**Regimen Monograph**



## A - Regimen Name

# NIVL+IPIL Regimen

**nivolumab-ipilimumab**

| | |
|---|---|
| **Disease Site** | Skin - Melanoma |
| **Intent** | Palliative |
| **Regimen Category** | **Evidence-Informed :**<br><br>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 or metastatic melanoma in previously untreated patients (conditional approval).<br><br>An improvement in progression-free survival with nivolumab plus ipilimumab therapy was seen only in patients with PD-L1 expression < 5%. An improvement in overall survival has not yet been established. |
| **Supplementary Public Funding** | **nivolumab**<br>New Drug Funding Program (Nivolumab plus Ipilimumab - Advanced Melanoma (Unresectable or Metastatic Melanoma)) |

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## B - Drug Regimen

| | | | |
|---|---|---|---|
| **nivolumab** | 1 mg /kg | IV | Day 1 |
| **ipilimumab** | 3 mg /kg | IV | Day 1 |

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## C - Cycle Frequency

Repeat every 21 days for a usual total of 4 cycles unless disease progression or unacceptable toxicity occurs.

Combination treatment is followed by Nivolumab maintenance treatment (see NIVL(MNT)).

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## D - Premedication and Supportive Measures

**Antiemetic Regimen:** Minimal

Consider premedication prior to the next infusion if an infusion-reaction develops (e.g. diphenhydramine 50 mg and acetaminophen 30 minutes prior to infusion).

Prophylactic antibiotics should be used to prevent opportunistic infections in patients receiving immunosuppressive medications.

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## E - Dose Modifications

Doses should be modified according to the protocol by which the patient is being treated. The following recommendations have been adapted from clinical trials or product monographs and may be considered.

**Dosage with toxicity**

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

Doses of ipilimumab and nivolumab should be interrupted due to toxicity as recommended. Both drugs should be held or discontinued when a hold or discontinuation is indicated. If indicated, upon recovery from hold, either combination therapy or nivolumab monotherapy may be resumed based

on individual patient evaluation.

**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**

**Infusion-related reactions (Larkin 2015):**

| Toxicity grade | Action (nivolumab and/or ipilimumab) |
|---|---|
| Grade 1 (e.g. localized rash, mild pruritus, flushing) | • Monitor patient until recovery<br>• Premedication is recommended for subsequent doses (e.g. diphenhydramine 50 mg and/or acetaminophen at least 30 minutes before infusion). |
| Grade 2 (e.g. generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP >80 mmHg) | • Interrupt nivolumab or ipilimumab infusion and give diphenhydramine 50mg IV; monitor patient closely. Corticosteroid or bronchodilator therapy may be administered if required.<br>• If resuming infusion, ↓ rate to 50%; may increase to initial rate if tolerated after 30 minutes.<br>• Premedication (diphenhydramine 50 mg and/or acetaminophen) is recommended for subsequent doses and follow infusion rate as above. |
| Grade 3 or 4 (e.g. bronchospasm, generalized urticaria, SBP <80 mm Hg, or angioedema) | • Discontinue nivolumab and/or ipilimumab permanently; monitor patient closely.<br>• Consider bronchodilators, epinephrine, diphenhydramine, corticosteroids as needed |

## Hepatic Impairment

See CCO guideline on immune-mediated toxicities for management of drug-induced hepatitis.

| 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 | Caution; no data | Caution; no data |
| Bilirubin > 3 x ULN | Caution; no data | Caution; no data |

## Renal Impairment

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.

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## F - Adverse Effects

Refer to nivolumab, ipilimumab, 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.

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

| Very common (≥ 50%) | Common (25-49%) | Less common (10-24%) | Uncommon (< 10%),<br><br>but may be severe or life-threatening |
|---|---|---|---|
| | • Diarrhea (may be severe)<br>• Fatigue<br>• Rash, pruritus (may be severe)<br>• Nausea, vomiting | • Fever<br>• Anorexia, weight loss<br>• Increased LFTs (may be severe)<br>• Hypothyroidism<br>• Vitiligo<br>• Musculoskeletal pain (may be severe)<br>• Headache<br>• Cough, dyspnea<br>• Constipation<br>• Abdominal pain | • Infections (including atypical)<br>• Infusion-related reaction<br>• Venous thromboembolism<br>• Arrhythmias<br>• Hypopituitarism<br>• Hyperthyroidism<br>• Hypophysitis<br>• Adrenal insufficiency<br>• Neuropathy<br>• Guillan-Barre syndrome<br>• Encephalitis/meningoencephalitis<br>• Myasthenia<br>• Nephrotoxicity, nephritis<br>• Hepatitis<br>• Uveitis, episcleritis, optic neuritis<br>• Pancreatitis<br>• GI perforation, hemorrhage<br>• Vasculitis<br>• Diabetes<br>• Cardiac/myocarditis<br>• Hemolysis/ITP<br>• DRESS<br>• Rhabdomyolysis, myositis |

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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 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.

Administration: ipilimumab

- Do not administer as an IV push or bolus injection.
- Infuse as an IV infusion over 90 minutes, with a compatible low protein binding in-line filter. (Evidence from clinical trials suggests a 30 minute infusion time may be used safely, Momtaz 2015).
- A separate infusion line must be used for infusing ipilimumab.

- 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.
- 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.

Special precautions

- Ipilimumab is contraindicated in patients with active, life-threatening autoimmune disease, or with organ transplantation graft where further immune activation is potentially imminently life-threatening
- Ipilimumab may cause severe and fatal immune-related reactions, which may affect multiple organ systems including GI, hepatic, skin, nervous, endocrine or others. Close monitoring, prompt diagnosis and appropriate management are essential to minimize life-threatening complications.
- Caution 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.
- Patients on anticoagulants are at increased risk of bleeding with ipilimumab.
- Use nivolumab with caution in patients on a controlled sodium diet. Each ml contains 0.1 mmol (2.3 mg) sodium.
- IgG1 is known to cross the placental barrier and may cause harm to the developing fetus. Effects are likely to be greater in the second and third trimesters. These drugs should not be used in pregnancy. Adequate contraception should be used by both sexes, during treatment and for at least 6 months after the last dose.
- Breastfeeding should be avoided.

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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.

Recommended Clinical Monitoring

- Liver function tests; Baseline and before each dose
- Renal function tests, including electrolytes; Baseline and before each dose
- Thyroid function tests; Baseline and periodic

- Blood glucose; Baseline, at each visit and as clinically indicated
- Blood pressure; Baseline and as clincally indicated
- Clinical toxicity assessment for infusion reactions, immune-related reactions, including diarrhea, GI perforation, hypophysitis, adrenal insufficiency, other endocrinopathies, hepatic, pulmonary, cardiac, ocular, skin or neurologic effects and fatigue; At each visit
- Immune-mediated reactions should be monitored up to 5 months after the last treatment dose

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

Suggested Clinical Monitoring

Monitor patients on anticoagulants carefully; Baseline and as clinically indicated

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## J - Administrative Information

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|---|---|
| Approximate Patient Visit | 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 and nivolumab drug monographs, 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.

**December 2020** Updated Drug administration section

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## M - Disclaimer

***Regimen Abstracts***

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