Regimen Monograph

A - Regimen Name

NIVL+RELA Regimen

Nivolumab-Relatlimab

Disease Site

Skin
Melanoma

Intent

Palliative

Regimen Category

Evidence-Informed :

Regimen is considered appropriate as part of the standard care of patients; meaningfully improves outcomes (survival, quality of life), tolerability or costs compared to alternatives (recommended by the Disease Site Team and national consensus body e.g. pan-Canadian Oncology Drug Review, pCODR). Recommendation is based on an appropriately conducted phase III clinical trial relevant to the Canadian context OR (where phase III trials are not feasible) an appropriately sized phase II trial. Regimens where one or more drugs are not approved by Health Canada for any indication will be identified under Rationale and Use.

Rationale and Uses

For the treatment of unresectable Stage III or metastatic (Stage IV) melanoma, in adult patients who are previously untreated or have received prior first-line BRAF-targeted therapy for unresectable or metastatic melanoma

(Refer to the NDFP eligibility form for detailed funding criteria)

Supplementary Public Funding

nivolumab / relatlimab
New Drug Funding Program (Nivolumab and Relatlimab - Advanced Melanoma (Unresectable or Metastatic Melanoma)) (NDFP Website)

back to top

B - Drug Regimen

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

nivolumab / relatlimab[1,2]	480 mg /160 mg	IV	Day 1

[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).

back to top

C - Cycle Frequency

REPEAT EVERY 28 DAYS

Until disease progression or unacceptable toxicity

back to top

D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

- Also refer to CCO Antiemetic Recommendations.

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

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.

Other:

- Avoid the use of corticosteroids or immunosuppressants before starting treatment.

back to top

E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated.

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).

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

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.

back to top

F - Adverse Effects

Refer to nivolumab / relatlimab and nivolumab drug monograph(s) for additional details of adverse effects.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Fatigue • Musculoskeletal pain • Rash, pruritus • Diarrhea	• Headache • Nausea, vomiting • Anorexia, weight loss • Cough, dyspnea • Hypothyroidism • Abdominal pain • Skin hypopigmentation • Fever, chills • Constipation • Infection	• Myocarditis • Adrenal insufficiency • Diabetes mellitus • Hyperthyroidism • Hypophysitis • Thyroiditis • Colitis • Hepatitis • Pancreatitis • Renal failure • Rhabdomyolysis • Myositis • Encephalitis • Guillain-Barre syndrome • Pneumonitis • Uveitis • Hemolytic anemia • Vogt Koyanagi-Harada syndrome • Hemophagocytic lymphohistiocytosis

back to top

G - Interactions

Refer to nivolumab / relatlimab drug monograph(s) for additional details.

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.

back to top

H - Drug Administration and Special Precautions

Refer to nivolumab / relatlimab drug monograph(s) for additional details.

Administration

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.

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.

Pregnancy/Lactation

- This regimen is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners while on treatment and after the last treatment dose. Recommended methods and duration of contraception may differ depending on the treatment. Refer to the drug monograph(s) for more information.
- Breastfeeding is not recommended during this treatment and after the last treatment dose. Refer to the drug monograph(s) for recommendations after the last treatment dose (if available).
- Fertility effects: Unknown

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

- 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
- 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
- Blood glucose; Baseline, and as clinically indicated, 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

K - References

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

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

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 Expanded into full regimen monograph

back to top

M - Disclaimer

Regimen Abstracts

A Regimen Abstract is an abbreviated version of a Regimen Monograph and contains only top level information on usage, dosing, schedule, cycle length and special notes (if available). It is intended for healthcare providers and is to be used for informational purposes only. It is not intended to constitute or be a substitute for medical advice, and all uses of the Regimen Abstract are subject to clinical judgment. Such information is provided on an "as-is" basis, without any representation, warranty, or condition, whether express, or implied, statutory or otherwise, as to the information's quality, accuracy, currency, completeness, or reliability, and Cancer Care Ontario disclaims all liability for the use of this information, and for any claims, actions, demands or suits that arise from such use.

Information in regimen abstracts is accurate to the extent of the ST-QBP regimen master listings, and has not undergone the full review process of a regimen monograph. Full regimen monographs will be published for each ST-QBP regimen as they are developed.

Regimen Monographs

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

The information set out in the drug monographs, regimen monographs, appendices and symptom management information (for health professionals) contained in the Drug Formulary (the "Formulary") is intended for healthcare providers and is to be used for informational purposes only. The information is not intended to cover all possible uses, directions, precautions, drug interactions or adverse effects of a particular drug, nor should it be construed to indicate that use of a particular drug is safe, appropriate or effective for a given condition. The information in the Formulary is not intended to constitute or be a substitute for medical advice and should not be relied upon in any such regard. All uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

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last revision will be visible on each page of the monograph and regimen. Since standards of usage are constantly evolving, it is advised that the Formulary not be used as the sole source of information. It is strongly recommended that original references or product monograph be consulted prior to using a chemotherapy regimen for the first time.

Some Formulary documents, such as the medication information sheets, regimen information sheets and symptom management information (for patients), are intended for patients. Patients should always consult with their healthcare provider if they have questions regarding any information set out in the Formulary documents.

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back to top