expression levels (≥1%); whereas a consistent

[1] Select AEs included endocrinopathies, diarrhoea/colitis, hepatitis, pneumonitis, interstitial nephritis, and rash.

clinical benefit with rela+nivo FDC over nivolumab in patients with PD-L1 expression <1% was observed.

The safety profile was as expected for dual checkpoint inhibition therapy with the predominant AEs being pruritus, diarrhoea, rash, hypothyroidism, vitiligo, AST/ATL increased, hyperthyroidism and hepatitis. These AEs were reported at higher incidences in the rela+nivo FDC arm compared to the nivolumab arm. Majority of these AEs were of low grades in severity (Grade 1-2) and resolved at the time of database lock. The overall toxicities of rela+nivo FDC was considered manageable with established management algorithms.

Overall, in the subset of adult patients with PD-L1 expression <1%, the clinical benefits of Opdualag outweighed the toxicities in the treatment of unresectable or metastatic melanoma.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Opdualag for the treatment of unresectable or metastatic melanoma in adult patients with PD-L1 expression <1% was deemed favourable and approval of the product registration was granted on 31 August 2023.

APPROVED PACKAGE INSERT AT REGISTRATION

Bristol Myers Squibb

OPDUALAG® (Nivolumab/Relatlimab)
Concentrate For Solution For Infusion 240 mg/80 mg

1. NAME OF THE MEDICINAL PRODUCT

Opdualag concentrate for solution for infusion 240 mg/80 mg.

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 unresectable or metastatic melanoma in adults 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.

Posology

- The recommended dose of Opdualag is 480 mg nivolumab and 160 mg relatlimab every 4 weeks administered as an intravenous infusion over 30-60 minutes.

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	AST or 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
Immune-related encephalitis	New onset moderate or severe neurologic signs or symptoms	Withhold dose(s) until symptoms resolve and management with corticosteroids is complete
	Immune-related encephalitis	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)

Table 1: Recommended treatment modifications for Opdualag

Immune-related adverse reaction	Severity	Treatment modification
	Grade 4 rash Confirmed SJS/TEN	Permanently discontinue treatment (see section 4.4)
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.

Opdualag should be permanently discontinued for:

- Grade 4 or recurrent Grade 3 adverse reactions;
- Persistent Grade 2 or 3 adverse reactions despite management;
- Exceptions include endocrine adverse reactions and rash (see table 1 and section 4.4).

Special populations

Paediatric population
The safety and efficacy of Opdualag in children below 18 years of age have not been established. No data are available.

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 30-60 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 any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

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 encephalitis
Immune-related encephalitis can occur with nivolumab in combination with relatlimab treatment. Withhold nivolumab in combination with relatlimab in patients with new-onset moderate to severe neurologic signs or symptoms and evaluate to rule out infections or other causes of moderate to severe neurologic deterioration. Evaluation may include, but not limited to, consultation with a neurologist, brain MRI and lumbar puncture.

If other aetiologies are ruled out, administer corticosteroids at a dose of 1 to 2 mg/kg/day methylprednisolone equivalents for patients with immune-related encephalitis, followed by

corticosteroid taper. Permanently discontinue nivolumab in combination with relatlimab for immune-related encephalitis.

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 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.

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, 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, cystitis noninfective, cytokine release syndrome, autoimmune haemolytic anaemia, aplastic anaemia, tumour lysis syndrome and pericarditis.

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.

<u>Other important warnings and precautions, including class effects</u>

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 trials 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 treatment 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 trial 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.

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 both an IgG4 antibodies; 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 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.

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 machinery 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 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% 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 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
Of the 355 patients treated with Opdualag, 47% were ≥ 65 years, 29% were 65-74 years, 17% were 75-84 years of age, 19% were ≥ 75 years and 2% were ≥ 85 years. Overall, no differences in safety were reported between elderly (≥ 65 years) and younger patients (see section 5.1).

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-L2and 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 metastatuc 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)

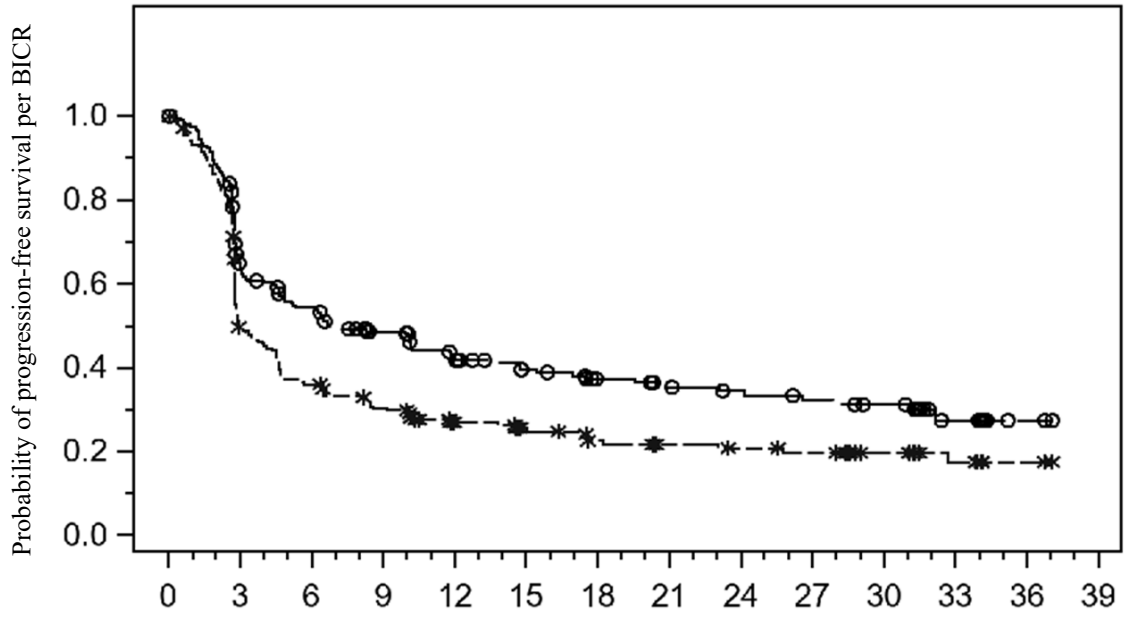
	Opdualag (n=209)	**Nivolumab (n=212)**
Progression-free survival		
Hazard ratio (95% CI)[a]	0.68 (0.53, 0.86)	
Median in months (95% CI)	6.7 (4.7, 12.0)	3.0 (2.8, 4.5)
Rate (95% CI) at 12 months	42.3 (35.1, 49.4)	26.9 (20.9, 33.3)
Overall Survival[b]		
Hazard ratio (95% CI)[a]	0.78 (0.59, 1.04)	
Median in months (95% CI)	NR (27.4, NR)	27.0 (17.1, NR)
Rate (95% CI) at 12 months	73.9 (67.4, 79.4)	67.4 (60.6, 73.3)
Rate (95% CI) at 24 months	59.6 (52.2, 66.2)	53.1 (45.8, 59.9)
Overall Response Rate (%) (95% CI)	36.4 (29.8, 43.3)	24.1 (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 hazard 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)

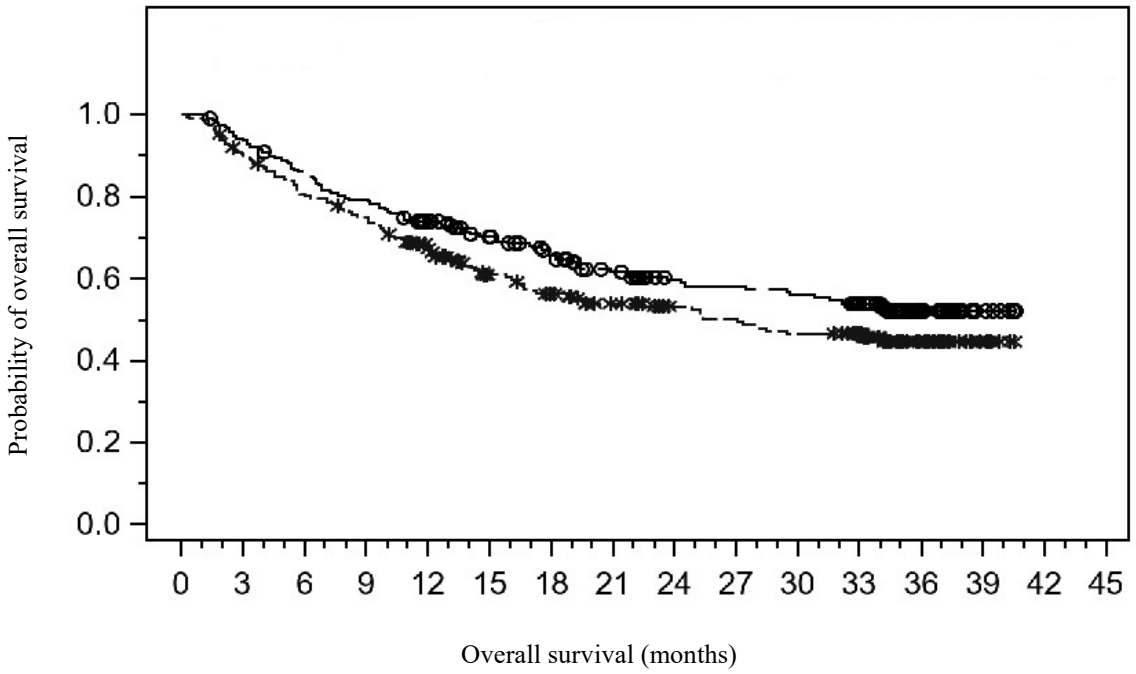


Number of subjects at risk

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.

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 relatlimab and nivolumab 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. 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, at exposure levels up to approximately 14 times higher than those observed for relatlimab at the clinical dose of 160 mg (based on AUC), 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Histidine
Histidine hydrochloride monohydrate
Sucrose
Pentetic acid (diethylenetriaminepentaacetic acid)
Polysorbate 80 (E433)
Water for injection

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 opening:

- From a microbiological point of view, once opened, the medicinal product should be prepared for infusion immediately.

After preparation of infusion:

- The prepared infusion 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 20°C to 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). The administration of the Opdualag infusion must be completed within 24 hours of preparation.

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, is 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 30-60 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 (S) Pte Ltd
80 Marine Parade Road,
#20-01/09 Parkway Parade,
Singapore 449269

8. DATE OF REVISION OF THE TEXT

August 2023