Drug Monograph

A - Drug Name

nivolumab / relatlimab

COMMON TRADE NAME(S): Opdualag™

back to top

B - Mechanism of Action and Pharmacokinetics

Nivolumab is a human monoclonal antibody (IgG4) that binds to the PD-1 receptor on T-cells, blocking interaction with its ligands, PD-L1 and PD-L2, and preventing PD-1 pathway-mediated inhibition of the tumour immune response. **Relatlimab** is a human monoclonal antibody (IgG4) that targets the LAG-3 T-cell receptors, blocking its interaction with MHC II and other ligands. This reduces LAG-3 pathway-mediated inhibition of the immune response. Both mechanisms promote T-cell proliferation and cytokine secretion, and the combination of nivolumab / relatlimab results in increased T-cell activation compared to either antibody alone.

Absorption	After the first dose, relatlimab concentration increased dose proportionally following q4 week dosing of nivolumab / relatlimab.	
	Time to reach steady state	16 weeks (for relatlimab, following q4 week dosing of nivolumab / relatlimab)
Metabolism	Expected to be degraded into small peptides, amino acids, and small carbohydrates via catabolic pathways	
Elimination	Half-life	~26 days

back to top

C - Indications and Status

Health Canada Approvals:

- Melanoma

Refer to the product monograph for a full list and details of approved indications.

back to top

D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

The following adverse effects occurred in ≥ 1% of patients from a Phase II/III study comparing nivolumab / relatlimab to nivolumab monotherapy for previously untreated metastatic or unresectable melanoma. Severe or life-threatening adverse events may also be included from other sources or post-marketing.

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Myocarditis (1%)	E
Dermatological	Alopecia (2%)	E
	Other (1%) (lichenoid keratosis)	E
	Photosensitivity (1%)	E
	Rash, pruritus (29%)	E D
	Skin hypopigmentation (13%) (vitiligo)	E D
Gastrointestinal	Abdominal pain (14%)	E
	Anorexia, weight loss (16%)	E
	Colitis (3%) (1% severe)	E D
	Constipation (11%)	E
	Diarrhea (26%)	E D
	Mucositis (3%)	E

	Nausea, vomiting (19%)	E
General	Edema (9%)	E
	Fatigue (41%) (2% severe)	E
	Fever, chills (12%)	E
Hematological	Eosinophilia (3%)	E
	Hemolytic anemia (rare)	E
Hepatobiliary	Hepatitis (1%)	E D
	Pancreatitis (1%)	E D
Hypersensitivity	Infusion related reaction (6%) (mild to moderate only)	I E
Immune	Hemophagocytic lymphohistiocytosis (rare)	E
Infection	Infection (11%)	E
Injection site	Phlebitis (1%)	E
Metabolic / Endocrine	Adrenal insufficiency (5%) (1% severe)	E D
	Diabetes mellitus (1%) (may be severe)	E D
	Hyperthyroidism (7%)	E D
	Hyperuricemia (3%)	E
	Hypophysitis (1%) (may be severe)	E D
	Hypothyroidism (16%)	E D
	Thyroiditis (3%)	E D
Musculoskeletal	Musculoskeletal pain (32%) (2% severe)	E
	Rhabdomyolysis (rare)	E
Nervous System	Confusion (2%)	E
	Dizziness (10%)	E
	Encephalitis (rare)	E
	Guillain-Barre syndrome (rare)	E
	Headache (20%)	E
	Myositis (rare)	E
	Peripheral neuropathy (6%)	E
Ophthalmic	Eye disorders (2%) (including uveitis)	E D
	Vogt-Koyanagi-Harada syndrome (rare)	E
Renal	Proteinuria (1%)	E
	Renal failure (2%)	E D
Respiratory	Cough, dyspnea (16%)	E
	Pneumonitis (5%)	E D

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for nivolumab / relatlimab include fatigue, musculoskeletal pain, rash, pruritus, diarrhea, headache, nausea, vomiting, anorexia, weight loss, cough, dyspnea, hypothyroidism and abdominal pain.

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of Immune-related toxicities and their management.

The presentation of adverse effects may be different compared to other anti-cancer agents and early diagnosis and appropriate management are critical.

Immune-related reactions including **rash, pneumonitis, colitis, hepatitis, pancreatitis, nephritis, endocrinopathies, meningoencephalitis, and neuropathies** have been reported and may be severe or fatal. Onset may vary from days to many months and may occur after treatment has ended.

CMV infection/reactivation has been reported in patients with immune-related colitis who are refractory to corticosteroids. Addition of an alternative immunosuppressive agent or replacement of the corticosteroid therapy should be considered in corticosteroid-refractory immune-related colitis, if other causes are excluded (including CMV infection/reactivation, other viral, bacterial and parasitic etiology).

Immune-mediated endocrinopathies, including hypo or hyperthyroidism, hypophysitis, adrenal insufficiency, and diabetes mellitus, have been reported. Cases of diabetic ketoacidosis have been observed with nivolumab monotherapy and could potentially occur with nivolumab / relatlimab.

Rare cases of SJS and TEN, which may be fatal, have been observed with nivolumab monotherapy and could potentially occur with nivolumab / relatlimab.

back to top

E - Dosing

Refer to protocol by which the patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Avoid the use of corticosteroids or immunosuppressants before starting treatment.

Pre-medications (prophylaxis for infusion reaction):

- Routine pre-medication is not recommended.
- May consider pre-medication with antipyretics and H1-receptor antagonists if an IR has occurred in the past.

Adults:

Intravenous[1,2]: nivolumab 480 mg / relatlimab 160 mg every 28 days

[1]Available as a fixed-dose combination product containing nivolumab 12 mg/mL and relatlimab 4 mg/mL.

[2]Patients must weigh > 40 kg (based on NDFP criteria).

Dosage with Toxicity:

- Healthcare professionals should also consult the most recent nivolumab / relatlimab product monograph for additional information.
- Do not restart nivolumab / relatlimab while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive drugs. Patients receiving immunosuppressive medications (e.g. high-dose corticosteroids) should receive prophylactic antibiotics to prevent opportunistic infections.

Summary of Principles of Management

- Immune-related adverse effects (irAEs) are different in their presentation, onset and duration compared to conventional chemotherapy. Patient and provider education is essential.
- Initial irAE presentation can occur months after completion of treatment and affect multiple organs.
- Dose escalation or reduction is not recommended.
- If no other cause can be identified (such as infection), any new symptom should be considered immune-related and prompt treatment initiated.
- Organ-specific system-based toxicity management is recommended.
- **Refer to the CCO guideline for detailed description of Immune-mediated toxicities and their management**

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • Once symptoms have resolved, the infusion may be restarted at a slower rate with close monitoring.	• Re-challenge with close monitoring and pre-medications.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Dosage with Hepatic Impairment:

Bilirubin		AST	Nivolumab/ Relatlimab Dose
≤ ULN	and	> ULN	No dose adjustment is required.
>1 to 1.5 x ULN	and	Any	
>1.5 to 3 x ULN	and	Any	
> 3 x ULN	and	Any	Has not been studied

Dosage with Renal Impairment:

Approximate Creatinine Clearance* (mL/min)	Nivolumab / Relatlimab Dose
≥ 30	No dose adjustment is required.
< 30	Not studied.

*Reported as eGFR in mL/min/1.73m^2

Dosage in the elderly:

No dose adjustment is required for patients ≥ 65 years. No overall differences in safety or effectiveness were observed between patients ≥ 65 years and younger patients.

Children:

The safety and efficacy of nivolumab / relatlimab have not been established in patients < 12 years or patients ≥ 12 years who weigh < 40 kg.

back to top

F - Administration Guidelines

Nivolumab/relatlimab is **not interchangeable** with other nivolumab-containing products.

- Nivolumab / relatlimab may be administered undiluted or diluted with 0.9% Sodium Chloride Injection or D5W.
- If diluted, the final infusion concentration should range between 3-12 mg/mL for nivolumab and 1-4 mg/mL for relatlimab. Total volume of infusion must not exceed 160 mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Infuse IV, do NOT administer as IV push or bolus.
- Infuse IV over 30 minutes via low protein binding in-line filter (0.2 to 1.2 micrometer).
- Nivolumab / relatlimab is compatible with ethylvinyl acetate (EVA), polyvinyl chloride (PVC) or polyolefin containers, PVC infusion sets and in-line filters with polyethersulfone (PES), nylon, and polyvinylidene fluoride (PVDF) membranes.
- Do not infuse concomitantly with other drugs; flush the line with normal saline or D5W after each dose.
- Store unopened vials in original packaging between 2^{o}C to 8^{o}C. Protect from light.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

back to top

G - Special Precautions

Contraindications:

- Patients who have a hypersensitivity to nivolumab, relatlimab, or any of their components.

Other Warnings/Precautions:

- The pivotal trial excluded patients with certain medical conditions, such as:
  - active brain metastases;
  - those requiring systemic treatment with moderate or high dose corticosteroids or immunosuppressive medicines;
  - uveal melanoma;
  - active autoimmune disease;
  - a history of myocarditis or myositis.

- Nivolumab / relatlimab may increase the risk of rejection in solid organ transplant recipients, or GVHD in patients with prior allogeneic HSCT or GVHD. Assess benefit-risk of nivolumab / relatlimab treatment in these patients.

Other Drug Properties:

- Carcinogenicity: Unknown

Pregnancy and Lactation:

- Mutagenicity: Unknown

- Fetotoxicity: Documented in animals
  Nivolumab and relatlimab are IgG4 antibodies; human IgG4 is known to cross the placenta.

- Pregnancy:
  Nivolumab / relatlimab is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during treatment, and for at least **5 months** after the last dose.

- Excretion into breast milk: Probable
  Immunoglobulins are known to be secreted into breast milk; therefore as a human IgG4 antibody, there is potential for infant exposure to nivolumab / relatlimab via breast milk.

- Breastfeeding:
  Breastfeeding is not recommended during treatment and for at least **5 months** after the last dose.

- Fertility effects: Unknown

back to top

H - Interactions

No formal drug interaction studies have been conducted. Nivolumab / relatlimab is unlikely to affect the pharmacokinetics of other drugs.

The use of systemic corticosteroids and other immunosuppressants before starting nivolumab / relatlimab should be avoided because of their potential interference with its activity; however, they can be used after starting nivolumab / relatlimab to treat immune-related adverse reactions.

Acetaminophen may affect the response to immune checkpoint inhibitors. Further clinical studies are needed to determine the exact mechanism and the appropriate clinical management (Bessede et al, 2022).

back to top

I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
CBC	Baseline and Q3-6 weeks, or as clinically indicated, for at least up to 5 months after the last dose
Liver function tests	Baseline and Q3-6 weeks, or as clinically indicated, for at least up to 5 months after the last dose
Renal function tests, including electrolytes	Baseline and Q3-6 weeks, or as clinically indicated, for at least up to 5 months after the last dose
Thyroid function tests	Baseline, and as clinically indicated, for at least up to 5 months after the last dose
Blood glucose	Baseline, and as clinically indicated, for at least up to 5 months after the last dose
Pituitary and adrenal function tests	Baseline, and as clinically indicated, especially when on physiologic replacement therapy and for at least up to 5 months after the last dose
GVHD or solid organ transplant rejection (if applicable)	As clinically indicated
Clinical toxicity assessment for infusion reactions, fatigue, immune-mediated reactions, including diarrhea, rash, endocrine, respiratory, musculoskeletal, neurologic, cardiac and ophthalmic effects	At each visit and for at least up to 5 months after the last dose

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

back to top

J - Supplementary Public Funding

New Drug Funding Program (NDFP Website)

- Nivolumab and Relatlimab - Advanced Melanoma (Unresectable or Metastatic Melanoma)

back to top

K - References

Bessede A, Marabelle A, Guegan JP, et al. Impact of acetaminophen on the efficacy of immunotherapy in cancer patients. Ann Oncol 2022;33(9):909-15.

CADTH Reimbursement Recommendation: Nivolumab and Relatlimab (Opdualag). Canadian Journal of Health Technologies. February 2024.

NHS: Somerset, Wiltshire, Avon and Gloucestershire Cancer Alliance. Nivolumab-Relatlimab (Opdualag®) (Melanoma). February 2024.

Nivolumab drug monograph. Ontario Health (Cancer Care Ontario).

Prescribing Information: Opdualag™ (nivolumab and relatlimab-rmbw) injection, for intravenous use. Bristol-Myers Squibb Company. March 2022.

Product Monograph: Opdualag™ (nivolumab and relatlimab for injection). Bristol-Myers Squibb Canada. September 2023.

Tawbi HA, Schadendorf D, Lipson EJ, et al. RELATIVITY-047 Investigators. Relatlimab and nivolumab versus nivolumab in untreated advanced melanoma. N Engl J Med 2022 Jan 6;386(1):24-34

November 2024 New drug monograph

back to top

L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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back to top