Regimen Monograph

A - Regimen Name

PEMB Regimen

Pembrolizumab

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

1. For the treatment of patients with unresectable or metastatic melanoma who have not received prior treatment with ipilimumab. Patients with BRAF mutant melanoma may or may not have received prior BRAF targeted therapy.*

2. For the treatment of patients with unresectable or metastatic melanoma and disease progression following treatment with ipilimumab and, if BRAF mutation positive, disease progression with BRAF targeted therapy.*

*See NDFP eligibility form for detailed funding criteria.

Supplementary Public Funding

pembrolizumab
New Drug Funding Program (Pembrolizumab - Advanced Melanoma (Unresectable or Metastatic Melanoma) and No Prior Ipilimumab) (NDFP

Website)

pembrolizumab
New Drug Funding Program (Pembrolizumab - Advanced Melanoma (Unresectable or Metastatic Melanoma) and Prior Ipilimumab) (NDFP Website)

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B - Drug Regimen

pembrolizumab[1]	2 mg /kg	IV (max 200mg)	Day 1, Q21 days
OR			
pembrolizumab[1]	4 mg /kg	IV (max 400mg)	Day 1, Q42 days

[1]Dosing based on NDFP funding criteria

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C - Cycle Frequency

2 mg/kg dosing: **REPEAT EVERY 21 DAYS**

4 mg /kg dosing: **REPEAT EVERY 42 DAYS**

Until disease progression or unacceptable toxicity up to a maximum of 2 years (35 doses given q3 weeks or 18 doses given q6 weeks), whichever occurs first

Refer to NDFP form for details on pembrolizumab retreatment.

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D - Premedication and Supportive Measures

Antiemetic Regimen: Minimal

Other Supportive Care:

Also refer to CCO Antiemetic Recommendations.

Avoid the use of corticosteroids or immunosuppressants before starting treatment.

Premedication (prophylaxis for infusion reactions):

- Routine pre-medication is not recommended.
- May consider antipyretic and H1-receptor antagonist in patients who experienced a grade 1-2 infusion reaction.

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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 pembrolizumab product monograph for additional information.

There are no dose reductions for pembrolizumab. Doses are either delayed or discontinued with toxicity.

Summary of Principles of Management or immune-related adverse effects (iRAEs)

- 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. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time.	• Consider re-challenge with close monitoring and pre-medications (antipyretic and H1-receptor antagonist).
3 or 4	• Stop the infusion. • Aggressively manage symptoms.	• Discontinue permanently (do not re-challenge).

Hepatic Impairment

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions for immune-related hepatitis management.

Impairment	Pembrolizumab Dose
Mild (bilirubin 1 - 1.5 x ULN or AST > ULN)	No dose adjustment necessary
Moderate (bilirubin >1.5 - 3 x ULN and any AST) to severe (bilirubin > 3 x ULN and any AST)	Caution; no data

Renal Impairment

Refer to CCO's Immune Checkpoint Inhibitor Toxicity Management Guideline for detailed descriptions for immune-related nephritis management.

CrCl (mL/min)	Pembrolizumab Dose
≥ 60	No dose adjustment necessary
30 to 59	No dose adjustment necessary
< 30	Caution; no data

Dosage in the Elderly

No dosage adjustment is required. No differences in safety or efficacy were reported between patients aged 65 and older and younger patients.

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F - Adverse Effects

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

Common (25-49%)	Less common (10-24%)	Uncommon (< 10%), but may be severe or life-threatening
• Fatigue	• Diarrhea (may be severe) • Rash / pruritus • Nausea / vomiting • Musculoskeletal pain	• Myocarditis • Colitis • Anemia • Hemolytic anemia • Myelosuppression ± infection, bleeding • Hepatitis • Pancreatitis • Sclerosing cholangitis • Infusion-related reaction • Hemophagocytic lymphohistiocytosis • Sarcoidosis • Graft loss - solid organ transplant recipients • Hyper / hypothyroidism • Hyperglycemia • Hypopituitarism / hypophysitis • Adrenal insufficiency • Encephalitis • Guillain-Barre syndrome • Myositis, myasthenia

		• Eye disorders • Nephritis / nephrotoxicity • Pneumonitis • Vasculitis • Vogt-Koyanagi-Harada syndrome • Stevens-Johnson syndrome • Toxic epidermal necrolysis

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G - Interactions

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

- Pembrolizumab is not expected to have pharmacokinetic drug-drug interactions as it is not metabolized by drug metabolizing enzymes.
- Use of systemic corticosteroids or immunosuppressants should be avoided prior to starting pembrolizumab because of potential interference with efficacy. They can be used to treat immune-mediated reactions after starting the drug. Corticosteroids may be used as premedication (e.g. antiemetic) when given with chemotherapy.

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H - Drug Administration and Special Precautions

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

Administration

- Dilute in 0.9% sodium chloride or D5W to final concentration of 1 to 10 mg/mL; mix by gentle inversion.
- Administer over 30 minutes using sterile, non-pyrogenic, low protein-binding 0.2 to 5 micron in-line or add-on filter.
- Do not co-administer other drugs through the same infusion line.
- If a planned dose is missed, administer as soon as possible. Adjust the schedule to maintain the prescribed dosing interval.

- Vials should be stored under refrigeration (2 to 8^{o}C). Do not freeze.

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.

Warnings/Precautions

- Patients with active infection, autoimmune disease, conditions that require systemic immunosuppressive therapy (i.e. transplant patients) and a history of pneumonitis, severe immune-mediated adverse reactions with ipilimumab or severe hypersensitivity to other monoclonal antibodies, etc. were excluded from clinical studies.
- Pembrolizumab may cause serious immune-mediated reactions affecting multiple organ systems, including GI, hepatic, renal, respiratory, endocrine and others. Use with caution and monitor closely in patients with pre-existing conditions such as colitis, hepatic impairment, respiratory or endocrine disorders, such as hypo or hyperthyroidism or diabetes mellitus.
- Patients with ECOG performance status ≥ 2 were excluded from clinical trials.
- Use of a PD-1 or PD-L1 blocking antibody with a thalidomide analogue plus dexamethasone is not recommended outside of controlled clinical trials, due to increased mortality reported

Pregnancy/Lactation

- Pembrolizumab is not recommended for use in pregnancy. Adequate contraception should be used by both sexes during treatment, and for at least **4 months** after the last dose.
- Breastfeeding is not recommended during treatment, and for at least **4 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.

Recommended Clinical Monitoring

- Liver function tests; Baseline, before each dose and as clinically indicated; frequent with severe toxicity
- Renal function tests; Baseline, before each dose and as clinically indicated; frequent with severe toxicity
- Thyroid function tests; Baseline, before each dose and as clinically indicated
- Electrolytes; Baseline, before each dose and as clinically indicated
- Blood glucose; Baseline, before each dose and as clinically indicated
- CBC; Baseline and as clinically indicated
- Clinical toxicity assessment for infusion-related and immune-mediated reactions, fatigue, ocular, endocrine, skin, GI, neurologic, musculoskeletal, cardiac and respiratory effects; At each visit
- Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

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J - Administrative Information

Approximate Patient Visit	0.75 hour
Pharmacy Workload (average time per visit)	19.75 minutes
Nursing Workload (average time per visit)	40.75 minutes

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K - References

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

Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019;20(9):1239-51.

Robert C, Schachter J, Long GV, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015 Jun 25;372(26):2521-32.

Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390(10105):1853-62.

January 2023 Updated adverse effects, and drug administration and special precautions 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

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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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