swissmedic

Date: 19 April 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Opdualag

International non-proprietary name: relatlimab, nivolumab
Pharmaceutical form: concentrate for solution for infusion
Dosage strength(s): 80 mg relatlimab/240 mg nivolumab per 20 ml
Route(s) of administration: intravenous
Marketing authorisation holder: Bristol-Myers Squibb SA
Marketing authorisation no.: 68609
Decision and decision date: approved on 23.12.2022

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

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AUC	Area under the plasma concentration-time curve
BICR	Blinded independent central review
BRAF	Serine/threonine-protein kinase B-Raf
CHO	Chinese hamster ovary
CI	Confidence interval
CL	Clearance
CTLA-4	Cytotoxic T-lymphocyte–associated antigen 4
CYP	Cytochrome P450
DBL	Database lock
DDI	Drug-drug interaction
ECOG	Eastern Cooperative Oncology Group
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
FDC	Fixed-dose combination
GLP	Good Laboratory Practice
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IMAE	Immune-mediated adverse events
LAG-3	Lymphocyte activation gene-3
LDH	Lactate dehydrogenase
LoQ	List of Questions
MAH	Marketing Authorisation Holder
MEK	Mitogen-activated protein kinase kinase
MTD	Maximum tolerated dose
NO(A)EL	No observed (adverse) effect level
OESI	Other events of special interest
ORR	Overall response rate
OS	Overall survival
PD-1	Programmed death-1 receptor
PD-L1	Programmed cell death 1 ligand
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PS	Performance status
Q	Intercompartmental clearance
Q2W	Once every 2 weeks
Q4W	Once every 4 weeks
RECIST	Response evaluation criteria in solid tumours
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
$t_{½}$	Terminal half-life
TIL	Tumour infiltrating lymphocytes

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New active substance status
The applicant requested new active substance status for relatlimab in the above-mentioned medicinal product.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Opdualag is indicated for the treatment of adult and paediatric patients (12 years and older and with 40 kg minimum body weight) 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 with a PD-L1 expression < 1%.

2.2.3 Requested dosage

The recommended dose and schedule is:

- Adult patients: 160 mg relatlimab and 480 mg nivolumab Q4W administered by IV infusion over 30 minutes.
- Paediatric patients ≥ 12 years and ≥ 40 kg: 2 mg/kg relatlimab and 6 mg/kg nivolumab (up to a maximum of 160 mg relatlimab and 480 mg nivolumab) Q4W administered by IV infusion over 30 minutes.

Treatment is recommended until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	17 August 2021
Formal control completed	19 August 2021
Preliminary decision	23 March 2022
Response to preliminary decision	9 June 2022
Labelling corrections	8 July 2022
Response to labelling corrections	8 August 2022
Labelling corrections	31 October 2022
Response to labelling corrections	22 November 2022
Final decision	23 December 2022
Decision	approval

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3 Medical context

Cutaneous melanoma is the most lethal type of cutaneous neoplasia. Incidence of malignant melanoma in 2020 in Europe was 20 per 100 000 and mortality was 3.5 per 100 000 in both sexes (age standardised rate).
Melanoma is rare in individuals younger than 20 years, with an estimated annual incidence rate of 4 per million in those aged 0 to 19 years, according to the Surveillance, Epidemiology, and End Results (SEER) Cancer Statistics Review 1975-2018.

In patients with unresectable stage III/IV tumours according to the American Joint Committee on Cancer (AJCC) 8th edition, immunotherapy or BRAF/MEK inhibition as two distinct therapeutic classes are recommended in the first-line setting. PD-1 immune checkpoint inhibitors are the standard of care for all patients regardless of their BRAF status. For patients with BRAF mutations, additional options are BRAF and MEK inhibitors, possibly combined with immunotherapy.
Patients with metastatic melanoma treated with the combination of PD-1 inhibitor and CTLA-4 inhibitor achieve a median overall survival (OS) of 72.1 months (CheckMate067, Wolchok et al. 2022). There are only very limited data on the efficacy of systemic therapy in children and adolescents with advanced melanoma and inclusion in clinical studies is recommended.
Lymphocyte activation gene-3 (LAG-3) is an immune checkpoint receptor which has been identified on the surface of multiple immune effector cells, most notably tumour infiltrating lymphocytes (TILs). Relatlimab, an anti-LAG-3 human IgG4 monoclonal antibody, binds selectively to LAG-3 with high affinity and blocks ligand binding, thereby stimulating enhanced *in vitro* antigen-specific T cell responses and cytokine signalling and promoting anti-tumour immunity.

Opdualag contains as a fixed-dose combination (FDC) the known active substance nivolumab (PD-1 Inhibitor, Opdivo®) and the new active substance relatlimab, a LAG-3 inhibitor.

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4 Quality aspects

4.1 Drug substance

Drug substance 1: Nivolumab-histidine (known active substance)
Nivolumab, a human monoclonal immunoglobulin G4 (IgG4) antibody, is a highly specific programmed death-1 (PD-1) immune checkpoint inhibitor. Nivolumab is a glycoprotein (molecular weight approx. 146,000 Da) composed of two heavy chains of 440 amino acids and two kappa light chains of 214 amino acids, which are linked by inter-chain disulphide bonds. Nivolumab is the same active substance as in the authorised medicinal product Opdivo. However, a new formulation of the nivolumab drug substance was developed for the purpose of the co-formulation with relatlimab.

Nivolumab is produced in Chinese hamster ovary (CHO) cells. The two-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) had been developed previously for Opdivo. After thawing of the WCB vial, the cells are grown in suspension culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The culture is harvested, and purification is performed with a series of chromatography, ultra-/diafiltration, and viral inactivation and viral filtration steps.

The fermentation and purification processes for the new formulation nivolumab drug substance are both validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.

Several changes were implemented during development of the manufacturing process for the new formulation nivolumab drug substance, including changes to the manufacturing site and production scale. However, the analytical comparability studies, which included batch release data, extended characterisation data and forced degradation studies, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the nivolumab drug substance were leveraged from the authorised medicinal product Opdivo. The characterisation of impurities was performed using state-of-the-art methods.

The specifications for release and stability of the new formulation nivolumab drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity and potency. Specifications are based on clinical experience, batch analysis data and stability data, and comply with current compendial or regulatory guidelines.

Batch analysis data for development, clinical, process performance qualification (PPQ) and post-PPQ batches of the new formulation nivolumab drug substance, were provided. All specific analytical methods are described and are fully validated.

The new formulation nivolumab drug substance is stored frozen. During storage, no significant changes were observed under the proposed storage conditions.

Drug substance 2: Relatlimab (new active substance)
Relatlimab is a human monoclonal IgG4 antibody directed against the LAG-3 receptor, a negative T-cell regulator associated with T-cell exhaustion. Relatlimab is a glycoprotein (molecular weight approx. 148,000 Da) composed of two heavy chains of 446 amino acids and two kappa light chains of 214 amino acids, which are linked by inter-chain disulphide bonds.

Relatlimab is produced in CHO cells. A two-tiered cell banking system of master cell bank (MCB) and working cell bank (WCB) is in place. After thawing of the WCB vial, the cells are grown in suspension

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culture in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The culture is harvested, and purification is performed with a series of chromatography, ultra-/diafiltration, and viral inactivation and viral filtration steps.

The fermentation and purification processes for relatlimab drug substance are both validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities. The use of additional equipment was validated in a second process performance qualification (PPQ) campaign.

Several changes were implemented during development of the manufacturing process for relatlimab drug substance, including changes to the manufacturing site and production scale. However, the analytical comparability studies, which included batch release data, extended characterisation data and forced degradation studies, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the relatlimab drug substance and its impurities were performed using state-of-the-art methods.

The specifications for release and stability of the relatlimab drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity and potency. Specifications are based on clinical experience, batch analysis data and stability data, and comply with current compendial or regulatory guidelines.

Batch analysis data for nonclinical, clinical, PPQ and post-PPQ batches of the relatlimab drug substance with novel formulation were provided. All specific analytical methods are described and are fully validated.

The relatlimab drug substance is stored frozen. During storage, no significant changes were observed under the proposed storage conditions.

4.2 Drug product

Opdualag is a sterile, non-pyrogenic, single-use, preservative-free, isotonic, aqueous solution for intravenous infusion. It contains nivolumab and relatlimab at a protein-mass ratio of 3:1, respectively, co-formulated as a fixed-dose combination in a single glass vial.
The 320 mg/vial presentation, containing 240 mg of nivolumab and 80 mg of relatlimab in a nominal volume of 20 mL, is packaged in a Type I glass vial, closed with a rubber stopper and an aluminium seal.
Opdualag may be administered undiluted or diluted with either 0.9% sodium chloride solution for injection (normal saline) or 5% dextrose solution for injection to the required concentration prior to administration.

The excipients (histidine, histidine hydrochloride monohydrate, sucrose, pentetic acid and water for injection) are of compendial grade and commonly used for the formulation of biopharmaceuticals.
Several formulations of the two drug substances as a single-agent vial were used during clinical development. The nivolumab and relatlimab drug substances for the commercial co-formulation are both formulated in a histidine-based buffer system. The final bulk drug product is obtained by dilution with a formulation buffer.
The materials of the Type I glass vial and rubber stopper meet compendial requirements.
Compatibility studies were conducted to establish the in-use stability of the undiluted and diluted drug product with the intended materials and conditions of use.

The drug product manufacturing process consists of thawing of both formulated drug substances, pooling and mixing of nivolumab and relatlimab at a 3:1 ratio, final formulation, bioburden-reducing

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filtration, sterile filtration and aseptic filling, capping, visual inspection, labelling and secondary packaging.

The drug product manufacturing process is validated with several consecutive batches. The data demonstrated consistent production.

The specifications for release and stability of the drug products include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug product, including registrational stability, clinical and process performance qualification batches, were provided. All batch release data comply with the drug product specifications valid at the time of batch release. All specific analytical methods are validated.

The vials are stored at 2°C to 8°C protected from light. The stability data support a shelf life of 36 months.

4.3 Quality conclusions

Satisfactory and consistent quality of the two drug substances and the drug product has been demonstrated.
Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

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5 Nonclinical aspects

For the nonclinical testing strategy, the applicant considered the recommendations outlined in ICH S9 and S6(R1).

5.1 Pharmacology

In vitro assays demonstrated high affinity of relatlimab to human lymphocyte activation gene 3 (LAG-3; K_D 0.12 nM), and selective binding to an 8-amino acid sequence of the extracellular domain. In studies using LAG-3 cDNA-transfected CHO cells and anti-CD3/anti-CD28-activated primary human CD4+ T cells, the EC_{50} values differed 20-fold (EC_{50} with transfected CHO cells: 2.33 nM versus activated primary human T cells: 0.11 nM). The applicant explained this with potential differences in LAG-3 receptor glycosylation or structure. Using this method, the investigators also identified the cynomolgus monkey as a relevant species (EC_{50} with transfected CHO cells: 28.73 nM; activated primary cynomolgus T cells: 29.11 nM). Relatlimab did not bind to LAG-3 from mice; other species were not investigated. In functional assays, the antibody blocked the interaction of the LAG-3 ligand major histocompatibility complex (MHC) class II and human fibrinogen-like protein 1 (hFGL-1) in the nanomolar range. The reversal of human LAG-3-mediated inhibition of antigen responsiveness by relatlimab appeared to be dose-dependent. *In vitro* combination studies with relatlimab and nivolumab also showed that the simultaneous blockage of LAG-3 and PD-1 could improve T-cell response compared to the individual antibodies. Further investigations using allogeneic-mixed lymphocyte reaction assays to determine the role of T regulatory cells (Tregs) also supported the combination of both antibodies. Experimental studies confirmed the lack of effector functions.

The applicant studied the anti-tumour activity of LAG-3 inhibition alone and in combination with inhibition of PD-1 *in vivo* in murine tumour models. As relatlimab did not bind to murine LAG-3, the investigators characterised and used surrogate rat anti-mouse LAG-3 antibodies, i.e. 19C7 and C9B7W, as well as the surrogate anti-mouse antibody 4H2 for nivolumab. In studies with Sa1N fibrosarcoma, MC38 and CT26 colon adenocarcinoma, as well as A20 B cell lymphoma cells using intraperitoneal (IP) administration, a fixed dose of 10 mg/kg of both antibodies confirmed that the combination is superior to the individual agents regarding tumour growth inhibition, number of tumour free animals and survival. The animals did not show significant changes in body weight. The requested 3:1 ratio was successfully tested in only one assay.

Studies on secondary pharmacodynamics were not conducted.

The repeat-dose toxicity studies in cynomolgus monkeys included safety pharmacology endpoints. The investigators did not identify any relevant effects on cardiovascular, respiratory and central nervous system (CNS) function at exposure levels exceeding the clinical exposure.

5.2 Pharmacokinetics

The applicant investigated the pharmacokinetic profile of relatlimab in cynomolgus monkeys following single and repeated intravenous (IV) administration. The PK parameters are typical for a monoclonal antibody.
Serum exposure increased approximately proportionally to dose and was comparable in male and female animals. The mean terminal half-life ($t_{½}$) was greater than 200 hours after a single dose and increased to 490 hours after repeated dosing. Clearance was low as was the volume of distribution, indicating limited distribution.
In line with ICH S6(R1), the applicant did not conduct studies on distribution, metabolism and excretion.
As the release of cytokines may alter the expression of CYP enzymes, the applicant conducted *in vitro* assays regarding potential cytokine release and peripheral blood mononuclear cell (PBMC)

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activation. The data indicate only a minor increase in IL12p70. Hence, the risk for PK drug interactions due to altered CYP expression is considered low.

5.3 Toxicology

The test programme consisted of three repeat-dose IV toxicity studies with relatlimab in cynomolgus monkeys with a treatment duration of 4 weeks to 3 months plus recovery periods of 6 to 10 weeks. The maximum treatment duration complies with the requirements in ICH S9. The dosing frequency in the animal studies (weekly) was higher than proposed for clinical use (once every 4 weeks). The applicant studied potential combination effects in the 4-week studies using nivolumab/relatlimab ratios of 1:1 (non GLP) and 1:2 (GLP); the 3:1 ratio proposed for clinical use was not tested. Overall, the test programme has shortcomings as outlined above, but no further studies will be requested. The applicant identified the cynomolgus monkey as a pharmacologically relevant species. The lower *in vitro* binding affinity of relatlimab to monkey LAG-3 vs. human LAG-3 had no impact on the *in vivo* assessment since there was sufficient exposure and effects related to the pharmacological action were observed. The applicant assessed the reproductive toxicity in mice with IP administration using the murine surrogate antibody C9B7W (4-5 doses).

Overall, the animals generally tolerated treatment with up to 100 mg/kg/week relatlimab and/or 50 mg/kg/week nivolumab; only individual animals showed adverse effects. The combination of 100/50 mg/kg/week relatlimab/nivolumab in the 4-week study resulted in moribundity of one out of five male monkeys. This was attributed to CNS vasculitis and considered related to relatlimab and nivolumab administration. Immune-related inflammation is adequately addressed in the RMP as well as in the information for healthcare professionals.
No NOAEL could be determined for relatlimab in combination with nivolumab.
Exposure at the highest (100 mg/kg/week) relatlimab dose in the pivotal 3-month GLP study was 223-fold the clinical AUC. In this study, one male showed symptoms of ADA-mediated hypersensitivity reactions after repeated dosing. Corresponding decreases in relatlimab exposure, decreases in serum complement activity (CH50 test) and increases in plasma complement split factor 3a were also noted in this monkey, indicative of complement fixation of drug/ADA-complexes. This was not considered to be of human relevance.
Immunogenicity occurred in both GLP studies, but the presence of ADAs had in general no substantial impact on systemic exposures.

In accordance with ICH S9 and S6(R1), the applicant did not perform genotoxicity or carcinogenicity studies with relatlimab; this also applies to the conduct of fertility and peri/postnatal studies. The applicant used the murine surrogate antibodies 19C7 and C9B7W to assess the potential impact on embryofetal development. The investigators studied syngeneic (CBA/CaJ females with CBA/CaJ males) versus allogeneic (CBA/CaJ females with C57Bl/6 males) pregnancies. There are published literature reports of an increased incidence of post-implantation loss in allogeneic control pregnancies versus syngeneic control pregnancies, and that allogeneic models can be used for hazard identification of immunomodulatory compounds that can disrupt fetomaternal tolerance. However, the studies submitted by the applicant showed that allogeneic breeding did not increase post-implantation loss over syngeneic concurrent or historical control rates. In the absence of an increased background sensitivity to resorptions in the allogeneic pregnancy model, it is unknown whether the absence of anti-LAG-3-related effects reflects an insensitive model or an absence of target-related effects. As relatlimab is to be used a fixed-dose combination with nivolumab, the recommendation for use in pregnancy for nivolumab is acceptable for the information of healthcare professionals.

In immunohistochemistry studies with human tissues, relatlimab was cross-reactive to immune cells in multiple tissues, but also to cells within the pituitary gland, where expression of LAG-3 was confirmed by PCR. In these studies, the staining was intracellular. Therefore, relatlimab binding is not expected *in vivo* and the finding is considered of no clinical significance.

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The presented PIP contains a waiver for the paediatric age group from birth to less than 12 years of age. No nonclinical measures are listed for the age group 12 to 18 years.

Since both relatlimab and nivolumab are monoclonal antibodies and hence proteins, there is no risk for the environment from their use in patients.
The summary of the key findings from the nonclinical studies in the RMP is acceptable. Overall, no safety risks were identified in the nonclinical studies that would prevent approval.

5.4 Nonclinical conclusions

The submitted pharmacology studies showed that relatlimab binds human LAG-3 with high affinity and potently blocks the interaction with endogenous ligands. No unexpected safety concerns were identified in a set of toxicity studies in a pharmacologically relevant animal species. From a nonclinical perspective, the application can be approved.

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6 Clinical and clinical pharmacology aspects

6.1 Clinical pharmacology

Pharmacokinetics of relatlimab
ADME
The PK of relatlimab were characterised in subjects with solid tumours who received relatlimab doses of 20 to 800 mg Q2W and 160 to 1440 mg Q4W either as monotherapy or in combination with nivolumab at doses of 80 or 240 mg Q2W or 480 mg Q4W.

The following section focuses on the results of a PopPK analysis, which was conducted with data from 1713 subjects with unresectable or metastatic melanoma and other advanced solid tumours. For details on the demographic characteristics see the “Special populations / intrinsic factors” section. The structural PopPK model for relatlimab was a 2-compartment model with zero-order, IV infusion and parallel non-linear and time-varying linear clearance (CL).

Absorption
Relatlimab is administered as an IV infusion.

Distribution
The mean volume of distribution at steady state of relatlimab was 6.6 L.

Metabolism and elimination
No studies regarding the metabolism of relatlimab have been conducted considering the biological nature of the molecule.

Relatlimab was eliminated by parallel non-linear (target-mediated) and time-varying linear CL. The non-linear CL was predicted to contribute up to approx. 31% of total CL of relatlimab at the recommended dose (relatlimab 160 mg Q4W). The maximum decrease in the linear CL over time was ~ 5% for subjects with performance score (PS) = 0 and ~ 18% for subjects with PS > 0.
The model-predicted effective half-life at the therapeutic dose was 25.7 days.

The following table summarises the model-predicted relatlimab PK parameters including washout time following administration of relatlimab/nivolumab 160/480 mg Q4W in melanoma patients.

Table 1: Relatlimab PK parameters for relatlimab/nivolumab 160/480 mg Q4W in melanoma patients

Exposure (µg/mL)	1L MEL Geo. Mean (%CV) N = 333	Prior-IO MEL Geo. Mean (%CV) N = 80	MEL (1L + Prior-IO) Geo. Mean (%CV) N = 413
CL0 (mL/h)	6.06 (38.9)	5.99 (35.2)	6.05 (38.2)
CLss (mL/h)	5.48 (41.3)	5.67 (35.6)	5.51 (40.2)
VC (L)	3.59 (22)	3.68 (20.7)	3.61 (21.7)
VP (L)	3 (26.9)	2.84 (28.3)	2.97 (27.2)
VSS (L)	6.65 (19.8)	6.58 (19.9)	6.64 (19.8)
VMAX (µg/h)	80.3 (32.3)	81.5 (42.9)	80.5 (34.7)
PEMAX (%)	90.3 (26.2)	94.6 (12.3)	91.2 (24.1)
RAC	1.94 (26.3)	1.84 (24.2)	1.92 (26)
Effective Half-life (days)	26.2 (37.2)	23.7 (37.1)	25.7 (37.3)
Washout Time (days)	68.6 (35.7)	65.2 (35.4)	67.9 (35.7)

Source: Applicant`s documentation

Special populations / intrinsic factors

There were no dedicated PK studies in special populations. Instead, the PK of relatlimab in special populations was investigated as part of the PopPK analysis. Covariate effects were assessed using a full model approach (see graph below). Among the included covariates, the following had no significant effect: patient population (prior-IO melanoma and others), race (Black and Asian), monotherapy, age on CL and baseline body weight on intercompartmental clearance (Q).

Sex, Eastern Cooperative Oncology Group (ECOG status), estimated glomerular filtration rate (eGFR), baseline lactate dehydrogenase (LDH), and drug product were statistically significant covariates, but the effect size was limited and is not considered to be of clinical relevance. Therefore, no dose adjustment is required based on these covariates. Body weight was also a significant covariate. However, a flat-dose regimen was applied in the pivotal clinical study. Therefore, no dose adjustment based on body weight was considered to be required in the investigated weight range.

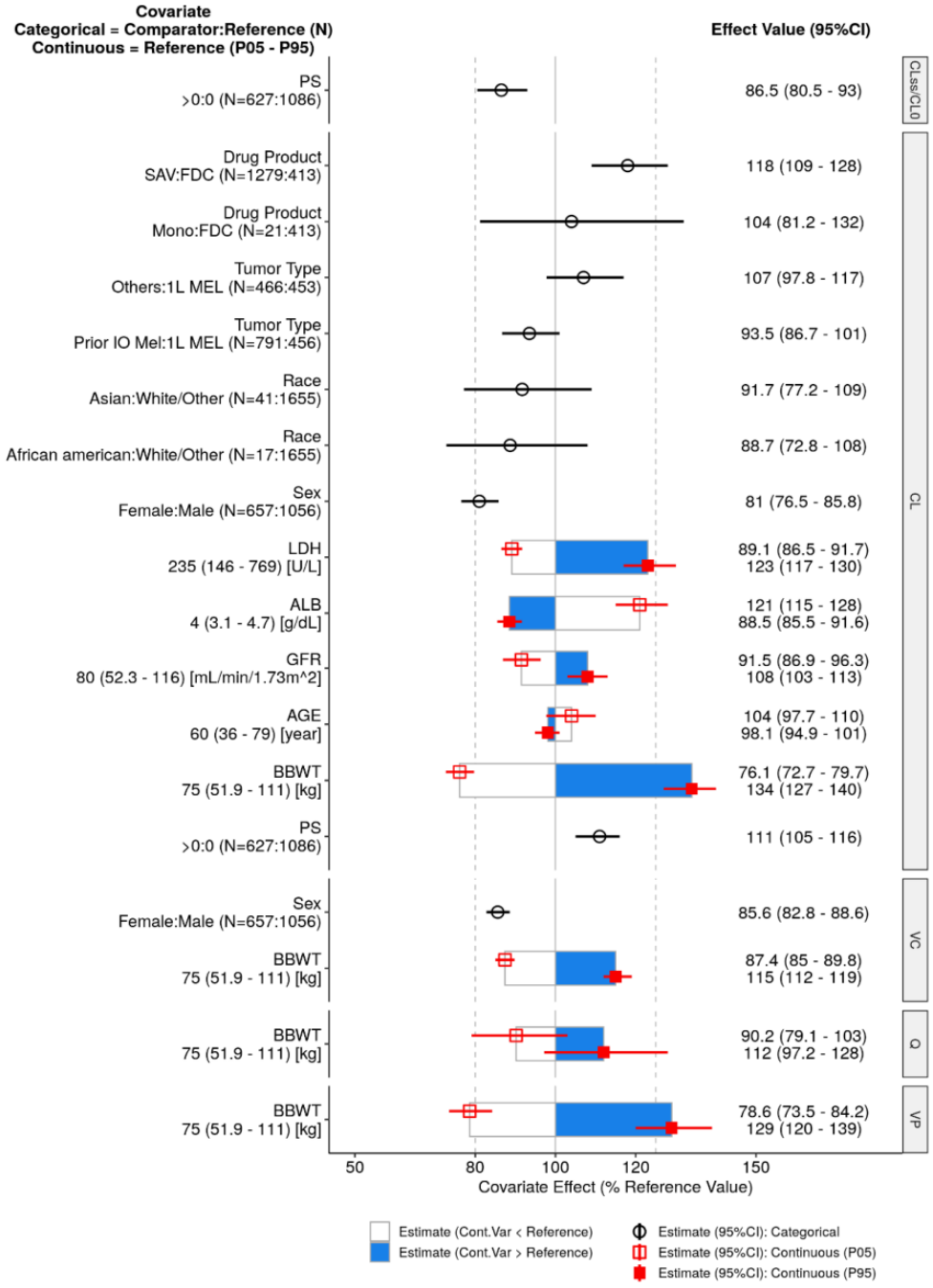

Figure 1: Covariate effects on full relatlimab population pharmacokinetic model parameters. Source: Applicant`s documentation

Hepatic and renal impairment

The PopPK dataset included 1445 subjects with normal hepatic function, 241 subjects with mild hepatic impairment, 12 subjects with moderate hepatic impairment and only one subject with severe hepatic impairment. At 160 mg Q4W, the exposures (Cavg1 and Cavgss) among subjects with mild and moderate hepatic impairment were similar compared with subjects with normal hepatic function (difference < 15%). The exposures of the one subject with severe hepatic impairment were higher.

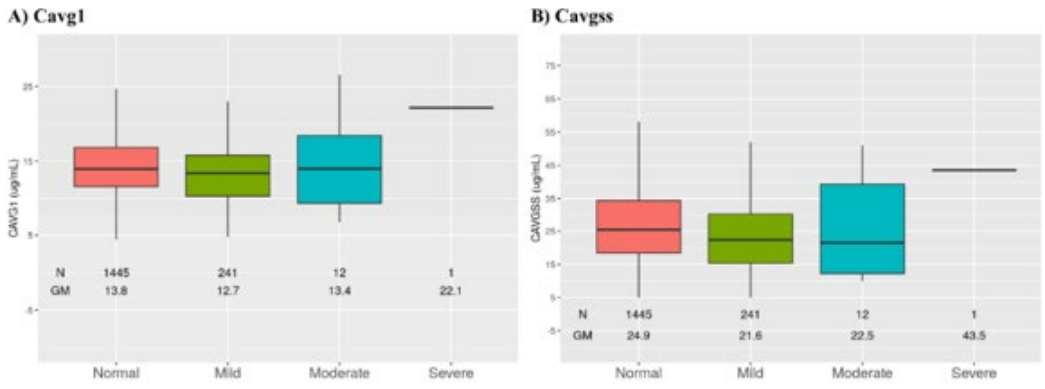

Figure 2: Distribution of model-predicted relatlimab exposures at 160 mg Q4W by hepatic function. Source: Applicant`s documentation

Baseline eGFR was a significant covariate on CL, and subjects with higher baseline eGFR had higher CL. At 160 mg Q4W, the exposures (Cavg1 and Cavgss) among subjects with mild (n=743) and moderate (n=160) renal impairment were similar compared with subjects with normal renal function (n=790) (difference < 17%). The exposures of the subjects with severe renal impairment were slightly higher. However, there were only two subjects with severe renal impairment.

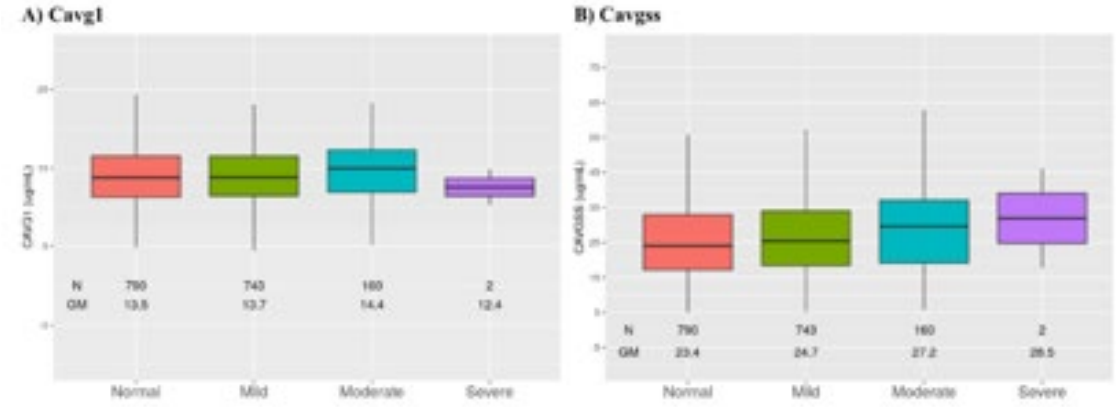

Figure 3: Distribution of model-predicted relatlimab exposures at 160 mg Q4W by renal function. Source: Applicant`s documentation

In conclusion, mild and moderate renal or hepatic impairment had a limited effect on the PK of relatlimab. However, data from subjects with severe hepatic impairment (n=1) and severe renal impairment (n=2) are too scarce to allow conclusions. The observed effects are in accordance with theoretical expectations. No dose adjustment is required in case of mild and moderate impairment but no recommendation can be given for severe impairment.

Interactions

No studies regarding DDIs have been conducted considering the biological nature of the molecule. This is acceptable.

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Pharmacokinetics of nivolumab

ADME

The PK of nivolumab have been characterised before. The following section focuses on the description of the nivolumab PK in combination with relatlimab in adults in the requested indication, which was characterised using a PopPK approach.

The PopPK model for nivolumab was a 2-compartment, zero-order IV infusion PK model, with time-varying CL (sigmoidal-Emax function) and a combined proportional and additive residual error model, and various covariate effects (see below).

Distribution

The mean volume of distribution at steady state of nivolumab was 6.65 L.

Elimination

Nivolumab was eliminated by time-varying clearance. The maximal decrease in the linear CL over time was ~21 %. The model-predicted effective half-life at the therapeutic dose was 26.5 days.

The following table summarises the model-predicted nivolumab PK parameters following administration of relatlimab/nivolumab 160/480 mg Q4W in melanoma subjects

Table 2: Nivolumab PK parameters for relatlimab/nivolumab 160/480 mg Q4W in melanoma subjects

Parameters	Adult 1L MEL Geo. Mean (%CV) (N = 334, G1)	Adult Prior-IO MEL Geo. Mean (%CV) (N = 77, G2)	Adult MEL (1L + Prior-IO) Geo. Mean (%CV) (N = 411, G3)
CL0 (mL/h)	9.59 (40.3)	7.49 (37.9)	9.16 (41.1)
CLss (mL/h)	7.57 (40.1)	7.26 (38.9)	7.51 (39.9)
VC (L)	3.88 (25.2)	3.63 (28.2)	3.83 (25.8)
VP (L)	2.72 (15.6)	2.66 (17.5)	2.71 (16.0)
VSS (L)	6.65 (19.2)	6.31 (22.0)	6.58 (19.8)
PEMAX (%)	78.9 (16.3)	97.0 (17.9)	82.0 (18.9)
T-HALFα (h)	32.7 (9.65)	31.9 (9.92)	32.6 (9.73)
T-HALFβ (d)	21.2 (25.6)	25.5 (25.5)	21.9 (26.8)
T-HALFα-SS (h)	33.1 (9.72)	32.0 (10.3)	32.9 (9.91)
T-HALFβ-SS (d)	26.5 (36.4)	26.2 (32.7)	26.4 (35.7)
Washout Time (d)	132 (36.4)	131 (32.7)	132 (35.7)

Source: Applicant`s documentation

Special populations / intrinsic factors

Based on previous experience, the nivolumab PopPK model contained covariate effects of baseline body weight (WTB), sex, race, baseline eGFR, and PS on CL, WTB and sex on VC, WTB on Q, and WTB on VP. During model development, additional covariate effects were included: age, albumin, patient population (POP, categorical covariate with categories < 12 years, 12-17 years, others), drug product, and combination therapy. Among these WTB, baseline albumin and paediatric versus adult patient population had the greatest influence. The effect of body weight was similar to that observed previously.

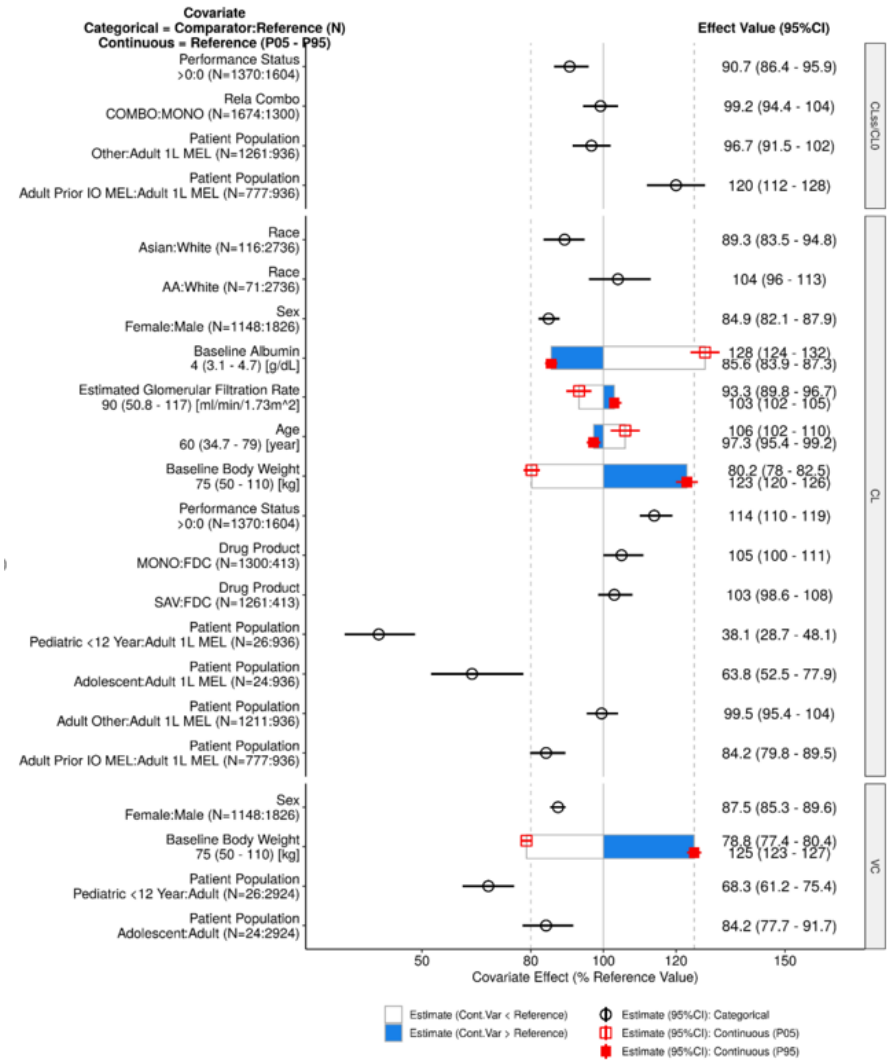

Figure 4: Covariate effects on full nivolumab population pharmacokinetic model parameters.
Source: Applicant`s documentation

Hepatic and renal impairment

The available data from patients with organ impairment and the effects on the PK of nivolumab were similar to those observed previously.

Evaluation of shorter infusion time (30 minutes)

Relatlimab + nivolumab was infused over 60 minutes in all clinical studies, while administration over 30 minutes is the approved dosing recommendation. Relatlimab exposures resulting from 30-minute and 60-minute infusion durations at 160 mg Q4W were predicted using the established PopPK model, and the predicted exposures were comparable. The two regimens were expected to differ mainly in the steepness of the rise in concentrations during the infusion phase with infusion rates 160 mg/30 min = 5.3 mg/min vs. 160 mg/60 min = 2.67 mg/min. The maximum infusion rate applied during clinical development was 1440 mg/60 min = 24 mg/min.

For nivolumab, the predicted exposures were also comparable between 30-minute and 60-minute infusions, and administration of 480 mg nivolumab over 30 minutes has been approved previously for other indications.

Therefore, the requested infusion duration of 30 minutes was acceptable from a clinical pharmacology perspective.

Pharmacodynamics of relatlimab
Mechanism of action and primary pharmacology
Relatlimab is an anti-LAG-3 human IgG4 monoclonal antibody which binds to LAG-3 and blocks ligand binding.

Secondary pharmacology (safety)
No studies regarding potential effects on the QT interval have been conducted considering the biological nature of the molecule.

Pharmacodynamics of nivolumab
The pharmacodynamics of nivolumab have been described previously.

6.2 Dose finding and dose recommendation

The proposed dose regimen was based primarily on study CA224020, where a flat dose of relatlimab and nivolumab was assessed.
In a dose escalation phase (part B) the initial dose of 80 mg /240 mg Q2W was selected for the expansion cohorts due to its favourable benefit-risk profile. No maximum tolerated dose (MTD) was identified.
Given that the 160/480 mg Q4W dose regimen provided similar Cavgss and peripheral receptor occupancy (based on an exploratory analysis) compared to the 80 mg/240 mg Q2W dose, the Q4W dosing was chosen for the pivotal study CA224047.

6.3 Efficacy

The applicant submitted one pivotal study (RELATIVITY-047) in stage III (unresectable) or stage IV melanoma patients who were previously untreated in the advanced disease setting, and a supportive dose-finding phase 1/2a study (CA224020) in patients with advanced solid tumours including metastatic melanoma.
RELATIVITY-047 is an ongoing, 1:1 randomised, active-controlled, double-blind, global, phase 2/3 study comparing relatlimab + nivolumab (Opdualag) to nivolumab monotherapy.
The primary endpoint of the study was progression-free survival (PFS) as assessed by a blinded independent central review (BICR) using RECIST v1.1. The secondary endpoints were overall survival (OS) and overall response rate (ORR) as assessed by a BICR. Patient-reported outcomes were descriptive.

Opdualag (relatlimab + nivolumab 160/480 mg IV q4W fixed-dose combination [FDC]) or nivolumab 480 mg IV Q4W were administered as a 60-minute IV infusion until progression or unacceptable toxicity. Patients were evaluated with a contrast-enhanced CT of the chest, abdomen, pelvis, and all known sites of disease at baseline, after randomisation at week 12, then every 8 weeks up to week 52, and every 12 weeks thereafter.
Patients aged ≥ 12 years at the time of informed consent and with an ECOG performance status of ≤ 1 or a Lansky Performance Score ≥ 80% for minors (ages 12-17 years) were eligible. For more detailed study characteristics, please refer to the attached information for healthcare professionals.
A sample size of 700 patients from phase 2 and 3 provided 85% power to detect a hazard ratio (HR) of 0.73 in PFS with an overall type I error of 0.05. Data provided within this submission are based on the final PFS analysis (database lock [DBL] 9 March 2021) and the final OS analysis (DBL 28 October 2021); the latter was provided during ongoing review.

Overall n=714 patients were enrolled, n=355 in the Opdualag arm and n=359 in the nivolumab arm. At DBL March 2021, the majority of the patients had discontinued study treatment in both arms (Opdualag: 66.8%; nivolumab: 64.9%). The reason for treatment discontinuation was mainly disease progression or treatment toxicity.

Treatment arms were balanced overall with respect to baseline and disease characteristics. The median age was 63 years in the Opdualag arm (range 20-94 years) and 62 years in the nivolumab arm (range 21-90 years). No adolescent patients were included in the study. Patients were primarily White (96.6%), male (58.3%) and had an ECOG PS of 0 (66.9%). Most of the patients had metastatic disease (Opdualag 90.1%; nivolumab 93.3%). The rate of locally advanced (unresectable) disease was 9.9% in the Opdualag arm and 6.4% in the nivolumab arm. PD-L1 expression ≥ 1% was reported in 41.1% of patients in the Opdualag arm and 40.9% in the nivolumab arm. LAG-3 expression ≥ 1% was found in 75.5% of patients in the Opdualag arm and 74.9% in the nivolumab arm.

At the final PFS analysis (DBL 9 March 2021), an exploratory analysis showed an improvement in the primary endpoint PFS per BICR in patients with PD-L1 negative (< 1%) tumours treated with Opdualag compared to nivolumab. The hazard ratio (HR) was 0.66 (95%CI: 0.51, 0.84).
The median OS in this population was not reached in the Opdualag arm and was 27.0 months in the nivolumab arm (0.78, 95%CI: 0.59, 1.04). For further details, please refer to the attached information for healthcare professionals.

6.4 Safety

The safety population of study RELATIVITY-047 consisted of n=355 patients treated with Opdualag (FDC) and n=359 patients treated with nivolumab monotherapy. The median duration of exposure to Opdualag was similar to nivolumab (5.6 months vs. 4.9 months).

Almost all patients had an adverse event (AE) of any grade (97.2% BMS-986213, 94.4% nivolumab). The most frequent AEs of any grade (≥ 20%) in the Opdualag arm were: fatigue (28.7%), pruritus (24.8%), arthralgia (23.7%), and diarrhoea (22.8%).
Grade 3-4 AEs were reported at a higher rate in the Opdualag arm (40.3% vs. 33.4%). The following AEs of grade 3-4 by preferred term were reported more frequently in the Opdualag arm (≥ 1% difference in incidence rate): arthralgia (1.7% vs. 0.6%), back pain (1.4% vs. 0.3%), weight decreased (1.1% vs. 0%), and dyspnoea (1.4% vs. 0.3%).
At data cut-off, a total of n=108 (30.4%) patients in the Opdualag arm and n=119 (33.1%) patients in the nivolumab arm had died. Death due to study drug toxicity was reported in n=3 patients (0.8%) and n=2 patients (0.6%) in the Opdualag and nivolumab arms, respectively. The reasons for the grade 5 AEs were haemophagocytic lymphohistiocytosis, acute oedema of the lung, and pneumonitis in the Opdualag arm, and sepsis + myocarditis and pneumonia in the nivolumab arm.
Serious adverse events (SAEs) were reported more frequently in the Opdualag arm compared to the nivolumab arm (34.1% vs. 29.2%). There was a higher incidence of patients with discontinuation of study therapy due to an AE in the Opdualag arm (19.4% vs. 11.4%).
Immune-modulated adverse events (IMAEs) within 100 days of last dose were reported more frequently in the Opdualag arm. Incidence rates of pneumonitis, diarrhoea, thyroiditis or hepatitis were approximately double compared to nivolumab. Adrenal insufficiency was 5-times more frequent in the Opdualag arm compared to nivolumab (4.2% vs. 0.8%). Only hyperthyroidism and diabetes mellitus were more frequent in the nivolumab arm; the rate of infusion-related reactions was similar in both treatment arms (1.1%).
Rates of other events of special interest (OESIs) within 100 days of last dose were comparable between the treatment arms. The most frequently reported OESI was troponin event (Opdualag: 11.5%; nivolumab: 10.0%). Myocarditis was reported more frequently in the Opdualag arm (n=6, 1.7% vs n=2, 0.6%). The rates of pancreatitis (1.1%) and encephalitis (0.6%) were similar in both treatment arms. There was n=1 event of Guillain-Barré syndrome and n=2 events of myositis/rhabdomyolysis in the Opdualag arm compared to none in the nivolumab arm.

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6.5 Final clinical and clinical pharmacology benefit-risk assessment

Cutaneous melanoma is the most lethal type of cutaneous neoplasia. The incidence of cutaneous melanoma in Switzerland is increasing, with new diagnoses having doubled in the last 20 years.

To date, first-line treatment for unresectable stage III/IV malignant melanoma is PD-1 blockade or PD-1 blockade combined with CTLA-4 blockade, regardless of BRAF status. In patients with BRAF mutations, additional options are the combination of BRAF and MEK inhibitors, possibly combined with immunotherapy.
First-line treatment with PD-1 blockade provides a median progression-free survival (mPFS) of 5-7 months and a median overall survival (mOS) of 33-37 months. The combination of a PD-1 inhibitor with a CTLA-4 inhibitor presented longer PFS and OS compared to monotherapy with PD-1 blockade (mPFS 11.5 months, mOS 72.1 months), but is associated with increased toxicity.
Therefore, there is an unmet medical need for new safe and tolerable drugs with improved efficacy.

Opdualag® is a fixed-dose combination (FDC) consisting of the new active substance relatlimab, an anti-LAG-3 human IgG4 monoclonal antibody, and the known PD-1 inhibitor nivolumab.

The PK of relatlimab and nivolumab in combination have been characterised sufficiently in adult melanoma patients.

The dose finding was performed in the supportive study CA224020 and is considered acceptable, although no maximum tolerated dose was reached. In addition, relatlimab monotherapy was not investigated in the intended indication, which is a clear weakness of the study programme.
The proposed dose of 160mg relatlimab/480 mg nivolumab as FDC is planned to be administered over a 30-minute infusion time. Relatlimab/nivolumab FDC was administered over 60 minutes in the dose-finding study CA224020 and the pivotal study RELATIVITY-047. The shortening of the infusion time is acceptable from a clinical and PK point of view, given that no significant exposure difference was observed between 30 and 60 minutes duration of infusion and the incidence of infusion-related reactions was similar across the different dose levels.

For evaluation of efficacy and safety, the applicant submitted the results of the pivotal study RELATIVITY-047, which is a randomised, double-blind, active-controlled phase 3 study, designed to evaluate the efficacy, safety and pharmacokinetics of first-line relatlimab + nivolumab FDC compared with nivolumab monotherapy in patients with stage III/IV melanoma.

The overall study design of RELATIVITY-047 is acceptable. The choice of comparator is appropriate at the time of study initiation.

The primary endpoint PFS is adequate, accepted in the literature and consistent with previous regulatory decisions. In addition, OS was a key secondary endpoint.

A clinical benefit with respect to PFS and OS was presented for Opdulag in comparison to nivolumab monotherapy in patients with PD-L1 level < 1% (exploratory analysis see above).

Patients treated with relatlimab + nivolumab FDC experienced adverse events (AEs) of any grade, G3-4 AEs, death due to study drug toxicity, serious adverse events, AEs leading to treatment discontinuation, and immune-mediated adverse events (IMAEs) more often. In the Opdualag arm a higher rate of arthralgia, neurologic AEs, and specific IMAEs such as pneumonitis, hepatitis, and adrenal insufficiency was reported. There is a relevant risk of myocarditis with combination immune checkpoint inhibition, and guidance on monitoring and management of the event is provided in the product information. Overall, the safety profile of relatlimab + nivolumab FDC is in line with known safety aspects of immune checkpoint inhibitors and is manageable in clinical practice.
Overall, the benefit-risk assessment is positive for the authorised indication.

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7 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.

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8 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.

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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 with a PD-L1 expression < 1%.

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
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, Guillain-Barre syndrome, myositis/rhabdomyolysis, encephalitis, haemolytic anaemia, Vogt Koyanagi-Harada syndrome (VKH) (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), myasthenia gravis, myasthenic syndrome, aseptic meningitis, gastritis, sarcoidosis, duodenitis, and hypoparathyroidism.

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

Other important warnings and precautions, including class effects

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

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

In patients treated with nivolumab before or after allogeneic 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 13.82 months, the most common adverse reactions (≥ 10%) were fatigue (39%), musculoskeletal pain (28%), rash (22%), pruritus (20%), arthralgia (20%), nausea (19%), diarrhoea (19%), headache (16%), decreased appetite (13%), cough (13%), abdominal pain (13%), constipation (12%), hypothyroidism (11%) and pyrexia (11%). The most common serious adverse reactions (≥ 1%) were abdominal pain, colitis, back pain and Dyspnoe. Incidences of Grade 3-5 adverse reactions in patients with unresectable or metastatic melanoma were 39% for nivolumab in combination with relatlimab and 32% 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). 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 (41.3%)[a], lymphopaenia (38.0%)[a], leucopaenia (12.3%)[a], neutropaenia (11.8%)[a]
Common	thrombocytopaenia[a], eosinophilia, blood lactate dehydrogenase increased
Uncommon	haemolytic anaemia
Endocrine disorders	
Very common	hypothyroidism (11.4%)
Common	adrenal insufficiency, hyperthyroidism, thyroiditis
Uncommon	Hypophysitis, hypopituitarism, hypogonadism
Metabolism and nutrition disorders	
Very common	hyponatraemia (23.7%)[a], hyperkalaemia (15.6%)[a], hypocalcaemia (15.6%)[a], decreased appetite (13.3%), hypomagnesaemia (10.7%)[a]
Common	diabetes mellitus, weight decreased, hypercalcaemia[a], hypokalaemia[a], hypermagnesaemia[a], hypernatraemia[a], hypoglycaemia[a], hyperalbuminaemia, dehydration, hyperuricaemia
Psychiatric disorders	
Common	confusional state
Nervous system disorders	
Very common	headache (15.5%)
Common	dizziness, peripheral neuropathy, dysgeusia
Uncommon	Guillain-Barre syndrome, optic neuritis
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 (12.7%)
Common	pneumonitis[b], dyspnoea, nasal congestion
Uncommon	asthma
Gastrointestinal disorders	
Very common	nausea (19.3%), diarrhoea (18.6%), abdominal pain (13.0%), constipation (11.6%)
Common	pancreatitis, colitis, gastritis, vomiting, dry mouth, lipase increased, amylase increased, stomatitis, dysphagia
Uncommon	oesophagitis
Hepatobiliary disorders	
Very common	increased AST (26.5%)[a], increased ALT (22.5%)[a], increased alkaline phosphatase (19.5%)[a]
Common	hepatitis, increased bilirubin[a], gamma-glutamyltransferase increased
Uncommon	cholangitis
Skin and subcutaneous tissue disorders	

Very common	rash (21.9%), pruritus (20.4%)
Common	vitiligo, alopecia, dry skin
Uncommon	pemphigoid, urticaria, lichenoid keratosis, photosensitivity reaction, psoriasis
Musculoskeletal and connective tissue disorders	
Very common	musculoskeletal pain (28.1%), arthralgia (19.5%)
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 (17.5%)[a]
Common	renal failure, proteinuria
Uncommon	nephritis
Reproductive system and breast disorders	
Uncommon	azoospermia
General disorders and administration site conditions	
Very common	fatigue (38.6%), pyrexia (10.7%)
Common	oedema, influenza-like illness, chills
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 3.0% (22/722) of patients. Incidences of Grade 3/4 events were 0.4% (3/722). Fatal events occurred in 0.3% (2/722) of patients. Median time to onset was 20 weeks (range: 3.6-111.4). Resolution occurred in 15/22 patients (68.2%) with a median time to resolution of 12 weeks (range: 1.9^{+}-58.3^{+}). 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 59.1% 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 11.9% (86/722), of patients. Incidences of Grade 3/4 events were 2.1% (15/722). Median time to onset was 11.7 weeks (range: 0.1-95.6). Resolution occurred in 71/88 patients (83.5%) with a median time to resolution of 3.4 weeks (range: 0.1-103.9^{+}). Immune-

related colitis 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 34.9% of patients with immune-related colitis.

Immune-related hepatitis
In patients treated with nivolumab in combination with relatlimab, liver function test abnormalities occurred in 10.5% (76/722) of patients. Incidences of Grade 3/4 events were 3.3% (24/722). Median time to onset was 8.2 weeks (range: 1.3-112.1). Resolution occurred in 61/75 patients (81.3%) with a median time to resolution of 5.1 weeks (range: 0.6-54.0). Immune-related hepatitis 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 32.9% 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 2.5% (18/722) of patients. Incidences of Grade 3/4 events were 0.7% (5/722). Median time to onset was 16.1 weeks (range: 1.9-98.1). Resolution occurred in 14/18 patients (77.8%) with a median time to resolution of 12.4 weeks (range: 0.9-120.9^{+}). Immune-related nephritis and renal dysfunction 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 22.2% 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 13.3% (96/722) of patients. There were no incidences of Grade 3/4 thyroid disorder. Incidences of Grade 3/4 events adrenal insufficiency occurred in 0.7% (5/722). Incidences of Grade 3/4 hypophysitis occurred in 0.3% (2/722). 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 13.4 weeks (range: 1.0-126.1). Resolution occurred in 22/118 patients (18.6%). Time to resolution ranged from 0.1^{+}-138.1^{+} 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 11.9% of patients with immune-related endocrinopathies.

Immune-related skin adverse reactions
In patients treated with nivolumab in combination with relatlimab, rash occurred in 34.6% (250/722) of patients. Incidences of Grade 3/4 events were 0.8% (6/722). Median time to onset was 5.8 weeks

(range: 0.1-97.9). Resolution occurred in 113/249 patients (45.4%) with a median time to resolution of 111.9 weeks (range: 0.1-160.0+). 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 3.2% 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 4.4% (32/722) of patients. Incidences of Grade 3/4 events were 0.1% (1/722).

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

L01XY03.
Pharmacotherapeutic group: Antineoplastic agents, combinations of antineoplastic agents.

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 exhausted T cells, promoting cytokine signalling and, ultimately, an anti-tumour response.

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). The most important secondary efficacy outcome measure was overall survival (OS) in the ITT population.

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. The baseline characteristics in patients with PD L1 expression < 1% were generally balanced between the treatment arms.

The median duration of treatment was 5.6 months (range: 0-31.5 months) in nivolumab in combination with relatlimab treated patients and 4.9 months (range: 0-32.2 months) in nivolumab treated patients.

At the time of the primary analysis, an exploratory analysis in patients with tumour PD-L1 expression < 1% and a median follow-up of 12.78 months (range: 0.03-33.05 months), showed an improvement in PFS with a median PFS of 6.37 months (95% CI: 4.60, 11.83) in the nivolumab in combination with relatlimab group (n = 209) as compared with 2.92 months (95% CI: 2.79, 4.50) in the nivolumab group (n = 212) (Hazard Ratio (HR) = 0.66, 95% CI: 0.51, 0.84). PFS events were observed in 112 patients (53.6%) of the nivolumab in combination with relatlimab group, and in 144 patients (67.9%) of the nivolumab group. The PFS rates at 6 months were 52.2% (95% CI: 44.6, 59.2) in the nivolumab in combination with relatlimab group, and 34.8% (95% CI: 28.0, 41.6) in the nivolumab group. The PFS

rates at 12 months were 42.3% (95% CI: 34.8, 49.6) in the nivolumab in combination with relatlimab group, and 25.3% (95% CI: 19.0, 32.1) in the nivolumab group.

In an exploratory analyses of the secondary efficacy endpoint in patients with a tumour PD-L1 expression < 1% with a median follow-up of 17.78 months (range: 0.26-40.64 months), the median OS was not reached (NR; 95% CI: 27.4, NR) in the nivolumab in combination with relatlimab group as compared with 27.0 months (95% CI: 17.1, NR) in the nivolumab group (HR = 0.78; 95% CI: 0.59, 1.04). OS events were observed in 89 patients (42.6%) of the nivolumab in combination with relatlimab group, and in 104 patients (49.1%) of the nivolumab group. The OS rates at 12 months were 73.9% (95% CI: 67.4, 79.4) in the nivolumab in combination with relatlimab group, and 67.4% (95% CI: 60.6, 73.3) in the nivolumab group. The OS rates at 24 months were 59.6% (95% CI: 52.2, 66.2) in the nivolumab in combination with relatlimab group, and 53.1% (95% CI: 45.8, 59.9) in the nivolumab group.

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 (1.5 mg/mL nivolumab and 0.5 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 2022