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ENGLISH SUMMARY

# Choosing nivolumab and pembrolizumab dosages

Une production de l'Institut national d'excellence en santé et en services sociaux (INESSS)

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Québec

# SUMMARY

## Choosing nivolumab and pembrolizumab dosages


### Introduction

Nivolumab and pembrolizumab are two monoclonal antibodies indicated for the treatment of several cancers. They act by preventing the interaction of the T-cell programmed cell death 1 (PD-1) receptor and its ligands, thereby removing the inhibition of the antitumour immune response. Several dosing regimens are proposed in the Canadian product monographs for these drugs, specifically, a choice between weight-based doses and fixed doses. Recently, the nivolumab and pembrolizumab product monographs also proposed higher doses administered at less frequent intervals. The PD-1 receptor plays an important physiological role in limiting autoimmunity, and nivolumab and pembrolizumab are already being used, in the initial dosing regimens, at doses that virtually saturate these receptors. The use of these higher doses therefore raises questions about the potential risks that this could pose in certain specific populations, such as patients with an autoimmune disease.

The Direction nationale du Programme québécois de cancérologie of the Ministère de la Santé et des Services sociaux (MSSS) therefore asked the Institut national d'excellence en santé et en services sociaux (INESSS) to develop a decision support tool for guiding clinicians in choosing nivolumab and pembrolizumab dosages. This report presents all of the information gathered for the purpose of this task and on which the recommendations presented in the tool are based.

### Methodology

To develop this tool, we examined scientific efficacy, safety and pharmacokinetic data from systematic reviews of primary studies, pharmacoeconomic data, and recommendations from clinical practice guidelines (CPGs). These data were enriched with information specific to the Québec context and with experiential knowledge provided by a number of experts in the field. The search for scientific information was conducted in several databases from the date of their inception to December 2019 and was limited to items published in French or English, while the search for CPGs and guidance documents was limited to items published from January 2014 to December 2019. The grey literature was searched as well, as were the bibliographies in the selected publications. The official Canadian product monographs for nivolumab and pembrolizumab were consulted to supplement the search for the conditions of use of these drugs.

The results of this systematic review are presented in the form of a narrative synthesis. For each efficacy and safety endpoint, a summary statement of scientific evidence is provided, to which an overall level of scientific evidence was assigned. The recommendations were developed in collaboration with the advisory committee. The

information on contextual and experiential data is presented in narrative form and is summarized in tables.

## Results

The search for scientific information yielded 5,668 publications, from which 25 scientific articles and 7 items containing recommendations that met the selection criteria were retained. It should be noted, however, that the data presented in several of these scientific articles were derived from mathematical models and that no data were available for several types of cancers for which nivolumab and pembrolizumab are indicated for treatment in Canada.

The results of the systematic review indicate, with a level of evidence deemed low to moderate, that there is no statistically significant difference in efficacy or safety between the different weight-based doses of nivolumab or pembrolizumab tested in the studies, or between fixed doses and weight-based doses. In addition, the predicted pharmacokinetic endpoints for fixed doses versus weight-based doses are generally similar, whereas the pharmacoeconomic analyses for pembrolizumab indicate a likely increase in the pharmacoeconomic ratios with the use of fixed doses. Given that nivolumab and pembrolizumab target the entire T-cell pool, not the tumour site directly, it was decided to propose, in the decision support tool, the use of a weight-based dose up to a maximum dose equal to the fixed dose, this in all the indications for nivolumab (as monotherapy) and pembrolizumab, and for nivolumab in combination with ipilimumab in the treatment of renal adenocarcinoma. The doses proposed for the combination phase in the treatment of unresectable or metastatic melanoma remain those recommended in the product monograph, because in this indication, nivolumab is administered at a dose of 1 mg/kg.

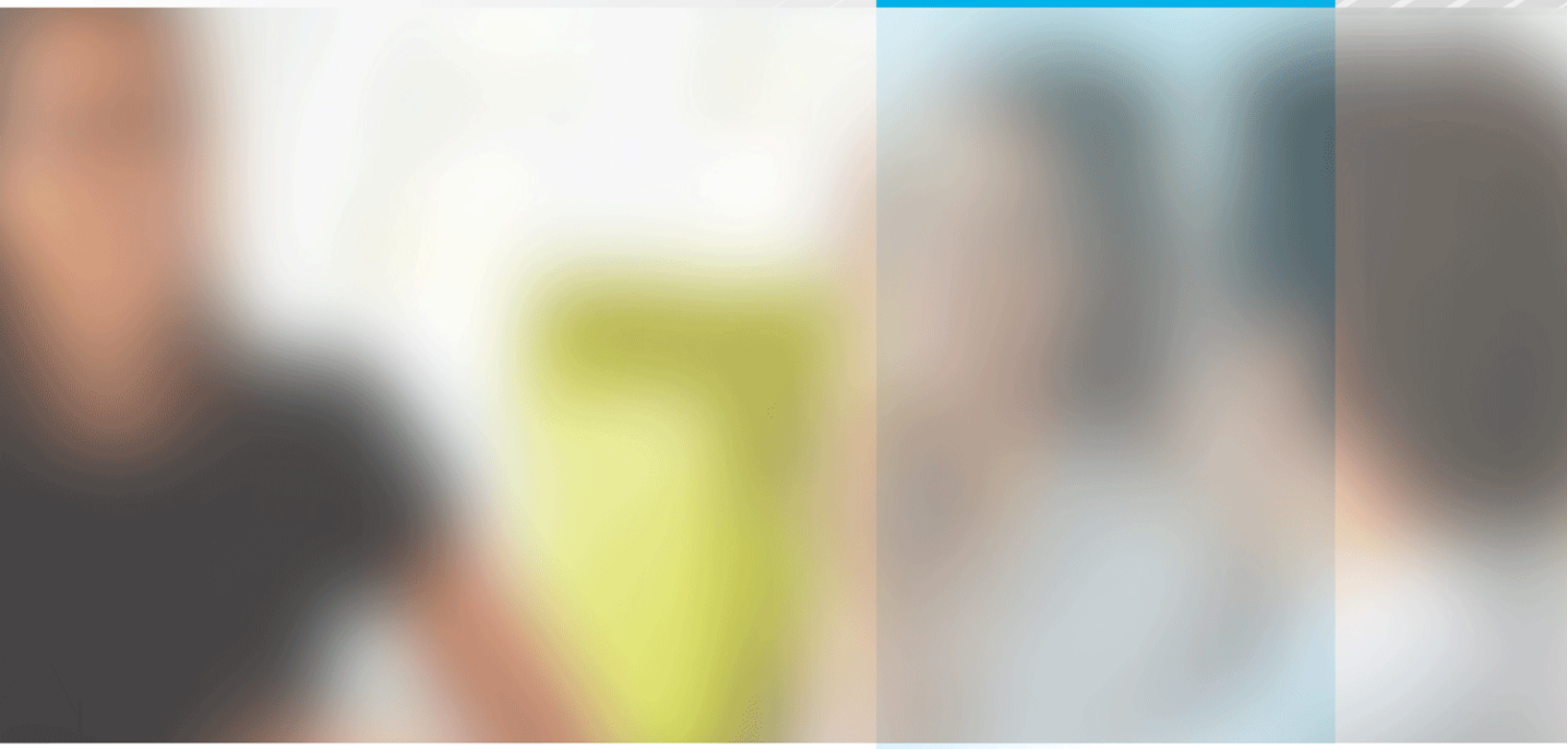
As regards the choice of dosing interval, the results of the systematic reviews indicate, with a level of evidence deemed low, that there is no statistically significant difference in efficacy or safety between nivolumab or pembrolizumab doses administered at extended intervals and those administered at standard intervals. However, for pembrolizumab, only simulated exposure data were used to compare the two modes of treatment. Pharmacokinetically, the use of higher doses administered at extended intervals appears to result in higher predicted peak concentrations and lower predicted trough concentrations than regular doses administered at standard intervals. It should be noted, however, that the predicted peak concentration achieved with high doses administered at extended intervals remains below the levels observed when the dose is 10 mg/kg administered every 2 weeks, a dose that is not used in practice but that has been evaluated in clinical studies, in which it was well tolerated by the participants. In addition, the decrease in the predicted trough concentrations is transient (about 3 days for pembrolizumab) and appears unlikely to have a significant effect on these drugs' efficacy. Also, since they lower the frequency of administration, extended intervals could provide certain benefits to both the health-care system and patients, by reducing, among other things, the costs associated with laboratory tests, parking costs and the inconveniences associated with more frequent trips. Thus, our findings support a choice of nivolumab dosing interval between an extended interval of 4 weeks and a standard interval of 2 weeks, whereas for pembrolizumab, only the standard interval is recommended, as

long as the extended interval is not indicated in the Canadian product monograph for this drug. Lastly, a more frequent follow-up of patients who receive a high dose at extended intervals, to monitor the adverse effects, therapeutic response and hyperprogression, should be provided so as to be able to detect a problem early and adjust the therapy, if necessary, as soon as possible.

Lastly, it is pointed out that certain populations are more likely to experience adverse effects following the administration of nivolumab or pembrolizumab, such as patients with a pre-existing autoimmune disease and those who have undergone a solid-organ transplant or a hematopoietic stem cell transplant (HSCT). However, these risks appear to be independent of the nivolumab or pembrolizumab dose administered because the PD-1 receptors are already virtually saturated at doses lower than those used, and this nearly complete receptor occupancy seems to be necessary to achieve the desired effect on the immune response. However, these patients could benefit from a closer follow-up and from starting the treatment at standard intervals for a few months before considering switching to extended-interval administration. These precautions are also mentioned with regard to treating patients who previously discontinued treatment because of adverse effects due to immunotherapy and patients with a lower tolerance for adverse effects.

## Conclusion

The development of the nivolumab and pembrolizumab dosing decision support tool required a collaborative approach that brought together scientific, contextual and experiential knowledge. This tool will serve to facilitate the prescribing of these drugs by reducing the confusion due to the multitude of dosage regimens proposed in the product monographs. The few points included in the tool for certain specific populations are important considerations when managing and following these patients.

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