Programme de
GESTION THÉRAPEUTIQUE
des médicaments

PGTM Clinical Intervention Model (CIM)

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

Background: Pembrolizumab is a selective monoclonal antibody that binds to the programmed death-ligand 1 (PD-L1) receptor. The PD-1 pathway is an immune checkpoint that can be used by tumour cells to inhibit immunological surveillance by activated T lymphocytes. Pembrolizumab is an antibody with a strong affinity for the PD-1 receptor that inhibits two ligands that block the PD-1 pathway, PD-L1 and PD-L2, on tumour cells or cells that present the antigen. By inhibiting the binding of the PD-1 receptor to its ligands, pembrolizumab reactivates tumour-specific cytotoxic T lymphocytes in the tumour microenvironment, which, as a result, reactivates antitumour immunity.

Between 2012 and 2015, in the first clinical trials (of the KEYNOTE series of studies) evaluating pembrolizumab, a dose of 2 mg/kg every 3 weeks had shown a superior survival benefit to that of the standard therapy in the treatment of metastatic melanoma and metastatic non-small cell lung cancer (mNSCLC). In light of these studies, Health Canada approved pembrolizumab at a dose of 2 mg/kg administered every 3 weeks for these indications.

In October 2016, the results of the pivotal study KEYNOTE-024 were published. It compared the efficacy and safety of pembrolizumab with those of conventional chemotherapy for the first-line treatment of mNSCLC in which at least 50% of the tumour cells expressed PD-L1 (TPS ≥ 50%). This study was the first to use a fixed dose of pembrolizumab of 200 mg for all the patients every 3 weeks. Consequently, this dose is the one that was approved by Health Canada for this indication.

Since KEYNOTE-024, almost all new studies evaluating pembrolizumab as monotherapy have used the 200-mg fixed dose administered every 3 weeks (e.g., KEYNOTE-177, KEYNOTE-164, KEYNOTE-122 and KEYNOTE-042 [for the complete list, consult the website clinicaltrials.gov]).

The PGTM is reviewing the approved dosage strategies and those proposed by various regulatory bodies. The quality of the efficacy and safety 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 mNSCLC because it was one of the first indications approved for pembrolizumab and because these patients constitute a population of great interest, with the possibility of extrapolating to other indications.

The PGTM's scientific recommendation

The PGTM notes that no clinical study has compared the pembrolizumab 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 melanoma and the second-line treatment of metastatic non-small cell lung cancer (mNSCLC) were carried out using a dose of 2 mg/kg, whereas those in the first-line treatment of mNSCLC, Hodgkin's lymphoma and urothelial carcinoma (as well as the future indications currently under investigation), with a dose of 200 mg every 3 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 pembrolizumab (a dose of 2 mg/kg administered every 3 weeks) is comparable to a fixed dose of 200 mg every 3 weeks. Consequently, the PGTM considers that it would be acceptable to administer 2 mg/kg up to a maximum of 200 mg every 3 weeks.

Programme de
GESTION THÉRAPEUTIQUE
des médicaments

PGTM Clinical Intervention Model (CIM)

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

The PGTM's recommendation in light of the pharmacoeconomic evaluation

Given the pharmacoeconomic findings, the PGTM recommends administering pembrolizumab at a dose of 2 mg/kg every 3 weeks up to a maximum dose of 200 mg to all patients and for all the approved indications.

Objective: To promote the use of an optimal dosage strategy for pembrolizumab in the 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 pembrolizumab CIM:

1. Submit the evaluation report to the Pharmacy and Therapeutics Committee and/or the Cancer/Oncology Subcommittee, if appropriate, and to the 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 pembrolizumab and pharmacists;
3. Improve the pembrolizumab 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 dosing frequency and the recommended maximum dose;
4. Create or modify a standing order as soon as possible when a new indication for pembrolizumab is approved;
5. Conduct a follow-up study, preferably in the form of a prospective drug utilization review (DUR), aimed at verifying if pembrolizumab is being prescribed according to the preferred dosage