Programme de
GESTION THÉRAPEUTIQUE
des médicaments

PGTM Clinical Intervention Model (CIM)

NIVOLUMAB (OPDIVO™) – What is the preferred strategy: a weight-based dosage, a fixed dose or a weight-based dosage with a maximum dose?

Background: Nivolumab is a selective monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with ligands PD-L1 and PD-L2, thereby countering immune response inhibition and re-establishing antitumour response.

Nivolumab is currently approved in Canada for the treatment of the following cancers: nonresectable or metastatic melanoma, locally advanced or metastatic non-small cell lung cancer (NSCLC), advanced or metastatic renal adenocarcinoma, recurrent or metastatic squamous cell carcinoma of the head and neck, classical Hodgkin's lymphoma (cHL) and advanced hepatocellular carcinoma (HCC). The dosage regimen approved for nivolumab has changed. In addition to a weight-based dose, there is now the option of a fixed dose, and the dosing interval has changed as well.

At an estimated average price of $4,225 per dose every 2 weeks (or approximately $8,450 per 28-day period), the use of this drug alone has a huge impact, amounting to millions of dollars, on the budgets of Quebec's health-care facilities. INESSS's initial evaluation for NSCLC estimated that $374 million would be necessary to treat 6329 patients over the next 3 years for this indication alone.

The PGTM is reviewing the approved dosage strategies and those proposed by various regulatory bodies and health technology assessment agencies. The quality of the safety and efficacy evidence and the aspects of costs and convenience for hospitals have been taken into account. For the purposes of this evaluation, the PGTM has looked at lung cancer because it is one of the first indications approved for nivolumab and because these patients constitute a substantial population, with the possibility of extrapolating to the other indications.

The PGTM's scientific recommendation

The PGTM notes that no clinical study has compared the nivolumab dosage strategies with each other and that there are no published studies aimed at demonstrating an equivalence or a difference in efficacy or safety between the different dosage strategies.

The pivotal phase III clinical studies in all the currently approved indications were carried out with a dose of 3 mg/kg every 2 weeks.

In light of the evidence, mainly from the currently published pharmacokinetic studies, and of the drug's pharmacological properties, the PGTM considers that the weight-based dosage of nivolumab (a dose of 3 mg/kg administered every 2 weeks) is comparable to a dose of 240 mg every 2 weeks and a dose of 480 mg every 4 weeks. Consequently, the PGTM considers that it would be acceptable to administer nivolumab 3 mg/kg up to a maximum of 240 mg every 2 weeks.

In the absence of studies, both clinical and pharmacokinetic, the administration of a weight-based dose of 6 mg/kg up to a maximum of 480 mg every 4 weeks has been debated. Based on pharmacological data and established evidence for a dose of 3 mg/kg, the PGTM has concluded that this dose would be a reasonable extrapolation.

The PGTM hopes that future studies, such as CHECKMATE-384, which is currently ongoing, will clarify the issue of an every-2-week or every-4-week dosing interval.

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The PGTM's recommendation in light of the pharmacoeconomic evaluation

Given the pharmacoeconomic findings, the PGTM recommends administering nivolumab at a dose of 3 mg/kg every 2 weeks or 6 mg/kg every 4 weeks (or the equivalent of 1.5 mg/kg/week) up to a maximum dose of 240 mg or 480 mg, respectively (or the equivalent of 120 mg/week), depending on the frequency chosen, to all patients and for all the recognized indications.

Objective: To promote the use of an optimal dosage strategy for nivolumab in the university teaching hospitals (UTHs).

Intervention measures: Each institution is to determine which interventions apply to its situation and to make one or more of them priorities.

Timetable: Institute applicable measures at each UTH within 12 months of September 2018.

The PGTM's intervention plan for the nivolumab CIM:

1. Submit the evaluation report to the Pharmacy and Therapeutics Committee and/or the Cancer/Oncology Subcommittee, if applicable, and to other committees concerned, if relevant;
2. Submit the evaluation report to the clinical practitioners concerned, specifically, hematologists/oncologists, the other specialists who might need to prescribe nivolumab and pharmacists;
3. Improve the nivolumab standing orders by indicating on them the indications for which the drug has been approved, as well as the weight-based dose in mg/kg, the dosage interval and the recommended maximum dose;
4. Create or modify a standing order as soon as possible when a new indication for nivolumab is approved;
5. Conduct a follow-up study, preferably in the form of a prospective drug utilization review (DUR), aimed at verifying if nivolumab is being prescribed according to the preferred dosage.