Regimen Monograph

A - Regimen Name

NIVL+IPIL(MNT) Regimen

Nivolumab-Ipilimumab (maintenance)

Disease Site
Lung
Non-Small Cell

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
As maintenance treatment after 2 cycles of platinum doublet chemotherapy+NIVL+IPIL, in patients with metastatic or recurrent NSCLC

Supplementary Public Funding

nivolumab
New Drug Funding Program (Nivolumab plus Ipilimumab - In Combination with Platinum Doublet Chemotherapy for First Line Metastatic or Recurrent Non-Small Cell Lung Cancer) (NDFP Website)

ipilimumab
New Drug Funding Program (Nivolumab plus Ipilimumab - In Combination with Platinum Doublet Chemotherapy for First Line Metastatic or Recurrent Non-Small Cell Lung Cancer) (NDFP Website)

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B - Drug Regimen

nivolumab*	4.5 mg /kg	IV	Day 1; q3 weeks

* NDFP funded dosing; maximum 360 mg per dose

ipilimumab	1 mg /kg	IV	Day 1; q6 weeks

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C - Cycle Frequency

Nivolumab: Repeat every 3 weeks

Ipilimumab: Repeat every 6 weeks

Unless disease progression or unacceptable toxicity, up to a maximum of 2 years (including doses given with platinum doublet chemotherapy), whichever comes 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):

Nivolumab:

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

Ipilimumab:

- Consider an antipyretic and H1-receptor antagonist.
- For **ipilimumab-related drug fever**, premedicate with acetaminophen for subsequent doses and may repeat the antipyretic at 6-12 hours after the ipilimumab infusion.

Other:

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

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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

Healthcare professionals should also consult the most recent nivolumab and ipilimumab product monographs for additional information.

Doses of ipilimumab and nivolumab should be interrupted due to toxicity as recommended. When nivolumab is administered in combination with ipilimumab, if either agent is withheld, the other agent should also be withheld. If indicated, upon recovery from hold, either combination therapy or nivolumab monotherapy may be resumed based on individual patient evaluation.

Do not restart nivolumab and ipilimumab 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**

Ipilimumab - 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 (ex. at 50% of the rate at which the IR occurred) with pre-medications and close monitoring.	• Re-challenge with a reduced infusion rate of 50% at which the IR occurred. • Consider an antipyretic and H1-receptor antagonist.
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Nivolumab - 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

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for management of immune-related hepatic toxicities.

Population pharmacokinetic data suggest the following for hepatic impairment:

LFTs	Ipilimumab dose	Nivolumab dose
Bilirubin 1 to 1.5 x ULN or AST > ULN	No change	No change
Bilirubin > 1.5 to 3 x ULN and any AST	Caution; no data	Caution; no data
Bilirubin > 3 x ULN and any AST	Caution; no data	

Renal Impairment

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for management of immune-related renal toxicities.

No dosage adjustment is necessary for either nivolumab or ipilimumab in patients with mild to moderate renal impairment. No data are available for severe renal impairment (GFR < 30 mL/min).

Dosage in the Elderly

No overall differences in safety or efficacy were reported for patients aged 65 and older compared to younger patients.

Higher rates of serious adverse reactions and/or discontinuation were observed in patients aged ≥ 75 years.

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F - Adverse Effects

Refer to nivolumab, ipilimumab, drug monograph(s) for additional details of adverse effects.

The following adverse events were reported in patients with unresectable or metastatic melanoma (Larkin et al 2015). Severe or life-threatening adverse events may also be included from the other clinical trials or post-marketing.

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

Immune-mediated adverse effects are more common with combination therapy compared to nivolumab monotherapy.

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Diarrhea (may be severe colitis) • Rash, pruritus (may be severe) • Fatigue	• Nausea, vomiting • Fever • Anorexia, weight loss • Hypo/hyperthyroidism • Abdominal pain • Musculoskeletal pain • Headache	• Hepatitis • Pancreatitis • Cholestasis • Infusion related reaction • GI perforation/ hemorrhage • Immunosuppression +/- Infection (may be severe, including CMV infection / reactivation in corticosteroid-refractory colitis) • Adrenal insufficiency • Cushingoid • Hypopituitarism (also hypophysitis) • Hypoparathyroidism • Hyperglycemia • Nephritis, Nephrotoxicity • Uveitis, episcleritis, iritis • Optic neuritis • Vogt-Koyanagi-Harada syndrome • Serous retinal detachment • TEN, SJS, erythema multiforme • DRESS • Pneumonitis • Histiocytic necrotizing lymphadenitis • Arrhythmia • Cardiotoxicity (including myocarditis, pericarditis) • VTE • Arteritis, vasculitis • Neuropathy

		• Guillain-Barre syndrome • Myasthenia gravis, myositis • Rhabdomyolysis • Encephalitis/ aseptic meningitis • Hemolysis (immune-mediated, also thrombocytopenia) • HLH • Sarcoidosis • Solid organ transplant rejection • GVHD (before or after allogenic HSCT)

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G - Interactions

Refer to nivolumab, ipilimumab, drug monograph(s) for additional details.

- Avoid systemic immunosuppressants (e.g. systemic corticosteroids, mycophenolate, cyclosporine), especially at baseline given potential anti-tumour effects. Systemic corticosteroids may be used to treat immune reactions.
- Anticoagulants may increase the risk of GI hemorrhage; monitor closely.

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H - Drug Administration and Special Precautions

Refer to nivolumab, ipilimumab, drug monograph(s) for additional details.

Nivolumab should be infused first, followed by ipilimumab on the same day. Use separate infusion bags and filters for each infusion.

Administration: Nivolumab

- 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.
- Store unopened nivolumab vials in original packaging between 2^{o}C to 8^{o}C. Protect from light.

Administration: Ipilimumab

- Do not administer as an IV push or bolus injection.
- Infuse IV over 30 minutes.
- Consider post-infusion monitoring for a short time after the infusion, as IRs have occurred up to 30 minutes after the infusion.
- A compatible low protein binding in-line filter and a separate infusion line must be used for infusing ipilimumab.
- Do not infuse with other medications.
- Must flush line with NS or D5W at the end of the infusion.
- Allow the vials to stand at room temperature for 5 minutes before withdrawing the drug to a compatible container.
- Ipilimumab may be administered without dilution after transferring to a compatible container.
- It may also be diluted in NS or D5W to a concentration between 1mg/mL to 4mg/mL.
- Do not shake the solution.
- Solution may contain translucent-to-white amorphous particles; discard if cloudy or discoloured.
- Compatible with glass, PVC and non-PVC bags
- Compatible with PVC IV extension or administration sets, polyethersulfone (0.2 and 1.2 micron) and nylon (0.2 micron) in-line filters.
- Refrigerate original vials (2 to 8°C) and protect them from light. Do not freeze.

Contraindications

- Patients who are hypersensitive to ipilimumab, nivolumab, or any of their components
- Patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life-threatening

Warnings/Precautions:

- Caution with ipilimumab in patients who have previously experienced severe or life-threatening skin reactions to prior cancer immune-stimulating therapy
- Usage of ipilimumab in patients with ocular melanoma or central nervous metastases has not been studied.
- Fatal or serious graft-versus-host disease (GVHD) can occur in patients who receive nivolumab or a CTLA-4 receptor blocking antibody (e.g. ipilimumab) either before or after allogeneic HSCT. Consider benefit versus risks of treatment.
- Use nivolumab and ipilimumab with caution in patients on a controlled sodium diet.
    - Each 10 mg (=1 mL) of nivolumab contains 0.1 mmol (2.3 mg) sodium.
    - Each 5 mg (=1 mL) of ipilimumab contains 0.1 mmol (2.3 mg) sodium.
- Use nivolumab within 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).
- Effects on fertility:
  - Ipilimumab: Unlikely
  - Nivolumab: 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 hemorrhage (especially in patients on anticoagulants), infusion reactions, immune-related reactions, including GI, skin, endocrine, pancreatitis, respiratory, musculoskeletal, cardiac, ophthalmic, neurologic effects and fatigue; 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	1.5-3 hours
Pharmacy Workload (average time per visit)	25.895 minutes
Nursing Workload (average time per visit)	51.5 minutes

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K - References

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

Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Sep 24;373(13):1270-1.

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

Paz-Ares L, Ciuleanu TE, Cobo M, et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. Lancet Oncol . 2021 Feb;22(2):198-211. doi: 10.1016/S1470-2045(20)30641-0.

pCODR Expert review committee final recommendation: Nivolumab in combination with ipilimumab and two cycles of platinum-based chemotherapy, March 2021.

November 2024 Expanded into full regimen monograph

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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.

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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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