Regimen Monograph

A - Regimen Name

IPIL Regimen

Ipilimumab

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 previously untreated patients with advanced melanoma (primary cutaneous, unresectable stage IIIC or IV melanoma or metastatic melanoma), regardless of BRAF mutations status, who have an ECOG performance status of ≤ 1, are asymptomatic/stable if they have known brain metastases, and are not currently receiving immunosuppressive therapy.*
- For initial treatment of unresectable stage III or IV melanoma in patients who have an ECOG performance status ≤ 1 and who have received at least one systemic therapy for advanced melanoma.*
- For re-induction in patients with ECOG ≤ 1, who have stable disease for at least three months or have previously experienced a complete or

partial response to ipilimumab.*

*See NDFP eligibility forms for detailed funding criteria.

Supplementary Public Funding	**ipilimumab** New Drug Funding Program (Ipilimumab - Previously Untreated Advanced Unresectable Melanoma) (NDFP Website)
	ipilimumab New Drug Funding Program (Ipilimumab - Previously Treated Advanced Unresectable Melanoma) (NDFP Website)

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B - Drug Regimen

ipilimumab	3 mg /kg	IV	Day 1

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C - Cycle Frequency

REPEAT EVERY 21 DAYS

Up to a total of 4 cycles, unless disease progression or unacceptable toxicity occurs. All doses must be administered within 16 weeks of the initial dose.

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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):

- Consider an antipyretic and H1-receptor antagonist

Other Supportive Care:

- For ipilimumab-related drug fever, premedicate with acetaminophen for subsequent doses. Consider repeating 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

Healthcare professionals should also consult the most recent ipilimumab product monograph for additional information.

Each 5 mg (=1 mL) of drug contains 2.3 mg (0.1 mmol) of sodium. The sodium content should be taken into consideration in patients on a controlled sodium diet.

Dosage with toxicity

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 CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions of Immune-related 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 (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).

Hepatic Impairment

Safety and efficacy have not been studied in patients with 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:

Impairment	LFTs	Ipilimumab dose
Mild	Bilirubin >1 to 1.5 x ULN or AST > ULN	No dose adjustment necessary
Moderate	Bilirubin > 1.5 to 3 x ULN and any AST	Caution; no data
Severe	Bilirubin > 3 x ULN and any AST	Caution; no data

Renal Impairment

Safety and efficacy have not been studied in patients with renal impairment.

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

Pharmacokinetic data suggest the following for pre-existing renal impairment:

Baseline Renal Impairment	Ipilimumab dose
Mild to moderate	No dose adjustment necessary
Severe	Caution; no data

Dosage in the Elderly

No dose adjustment required. No differences in efficacy or safety were reported in those ≥ age 65.

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F - Adverse Effects

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

Refer to the CCO guideline for detailed description of Immune-mediated toxicities and their management.

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 • Anorexia, weight loss • Abdominal pain	• Hepatitis • Pancreatitis • GI perforation/ hemorrhage • Infection (atypical) • Adrenal insufficiency • Cushingoid • Hypopituitarism • Hyper/hypothyroidism • Hypoparathyroidism • Hyperglycemia • Nephritis • Uveitis, episcleritis, iritis • Optic neuritis • Vogt-Koyanagi-Harada syndrome • Serous retinal detachment • Hypersensitivity • TEN, SJS, erythema multiforme • Pneumonitis • Arteritis, vasculitis • Arrhythmia • Cardiotoxicity • Myocarditis, pericarditis • DRESS • Neuropathy • Guillain-Barre syndrome • Myasthenia gravis • Encephalitis/ aseptic meningitis • Hemolytic anemia • HLH • Myositis • Sarcoidosis

		• Solid organ transplant rejection • GVHD (before or after allogenic HSCT)

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G - Interactions

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

- Use of systemic corticosteroids or immunosuppressants should be avoided prior to starting ipilimumab because of potential interference with efficacy. They can be used to treat immune-mediated reactions after starting the drug.
- Concurrent use of ipilimumab and vemurafenib is not recommended as severe LFT increases have been reported in clinical trials.
- Anticoagulants may increase the risk of GI hemorrhage; monitor patients closely if used together.

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H - Drug Administration and Special Precautions

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

Administration

- 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 IV 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 discolored.
- 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.
- If a scheduled dose is missed, it should be administered as soon as possible. Adjust administration schedule to maintain the prescribed dosing interval.
- Refrigerate original vials (2 to 8°C) and protect them from light. Do not freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Contraindications

- Patients who are hypersensitive to ipilimumab or any of its 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 in patients who have previously experienced severe or life-threatening skin reactions to prior cancer immune-stimulating therapy
- Usage 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 a CTLA-4 receptor blocking antibody (e.g. ipilimumab) either before or after allogeneic HSCT. Consider benefit versus risks of treatment with ipilimumab after allogeneic HSCT.

Pregnancy and Lactation

- IgG1 is known to cross the placental barrier and may cause harm to the developing fetus. Effects are likely to be greater during the second and third trimesters. Ipilimumab is not

recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **3 months** after the last dose.

- Breastfeeding should be avoided during treatment, and for at least **3 months** after the last dose.
- Fertility effects: Unlikely

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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 as clinically indicated
- Liver function tests; Baseline, before each dose and as clinically indicated
- Electrolytes; Baseline, before each dose and as clinically indicated
- Thyroid function tests; Baseline, before each dose and as clinically indicated
- ACTH (+ cortisol, sex hormone levels); Baseline, before each dose and as clinically indicated
- Renal function tests; Baseline and as clinically indicated
- Monitor patients on anticoagulants carefully; Baseline and as clinically indicated
- Clinical toxicity assessment for fatigue, infusion-related and immune-related reactions, including GI, skin, endocrine, pancreatitis, musculoskeletal, respiratory, ocular, cardiac, or neurologic effects; At each visit and as clinically indicated
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	2 hours
Pharmacy Workload (average time per visit)	17.795 minutes
Nursing Workload (average time per visit)	42.417 minutes

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K - References

Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23.

Momtaz P, Park V, Panageas KS, et al. Safety of infusing ipilimumab over 30 minutes. J Clin Oncol 2015;33(30):3454-8.

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

March 2023 Updated Other supportive care, Administration, Warnings, 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 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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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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