Regimen Monograph

A - Regimen Name

NIVL Regimen

nivolumab

Disease Site

Genitourinary
Bladder / Urothelial

Intent

Adjuvant

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

Adjuvant treatment for patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC.

Treatment is only for patients who have no evidence of recurrence confirmed prior to initiating therapy, no metastatic disease or active autoimmune disease, and with good performance status.

(Refer to NDFP form for full details.)

Supplementary Public Funding

nivolumab
New Drug Funding Program (Nivolumab - Adjuvant Treatment of Urothelial Carcinoma) (NDFP Website)

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B - Drug Regimen

Start within 120 days of surgical resection:

nivolumab†	3 mg /kg	IV (max 240 mg)	Day 1

OR

nivolumab†	6 mg /kg	IV (max 480 mg)	Day 1

† Dosing based on NDFP funding criteria.

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C - Cycle Frequency

3 mg/kg dosing: REPEAT **EVERY 2 WEEKS**
OR
6 mg/kg dosing: REPEAT **EVERY 4 WEEKS**

Until disease progression or unacceptable toxicity, up to a maximum of 1 year, (i.e. 26 doses given q2 weeks or 13 doses given q4 weeks), whichever occurs first

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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	• Stop or slow the infusion rate. • Manage the symptoms. Restart: • Once symptoms have resolved, the infusion may be restarted 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

Hepatic Impairment	Nivolumab Dose
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

Renal Impairment	Nivolumab Dose
Mild to Moderate	No dose adjustment needed.
Severe	Insufficient data available.

Dosage in the Elderly

No overall differences in safety or efficacy were reported for patients aged ≥ 65 years compared to younger patients. Limited data is available in patients aged ≥ 75 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
• Fatigue • Rash (may be severe)	• Diarrhea (may be severe) • Electrolyte imbalances (including potassium, calcium, magnesium, sodium) • Nausea, vomiting • Musculoskeletal pain • Headache	• 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 discolouration 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.
- 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

- 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

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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

- 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

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J - Administrative Information

Approximate Patient Visit	1 hour
Pharmacy Workload (average time per visit)	18.7 minutes
Nursing Workload (average time per visit)	40.75 minutes

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K - References

Bajorin DF, Witjes JA, Gschwend JE, et al. Adjuvant nivolumab versus placebo in muscle-invasive urothelial carcinoma. N Engl J Med 2021;384(22):2102-14.

CADTH reimbursement recommendation: Nivolumab (as a monotherapy for the adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC). Oct 2022.

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

August 2024 Updated Dosing, Pregnancy/Lactation, and Monitoring 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 uses of the Formulary are subject to clinical judgment and actual prescribing patterns may not follow the information provided in the Formulary.

The format and content of the drug monographs, regimen monographs, appendices and symptom management information contained in the Formulary will change as they are reviewed and revised on a periodic basis. The date of 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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