INESSS
LE SAVOIR PREND FORME

DOSAGES FOR ANTI-PD-1 AND ANTI-PD-L1 MONOCLONAL ANTIBODIES

- At the start of treatment (especially in the case of extended-interval administration):
  - Consideration could be given to more frequent monitoring in terms of adverse effects, the therapeutic response and hyperprogression.
- In addition to more frequent monitoring, especially at the start of treatment, it may be prudent, in the following clinical situations, to initiate treatment at standard intervals for a few months before moving to extended-interval dosing.
  - Pre-existing autoimmune disease (with the exception of an endocrine disorder), because of the risk of exacerbating the autoimmune disease (which should be well controlled prior to initiating treatment with an PD-1 or PD-L1 monoclonal antibody);
  - Solid organ transplantation, because of the lack of quality data and the risk of graft rejection;
  - Hematopoietic stem cell transplantation, because of the lack of quality data and risk of graft-versus-host disease;
  - An individual who previously discontinued treatment because of adverse effects related to immunotherapy or who has a lower tolerance for adverse effects.
- When switching from a standard to an extended dosing interval:
  - Provide a closer follow-up to monitor the patient for adverse effects.
- Based on the expertise of the clinicians consulted, strategies to minimize the wastage of anti-PD-1 and anti-PD-L1 monoclonal antibodies should be put in place according to the needs of and as feasible in the clinical setting (e.g., the consolidation of treatment preparation and administration, and the recovery of unadministered doses, based on the available stability data).

Only the indications approved by Health Canada at the time of publication of this tool were considered. Some of these indications may not be on the lists of drugs covered by the RAMQ.

DRUG	INTERVAL	DOSE	MAIN FINDINGS SUPPORTING THE RECOMMENDATIONS
Atezolizumab	2 weeks	840 mg	▶ Fixed doses every 2, 3 and 4 weeks are recommended in the North American product monographs. No weight-based dose was previously recommended in the monographs. ▶ Safety is similar for doses of 10 to 20 mg/kg every 3 weeks (low level of evidence), but the data do not permit an efficacy comparison between dose levels (insufficient level of evidence). ▶ No studies were found that compared the efficacy of fixed doses with that of weight-based doses (insufficient level of evidence). However, the safety of the 1200 mg fixed dose is similar to that of the 20 mg/kg dose every 3 weeks, according to a modeling study. ▶ No studies were found that compared the efficacy or safety of the different dosing intervals recommended in the product monographs (insufficient level of evidence). ▶ Its pharmacokinetics are linear.
	3 weeks	1200 mg	
	4 weeks	1680 mg	

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DRUG	INTERVAL	DOSE	MAIN FINDINGS SUPPORTING THE RECOMMENDATIONS
Avelumab	2 weeks	10 mg/kg (max. 800 mg)	▶ The Canadian product monograph recommends a dose of 10 mg/kg every 2 weeks, while the U.S. product monograph recommends a fixed dose of 800 mg for the same indications. ▶ Efficacy and safety are similar for doses of 3 mg/kg to 20 mg/kg every 2 weeks (low level of evidence). ▶ The efficacy and safety of the 800 mg fixed dose are similar to those of the 10 mg/kg dose every 2 weeks, according to a modeling study. ▶ Its pharmacokinetics are linear.
Cemiplimab	3 weeks	350 mg	▶ Only the fixed dose is recommended in the product monographs. The 3 mg/kg dose every 3 weeks for underweight patients is no longer recommended in the monographs. ▶ The efficacy and safety of the fixed dose of 350 mg every 3 weeks are similar to those of the 3 mg/kg dose every 2 weeks (low level of evidence). ▶ The pharmacokinetic parameters are comparable between the doses, regardless of the patient's weight.
Durvalumab	2 weeks	10 mg/kg (max. 750 mg)	▶ Fixed (every 3 or 4 weeks) and weight-based (every 2 weeks) doses are recommended in the product monographs. ▶ Efficacy and safety are similar for doses of 1 to 10 mg/kg every 2 weeks, and for doses of 10 mg/kg every 2 weeks or 20 mg/kg every 4 weeks (low level of evidence). There are no studies comparing the every-3-week dose with other doses (insufficient level of evidence). ▶ No studies were found that compared the efficacy or safety of fixed doses with weight-based doses (insufficient level of evidence). ▶ Modeling studies suggest that doses of 10 mg/kg and 750 mg every 2 weeks and 1500 mg every 4 weeks have similar pharmacokinetic parameters. The dose of 15 mg/kg every 3 weeks is a reasonable extrapolation, given the linear pharmacokinetics, based on the expertise of the clinicians consulted.
	3 weeks	15 mg/kg (max. 1125 mg)	
	4 weeks	20 mg/kg (max. 1500 mg)	
Nivolumab	2 weeks	3 mg/kg (max. 240 mg)	▶ Fixed (every 2, 3 and 4 weeks) and weight-based (every 2 weeks) doses are recommended in the product monographs. ▶ Efficacy and safety are similar for doses of 1 to 10 mg/kg every 2 weeks and 0.3 to 10 mg/kg every 3 weeks (low to moderate level of evidence). ▶ The efficacy and safety of the fixed dose of 240 mg every 2 weeks are similar to those of the dose of 3 mg/kg every 2 weeks (low level of evidence). ▶ Pharmacokinetic models suggest that doses of 3 mg/kg and 240 mg every 2 weeks and 480 mg every 4 weeks are similar. ▶ The efficacy and safety of the extended-interval fixed doses (360 mg every 3 weeks or 480 mg every 4 weeks) are similar to those of the standard dose of 3 mg/kg every 2 weeks (low level of evidence). ▶ No studies were found that compared the efficacy or safety of doses of 4.5 mg/kg every 3 weeks or 6 mg/kg every 4 weeks with those of fixed doses (insufficient level of evidence), but these doses are reasonable extrapolations, given this drug's linear pharmacokinetics, based on the expertise of the clinicians consulted.
	3 weeks	4,5 mg/kg (max. 360 mg)[1]	
	4 weeks	6 mg/kg (max. 480 mg)	
Pembrolizumab	3 weeks	2 mg/kg (max. 200 mg)	▶ Only fixed doses every 3 and 6 weeks are recommended in the North American product monographs, but weight-based doses every 3 weeks were previously recommended in the monographs. ▶ Efficacy and safety are similar between doses of 2 mg/kg and 10 mg/kg every 3 weeks (moderate level of evidence). ▶ The safety of and progression-free survival rate for the 200 mg fixed dose are similar to those for the 2 mg/kg dose every 3 weeks (low level of evidence). ▶ The safety of the 400 mg dose every 6 weeks is similar to that of the 200 mg dose every 3 weeks (low level of evidence), but the data do not permit an efficacy comparison between these two dosage regimens (insufficient level of evidence). ▶ No studies were found that compared the efficacy or safety of 4 mg/kg doses every 6 weeks with other doses (insufficient level of evidence), but this dose is a reasonable extrapolation, given this drug's linear pharmacokinetics, based on the expertise of the clinicians consulted.
	6 weeks	4 mg/kg (max. 400 mg)	

1. When used in combination with ipilimumab, lower doses than in monotherapy should be used, i.e., 1 mg/kg or 3 mg/kg (max. 240 mg), depending on the indication.

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