

Regimen Monograph

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A - Regimen Name

NIVL Regimen

nivolumab

Disease Site Head and Neck

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 recurrent or metastatic squamous cell cancer of the head and neck (SCCHN) progressing on or after platinum-based chemotherapy. Funded by NDFP for patients with good performance status, who have:

- a recurrence within 6 months of potentially curative neoadjuvant/adjuvant platinum-based therapy, OR
- a recurrence after receiving platinum-based therapy in a non-curative setting, OR
- a documented intolerance or contraindication to platinum-based therapy and is being treated with palliative intent

Supplementary Public Funding [nivolumab](#)
 New Drug Funding Program (Nivolumab - Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck which is Platinum Resistant or Refractory) ([NDFP Website](#))

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B - Drug Regimen

| | | | |
|---------------------------|----------|----------------------------|-------|
| nivolumab | 3 mg /kg | IV (up to 240 mg maximum)* | Day 1 |
| OR | | | |
| nivolumab | 6 mg /kg | IV (up to 480 mg maximum)* | Day 1 |

*Dosing based on NDFP funding criteria

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C - Cycle Frequency

Nivolumab **3 mg/kg** dosing: **REPEAT EVERY 14 DAYS**

Nivolumab **6 mg/kg** dosing: **REPEAT EVERY 28 DAYS**

Until disease progression or unacceptable toxicity.

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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.

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E - Dose Modifications

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

Dosage with toxicity

- Health care professionals should also consult the most recent nivolumab product monograph for additional information.
- Do not restart nivolumab while the patient is receiving immunosuppressive doses of corticosteroids or other immunosuppressive drugs. Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive medications (e.g. high-dose corticosteroids).

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 | <ul style="list-style-type: none"> Stop or slow the infusion rate. Manage the symptoms. Restart: <ul style="list-style-type: none"> Once symptoms have resolved, the infusion may be restarted with close monitoring. | <ul style="list-style-type: none"> Re-challenge with close monitoring and pre-medications. |
| 3 or 4 | <ul style="list-style-type: none"> Stop treatment Aggressively manage symptoms. | <ul style="list-style-type: none"> Discontinue permanently (do not re-challenge). |

Hepatic Impairment

| Hepatic Impairment | Action |
|--|----------------------------|
| Mild (bilirubin >1 - 1.5 x ULN or AST > ULN) | No dose adjustment needed |
| Moderate (bilirubin >1.5 - 3 x ULN and any AST) or Severe (bilirubin >3 x ULN and any AST) | No data. Not been studied. |

Renal Impairment

No clinically important differences in drug clearance were found between patients with mild or moderate renal impairment and patients with normal renal function. Insufficient data available for severe renal impairment (GFR < 30 mL/min).

Dosage in the Elderly

Limited data is available in patients aged \geq 65 years.

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F - Adverse Effects

Refer to [nivolumab](#) drug monograph(s) for additional details of adverse effects.

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

| Common (25-49%) | Less common (10-24%) | Uncommon (< 10%), but may be severe or life-threatening |
|---|--|--|
| <ul style="list-style-type: none"> • Fatigue • Rash (may be severe) | <ul style="list-style-type: none"> • Diarrhea (may be severe) • Electrolyte imbalances (including potassium, calcium, magnesium, sodium) • Nausea, vomiting • Musculoskeletal pain • Headache | <ul style="list-style-type: none"> • Rhabdomyolysis • Hypo / hyperthyroidism • Hypopituitarism (also hypophysitis) • Hypoparathyroidism • Adrenal insufficiency • Hyperglycemia (including diabetes and DKA) • Infusion related reaction • Peripheral neuropathy • Immunosuppression +/- Infection (may be severe, including CMV infection / reactivation in corticosteroid-refractory colitis) • Arrhythmia • Cardiotoxicity (including myocarditis, pericarditis) • Venous thromboembolism • Hemolysis (immune-mediated, also thrombocytopenia) • Hemophagocytic lymphohistiocytosis • Sarcoidosis • Encephalitis/meningitis • Cholestasis • Pancreatitis • Pneumonitis • Guillain-Barre syndrome • Solid organ transplant rejection • Vogt-Koyanagi-Harada syndrome • Uveitis • Myasthenia gravis, myositis • Nephrotoxicity, nephritis • Vasculitis • Histiocytic necrotizing lymphadenitis |

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G - Interactions

Refer to [nivolumab](#) drug monograph(s) for additional details

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

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

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H - Drug Administration and Special Precautions

Refer to [nivolumab](#) drug monograph(s) for additional details.

Administration

- Withdraw the required volume of nivolumab 10 mg/mL injection and aseptically transfer into a sterile IV container (PVC container, non-PVC container, or glass bottle).
- Nivolumab may be administered undiluted or diluted with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
- If diluted, the final infusion concentration should range between 1 to 10 mg/mL. Final volume of infusion must not exceed 160 mL.
- For patients < 40 kg, the total volume of infusion must not be > 4 mL/kg of patient weight.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard if solution is cloudy, if there is pronounced discoloration or if there is foreign particulate matter.
- Administer by IV infusion over 30 minutes via a sterile, non-pyrogenic, low protein binding in-line filter (pore size 0.2 to 1.2 micrometer).
- Do not infuse concomitantly with other agents.
- Flush the line with normal saline or D5W after each dose.

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- If a dose is missed, it should be administered as soon as possible. Adjust administration schedule to maintain the prescribed dosing interval.
 - Store unopened nivolumab vials in original packaging between 2°C to 8°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 this drug or any of its components.

Other Warnings/Precautions

- Use with caution in patients on a controlled sodium diet. Each 10 mg (=1 mL) of nivolumab contains 0.1 mmol (2.3 mg) sodium.
- Use of a PD-1 blocking antibody with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials, due to increased mortality reported.
- Use with caution in patients with:
 - autoimmune disease
 - history of pneumonitis or interstitial lung disease or recent chest radiation
 - prior or planned allogeneic stem cell transplant
 - infection with HIV, or active coinfection with HBV/HCV or HBV/HDV as these patients were excluded from clinical trials

Pregnancy/Lactation

- Nivolumab is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **5 months** after the last dose.
- Breastfeeding is not recommended during treatment, and for at least **5 months** after the last dose.
- Fertility effects: Unknown

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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

- Liver function tests; Baseline, before each dose and as clinically indicated for at least up to 5 months after the last dose
- Renal function tests, including electrolytes; Baseline, before each dose and as clinically indicated for at least up to 5 months after the last dose
- Thyroid function tests; Baseline, before each dose, especially when on physiologic replacement therapy and for at least up to 5 months after the last dose
- Blood glucose; Baseline, at each visit, as clinically indicated and 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
- Patients with tumours that are PD-L1 negative or unknown status should be monitored closely for progression during the first months of treatment
- 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](#)

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K - References

Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck. *N Engl J Med* 2016;375(19):1856-1867.

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

Zhao X, Ivaturi V, Gopalakrishnan M, et al. Abstract CT101: A model-based exposure-response (ER) assessment of a nivolumab (NIVO) 4-weekly (Q4W) dosing schedule across multiple tumor types. *Cancer Res* 2017;77(13 suppl):DOI: 10.1158/1538-7445.AM2017-CT101.

Zhao X, Suryawanshi S, Hruska M, et al. Assessment of nivolumab benefit-risk profile of a 240-mg flat dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. *Ann Oncol* 2017;28(8):2002-8.

March 2023 Modified Dosage in the elderly, Warnings/precautions, and Pregnancy/lactation sections

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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

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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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