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Dosing and Timing of Immuno-Oncology Drugs

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Table of Contents

Reviewers 3
External Reviewers 3
Background 6
Policy Issue 7
Policy Questions 8
Research Questions 8
Pharmacometric Review 9
Methods 9
Nivolumab Dosing (Research Question 1) 11
Pembrolizumab Dosing (Research Question 2) 17
Conclusion 23
Nivolumab Elimination (Research Question 3a) 24
Pembrolizumab Elimination (Research Question 3b) 32
Durvalumab Elimination (Research Question 3c) 38
Clinical Review 42
Results (Research Questions 4 to 6) 42
Implications for Decision-Making 43
References 46

Tables

Table 1: Selection Criteria (Research Questions 1 and 2: Exposure Response and Dosing) 10
Table 2: Selection Criteria (Research Question 3: Elimination) 10
Table 3: Nivolumab Dose Banding Proposed by Ogungbenro et al.[19] 16
Table 4: Pembrolizumab Dose Response 18
Table 5: Peak, Average, and Trough Concentrations at Steady State in a Patient Weighing 70 kg 21
Table 6: Peak, Average, and Trough Concentrations at Steady State in a Patient Weighing 100 kg 22
Table 7: Peak, Average, and Trough Concentrations at Steady State in a Patient Weighing 150 kg 23
Table 8: Health Canada–Approved Product Monograph Pharmacokinetics Information 24
Table 9: Nivolumab Pharmacokinetic Summary 27

Table 10: Health Canada–Approved Product Monograph Pharmacokinetics Information 32
Table 11: Pembrolizumab Pharmacokinetic Metric Summary of Full Publications Arranged by Date of Publication 33
Table 12: Patient and Pharmacokinetic Observation Summary of NONMEM Data Set..... 35
Table 13: Health Canada–Approved Product Monograph Pharmacokinetics Information 38
Table 14: Durvalumab Pharmacokinetic Metric Summary 39
Table 15: Selection Criteria..... 42
Table 16: Summary of Immuno-Oncology Drug Half-Lives and Washout Periods..... 45
Table 17: Pembrolizumab Dosing by Jurisdiction 49
Table 18: Nivolumab Dosing by Jurisdiction 50

Figures

Figure 1: Body Weight Distribution 12
Figure 2: Simulated Nivolumab Exposure Distribution..... 13
Figure 3: Time-Averaged Concentration After the First Dose Variation According to Two Dosing Regimens 14
Figure 4: Pembrolizumab Target Engagement..... 19
Figure 5: Overall Survival With Various Pembrolizumab Doses 20
Figure 6: Pembrolizumab Clearance Depending on Concentration..... 34
Figure 7: Programmed Cell Death Protein 1 Modulation 35
Figure 8: Simulated Pharmacokinetic Profiles of Durvalumab..... 40

Background

Immuno-oncology (IO) drugs (also called immune checkpoint inhibitors or immunotherapy drugs) have transformed the field of medical oncology. By impeding on a tumour's ability to disrupt recognition by the immune system, these drugs have elicited exceptional therapeutic responses, allowing significant regression and sometimes resolution of several cancer types, including metastatic melanoma, renal cell carcinoma, and lung cancer.

Nivolumab and pembrolizumab are antibodies that target and block the programmed cell death-1 (PD-1) immune checkpoint receptor, while atezolizumab and durvalumab block the associated cell surface ligand, programmed death-ligand 1 (PD-L1). Finally, ipilimumab inhibits the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) immune checkpoint axis. All of these drugs are approved by Health Canada and recommended for reimbursement by CADTH's pCODR Expert Review Committee (pERC) for a variety of indications (see Appendix 1). IO drugs can be given either in the adjuvant setting (i.e., post-surgery to prevent recurrence) or in the metastatic setting. As it stands, IO drugs can be used for the treatment of melanoma, non–small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck, and renal cell carcinoma in the metastatic setting. In contrast, pembrolizumab and nivolumab are approved for adjuvant therapy for melanoma only, whereas durvalumab is approved for consolidation therapy following curative-intent chemo-radiation therapy for NSCLC.

Dosing of IO drugs varies. It can be based on patient weight (e.g., 3 mg/kg every two weeks), as a fixed (or "flat") dose (e.g., 200 mg every three weeks), or weight-based up to a fixed maximum dose. Timing of dosing (e.g., every three weeks versus six weeks) can also vary. The Health Canada–approved product monographs states the following regarding dosing of nivolumab and pembrolizumab.

Nivolumab

Based on dose/exposure efficacy and safety analyses, no clinically significant differences in safety and efficacy were observed between a nivolumab dose of 240 mg every 2 weeks or 480 mg every 4 weeks or 3 mg/kg every 2 weeks.[1]

Pembrolizumab

The pharmacokinetics of pembrolizumab was studied in 2993 patients with various cancers who received doses in the range of 1 to 10 mg/kg every 2 weeks, 2 to 10 mg/kg every 3 weeks, or 200 mg every 3 weeks. There are no clinically meaningful differences in pharmacokinetics of pembrolizumab across indications.[2]

It is worth noting that the dose-response relationship of PD-1 inhibitors is not linear and flattens beyond a certain concentration.[3,4] Moreover, the drugs target a molecule expressed by the host immune system, not by the tumour. As a result, some literature suggests that the dose response to these inhibitors should not vary by tumour type;[5,6] however, clinical evidence may be needed to substantiate this theory.

Policy Issue

In recent years, pERC has issued various positive recommendations for reimbursing nivolumab and pembrolizumab. Notably, these recommendations included considerations of dosing schedules that were not always consistent across drug reviews, but instead were based on the underlying clinical trials. For example, pERC felt it was reasonable that pembrolizumab for first-line treatment of locally advanced or metastatic NSCLC be administered at 2 mg/kg up to a total dose of 200 mg every three weeks while the same committee recommended a fixed 200 mg dose every three weeks for relapsed or refractory classical Hodgkin lymphoma (cHL) due to lack of evidence on the alternative schedule for this indication. Similarly, pERC recommended weight-based dosing for nivolumab (3 mg/kg every two weeks) with no upper limit for adjuvant melanoma, but specified a maximum dose of 240 mg every two weeks for metastatic melanoma. (See Appendix 1 for a summary of recent recommendations and uptake by jurisdictions.)

Given that weight-based dosing with a cap may be a more cost-effective dosing scheme,[7] the Provincial Advisory Group and the Cancer Drug Implementation Advisory Committee are seeking clarity on the optimal dosing schedule to consistently implement for all future uses of nivolumab and pembrolizumab. To support such a decision, the committees are requesting a review and appraisal of the literature on the drugs' pharmacokinetics (PKs) and exposure response.

Another issue identified by the Provincial Advisory Group and the Cancer Drug Implementation Advisory Committee relates to re-treatment with IO drugs in the metastatic setting after they have been used in the adjuvant or consolidation setting. For example, nivolumab is approved for use in melanoma in both settings. Another recent example is the recommendation of durvalumab for stage III NSCLC (after completion of chemo-radiation) and treatment if a patient were to progress after one year of durvalumab therapy. However, it is controversial to provide repeated treatment with a drug (or drug class) that essentially failed to prevent progression. It is generally agreed that re-treatment is not advised when progression occurs during adjuvant IO therapy, but re-treating patients who relapse while off treatment is being seriously considered. However, the time that must be allowed for the patient to be considered "off treatment" (i.e., having no remaining drug in their system) is uncertain. The evidence behind such an approach, either clinical or pharmacological, needs to be explored.

The pCODR Clinical Guidance Panel on nivolumab for adjuvant melanoma therapy made the following statement:

> "The CGP agreed that there is evidence available on the use of an anti-PD1 therapy in the metastatic setting in patients who had already received an anti-PD1 agent. These were however patients that had been responsive to prior anti-PD1 treatment in the metastatic setting. The CGP do however agree that the option to reuse an anti-PD1 agent following its use in the adjuvant setting should be made available."[8]

pERC deliberated on this statement in addition to all evidence presented in the review and indicated that "although there is some data demonstrating the efficacy of using anti-PD-1 agents in sequence (all treatments given in the metastatic setting), […] it would be difficult to generalize that data to the current setting." pERC further noted that "there is no evidence to determine the appropriate time frame from progression on adjuvant therapy to initiation of treatment in the metastatic setting."[9]

In light of these issues, decision-makers are requesting a literature review to identify evidence informing both dosing and timing of re-treatment with IO drugs. Policy questions were developed in consultation with the requestors to summarize the two overarching issues to address.

Policy Questions

PQ1. Are there any potential issues with implementing a consistent dosing schedule (i.e., weight-based dosing with a cap) of nivolumab and pembrolizumab for all oncology indications?

PQ2. Is immuno-oncology (IO) drug re-treatment after adjuvant IO therapy effective? How long after end of adjuvant IO therapy can patients with progressing melanoma or non–small cell lung cancer be considered eligible for a second IO treatment?

Research Questions

For Policy Question 1 (Dosing Schedule)

RQ1. What are the comparative pharmacokinetic and exposure-response outcomes of dosing schedules (weight-based ± cap, fixed dose, considering different dosing frequencies) of nivolumab for any indication?

RQ2. What are the comparative pharmacokinetic and exposure-response outcomes of dosing schedules (weight-based ± cap, fixed dose, considering different dosing frequencies) of pembrolizumab for any indication?

For Policy Question 2 (Washout and Re-treatment)

RQ3. What are the elimination kinetics of:

- nivolumab
- pembrolizumab
- durvalumab?

RQ4. What is the clinical effectiveness of nivolumab, pembrolizumab, or ipilimumab-nivolumab in patients with melanoma who progressed after adjuvant therapy with nivolumab or pembrolizumab?

RQ5. What is the clinical effectiveness of atezolizumab, nivolumab, or pembrolizumab in patients with recurrent or metastatic non–small cell lung cancer who progressed after consolidation therapy with durvalumab?

RQ6. What are the evidence-based guidelines on the timing of re-treatment with immune checkpoint inhibitors?

To address the policy and research questions, this Optimal Use 360 report combines two complementary reviews.

A) Pharmacometric Review of Immuno-Oncology Drugs

A synthesis and appraisal of the pharmacometric literature, including models of population pharmacokinetics and exposure-response relationships. This review is designed to address research questions 1 to 3.

B) Clinical Review of Re-treatment Following Immuno-Oncology Adjuvant Therapy

A summary and appraisal of clinical trials and/or evidence-based guidelines that evaluate re-treatment with IO drugs after relapse following adjuvant therapy. The time period defined as "off treatment" or "washout" and any related considerations will be extracted from the literature. As an initial step, a CADTH Rapid Response List of References was commissioned to determine if any relevant evidence exists. Should any be found, the review would be upgraded to a Summary With Critical Appraisal to more closely examine the identified studies. This review is designed to address research questions 4 to 6.

Pharmacometric Review

Methods

Literature Search

The literature search for clinical studies was performed by an information specialist using a peer-reviewed search strategy according to the *PRESS Peer Review of Electronic Search Strategies* checklist.[10] The search strategy is available on request.

Published literature was identified by searching the following bibliographic databases: MEDLINE All (1946–) via Ovid, and Embase (1974–) via Ovid. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were nivolumab or pembrolizumab or durvalumab and dosing or PKs.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date but was limited to the English language. The search was completed on August 28, 2019.

Grey literature (literature that is not commercially published) was identified by searching Canadian and major international health technology agencies as well as with a focused Internet search. These searches were supplemented by reviewing bibliographies of key papers and through contacts with experts and industry, as appropriate.

Literature Selection

The review was meant to address research questions1 to 3, as stated previously. A single researcher screened the search results and selected articles for review. The inclusion criteria used for the selection of relevant studies are detailed in Table 1 and **Error! Reference source not found.**.

Table 1: Selection Criteria (Research Questions 1 and 2: Exposure Response and Dosing)

Population	Patients with any cancer at any stage
Intervention	**Nivolumab (MDX-1106)** Any dosing schedule including: • 240 mg Q2W • 480 mg Q4W • 3 mg/kg ± 240 mg cap Q2W • 6 mg/kg ± 480 mg cap Q4W **Pembrolizumab (MK-3475)** Any dosing schedule including: • 200 mg Q2W • 200 mg Q3W • 400 mg Q4W • 400 mg Q6W • 2 mg/kg ± 200 mg cap Q2W • 2 mg/kg ± 200 mg cap Q3W • 4 mg/kg ± 400 mg cap Q4W • 4 mg/kg ± 400 mg cap Q6W
Comparator	Other dosing schedules for the same interventions
Outcomes	Drug exposure (e.g., AUC_{ss}, C_{avg1}) Clinical response (e.g., change in tumour size, PFS, OS) Safety outcomes Exposure-response relationship Exposure-safety relationship
Study Designs	PPK modelling or simulation studies Dose- or exposure-response analyses Systematic reviews of the previously mentioned studies and analyses Excluded clinical trials not reporting pharmacometric concepts or relationships between dose or exposure and clinical response

AUC_{ss} = steady state area under the curve; $C_{avg}1$ = time-averaged concentration after the first dose; OS = overall survival; PFS = progression-free survival; PPK = population pharmacokinetic; Q2W = every two weeks; Q3W = every three weeks; Q4W = every four weeks; Q6W = every six weeks.

Table 2: Selection Criteria (Research Question 3: Elimination)

Population	Patients with any cancer at any stage, or heathy individuals
Intervention	Nivolumab (MDX-1106) Pembrolizumab (MK-3475) Durvalumab (MEDI4736) Any initial dose or dosing schedule
Comparator	NA
Outcomes	Elimination half-life Biological half-life after last dose Elimination curves Kinetics from last dose to loss of biological activity (e.g., PD-1/PD-L1 occupancy, immune checkpoint inhibition)
Study Designs	Dosing studies Phase I clinical trials Pharmacokinetics studies Systematic reviews of the previously mentioned studies and trials

NA = not applicable; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1.

Nivolumab Dosing (Research Question 1)

Nivolumab (Opdivo) Product Monograph

Nivolumab was first approved in Canada in September 2015 with a Notice of Compliance With Conditions (NOC/c). In the most recent product monograph, nivolumab is indicated for the treatment of unresectable or metastatic melanoma, metastatic NSCLC, metastatic renal cell carcinoma (RCC), squamous cell carcinoma of the head and neck, or cHL, adjuvant treatment of melanoma or hepatocellular carcinoma at doses of either 3 mg/kg every two weeks, 240 mg every two weeks, or 480 mg every four weeks.

Exposure Response in Weight-Based Dosing Regimens

Feng et al.[4] performed exposure-response analyses of efficacy and safety with data from 648 patients with squamous NSCLC (n = 293) and non-squamous NSCLC (n = 354) enrolled in four clinical studies (CA209-003, CA209-017, CA209-057, and CA209-063). Data from patients in CA209-003 whose primary cancer was not NSCLC were excluded from analysis. Patients received doses of 1 mg/kg every two weeks (n = 33), 3 mg/kg every two weeks (n = 557), or 10 mg/kg every two weeks (n = 57). The relationships between nivolumab exposure (average concentration following the first dose) and OS were described by semiparametric Cox proportional hazards models.

OS is presented in figures within the article, separated by dose and squamous versus non-squamous NSCLC, but is never explicitly stated in a text or table. A pooled evaluation indicates a median OS of 8.15 months at 1 mg/kg compared with 9.23 months at 3 mg/kg and 9.03 months at 10 mg/kg. When analyzed by the semiparametric Cox proportional hazards model, the study demonstrated that nivolumab exposure (average concentration observed following the first dose) was not associated with OS in patients with squamous NSCLC (hazard ratio [HR], 0.802; 95% confidence interval [CI], 0.555 to 1.16) or non-squamous NSCLC (HR, 0.94; 95%CI, 0.683 to 1.29). Similarly, nivolumab exposure was not associated with adverse events (HR, 0.917; 95% CI, 0.644 to 1.31). The authors conclude that nivolumab had a wide therapeutic margin over the range of exposure produced by doses from 1 mg/kg to 10 mg/kg every two weeks.

Fixed 240 mg and 480 mg Every Two Weeks Dosing Regimens

Early registration trials used a dose of 3 mg/kg every two weeks for nivolumab.[11] A fixed dose of 240 mg every two weeks was proposed to improve the ease of nivolumab use and administration, as well as to reduce prescription errors.[12] Long et al.[13] justified the flat 480 mg every four weeks dosage indicating that less frequent fixed dosing was convenient, flexible, and also likely to reduce the scheduling burden on cancer care institutions, dosage preparation time compared with body weight-based dosing, and the overall burden on pharmacy staff.

To demonstrate equivalence between the proposed 240 mg every two weeks and the 3 mg/kg every two weeks dosing regimens, concentration–time profiles were simulated using a published population-based PK regimen to ensure similar exposures.[14] This was then supplemented by a quantitative clinical pharmacology assessment of the risk-benefit profile.

These analyses were conducted by employees of the Bristol-Myers Squibb Company (BMS),[12,13] and while exposure, response, and adverse events have been balanced, these publications did not consider the relative cost or wastage of each regimen.

Zhao et al.[12] — Fixed 240 mg Every Two Weeks Dosing Regimen

The objective of the analysis by Zhao et al.[12] was to assess the benefit–risk profile of nivolumab 240 mg every two weeks relative to 3 mg/kg every two weeks through a quantitative clinical pharmacology approach, thereby supporting the dosage changes for nivolumab.

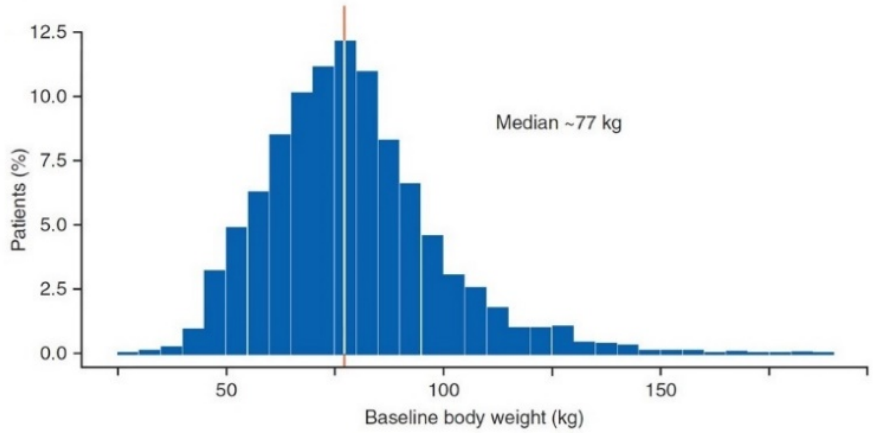
To select the appropriate fixed dose of nivolumab, the investigators used observed baseline body weights from 3,458 patients enrolled in 18 nivolumab clinical studies across tumour types, including melanoma, NSCLC, RCC, cHL, squamous cell carcinoma of the head and neck, urothelial cancer, gastric cancer, and small cell lung cancer. The fixed dose was selected such that there was a high degree of overlap in nivolumab exposures over the observed body weight range.

A previously developed population PK model was used to predict the nivolumab exposures resulting from a fixed dose in patients across tumour types and to compare these exposures with those produced by the 3 mg/kg every two weeks dose[14]. The kinetics of nivolumab was described by a linear two-compartment model with time-varying clearance.

The fixed dose of 240 mg of every two weeks of nivolumab was selected to achieve a high degree of overlap in exposures with the 3 mg/kg dose. This dose was selected by multiplying the initially approved 3 mg/kg every two weeks dose by the observed median body weight of approximately 80 kg of patients in the nivolumab clinical program.

The population PK model was used to simulate a total of 100 clinical trials in the 3,458 cancer patients with covariate values corresponding to those in the original analysis data set. Body weights ranged from 34 kg to 180 kg, with approximately 5% of patients below 50 kg and 6% of patients above 110 kg. (Body weight distribution is shown in Figure 1).

Figure 1: Body Weight Distribution

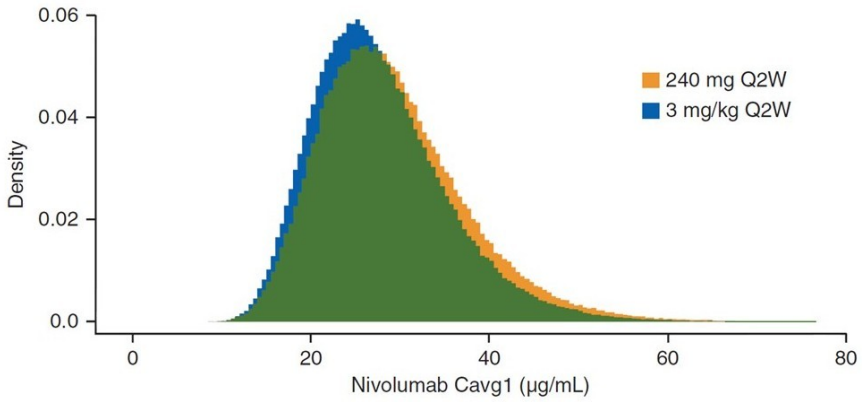


Source: Figure 1A from Zhao et al. Assessment of nivolumab benefit-risk profile of a 240-mg fixed dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Ann Oncol. 2017 Aug 01;28(8):2002-2008. Distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC 4.0). https://creativecommons.org/licenses/by-nc/4.0/.

The model-predicted average concentration following the first dose ($C_{avg}1$) was 26.7 mcg/mL for the 3 mg/kg dose and 28.1 mcg/mL for the 240 mg dose. The exposures produced by the 240 mg dose will therefore be identical to those produced by the 3 mg/kg dose for patients at the median body weight of 77 kg.

The simulated nivolumab exposure distribution of $C_{avg}1$ in patients across tumour types given 240 mg every two weeks and 3 mg/kg every two weeks is shown in Figure 2.

Figure 2: Simulated Nivolumab Exposure Distribution



$C_{avg}1$ = time-averaged concentration after the first dose; Q2W = every two weeks.

Source: Figure 1C from Zhao et al. Assessment of nivolumab benefit-risk profile of a 240-mg fixed dose relative to a 3-mg/kg dosing regimen in patients with advanced tumors. Ann Oncol. 2017 Aug 01;28(8):2002-2008. Distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC 4.0). https://creativecommons.org/licenses/by-nc/4.0/.

Following the simulation, the risk-benefit profile of nivolumab 240 mg every two weeks relative to 3 mg/kg every two weeks was assessed by the following analyses: first, comparison of nivolumab exposures at 240 mg every two weeks and 3 mg/kg every two weeks across the body weight range and tumour types; second, evaluation of the exposure margin for safety based on the well-tolerated dose of 10 mg/kg every two weeks; third, evaluation of the clinical safety of nivolumab 3 mg/kg every two weeks by body weight groups; fourth, prediction of risk of any-grade adverse events leading to drug discontinuation or death at 240 mg every two weeks relative to 3 mg/kg every two weeks across indications of melanoma, NSCLC, and RCC; and fifth, prediction of risk of death at 240 mg every two weeks relative to 3 mg/kg every two weeks in patients with melanoma, NSCLC, and RCC.

Based on predicted nivolumab exposures with a 240-mg every two weeks fixed dose, the established safety profile of nivolumab up to the 10-mg/kg dose level, and well-characterized and relatively flat exposure-response relationships for safety and efficacy, Zhao et al.[12] judged the risk-benefit profile for 240 mg every two weeks to be comparable with the originally approved 3 mg/kg every two weeks dose.

Long et al.[13] — Flat 480 mg Every Four Weeks Dosing Regimen

A similar analysis was completed by Long et al.[13] for a fixed dose of 480 mg every four weeks. A pooled PK data set was created from 3,817 patients with different tumour types and nivolumab concentration–time profiles were predicted using the previously developed population model.[14]

Although the maximal concentration at steady state with 480 mg every four weeks was higher than that of either 3 mg/kg or 240 mg every two weeks, it was 57% lower than with the maximal concentration at steady state produced in patients receiving 10 mg/kg every two weeks.[13] Given that the 10 mg/kg dose has previously been demonstrated to have an acceptable tolerability and safety profile, while the nivolumab 480 mg every four weeks

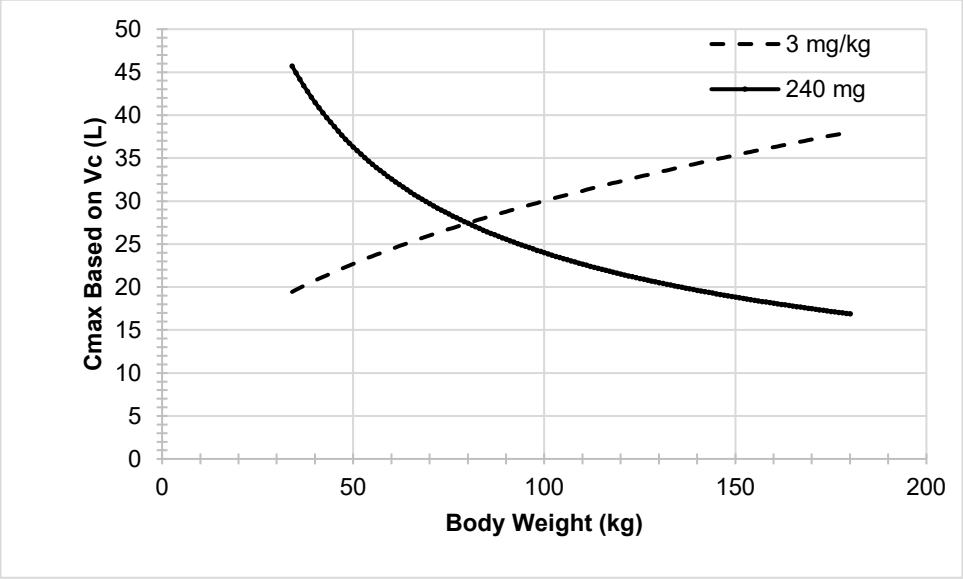
regimen also resulted in a modest increase in the interpatient variability in exposure relative to 3 mg/kg every two weeks, this fixed dose was considered safe and effective. However, it should be pointed out that only 15 patients in the data set were in the low body weight group (between 36 kg and 70 kg).[13]

Interpretation

The publication of Zhao et al.[12] supported the revision to the approved US prescribing information to reflect a nivolumab flat-dosing regimen of 240 mg every two weeks, regardless of a patient's body weight. It should be pointed out that in the time-averaged nivolumab $C_{avg}1$ distribution (Figure 2), the green and yellow shaded area reflects the number of patients (based on the body weight distribution) that would receive a 240 mg dose and experience a $C_{avg}1$ larger than those experienced by patients receiving a 3 mg/kg dose. It is the patients with a body weight between 34 kg and 77 kg that would experience the greatest exposure. At 80 kg, (population PK average does not consider the difference in volume due to gender; therefore, average weight is 80 kg not 77 kg) patients would all receive 240 mg and experience the same peak following the IV infusion. Patients weighting 34 kg and receiving 240 mg (dosage equivalent to 7.06 mg/kg) would experience a peak concentration 2.35 times higher than patients receiving 3 mg/kg. Alternatively, patients weighting 180 kg would experience a peak concentration of less than half (0.444 to 2.25 times lower) than patients receiving 3 mg/kg.

Using the population kinetic model, Figure 3 illustrates the relative $C_{avg}1$ that patients would experience following a 3 mg/kg dose (shown as a broken line) compared with patients of the same weight receiving 240 mg (shown as a solid line).

Figure 3: Time-Averaged Concentration After the First Dose Variation According to Two Dosing Regimens



c_{max} = maximum concentration; Vc = central volume.

Even though a flat response between doses of 1 mg/kg and 10 mg/kg suggests that both the high exposures of a 240 mg dose in a 34 kg patient or the low exposures in a 180 kg patient are safe and effective, they are justified on the basis of ease of use and the likelihood of reduced prescription errors.[12] This justification was further expanded by Long et al.[13] by explaining that less frequent fixed dosing was also likely to reduce the scheduling burden on cancer care institutions, dosage preparation time compared with body weight-based dosing, and the overall burden on pharmacy staff. However, these analyses were conducted by employees of the manufacturer of Opdivo (BMS),[12,13] which may have biased conclusions, and while exposure, response, and adverse events have been balanced, these publications did not consider the relative cost or wastage of each regimen or the effect of vial size on cost and wastage.

Giuliani[15] conducted a retrospective analysis of the nivolumab cost in nine patients with NSCLC, using 100 mg vials. Only direct costs were considered, while outpatient and in-patient administration costs, treatment-related adverse event costs, and health-related quality of life were not. The average cost for a patient treated with the fixed dose of 240 mg every two weeks was €29,025 (C$42,377) compared with €26,875 (C$39,238) for a fixed dose of 480 mg every four weeks and €20,305 (C$29,645) for a 3 mg/kg every two weeks regimen. Much of this difference was due to wastage, as at a dose of 240 mg, 60 mg (around €600, equivalent to C$876) was discarded, and at a dose of 480 mg, 20 mg (around €200, equivalent to C$292) was discarded. These differences are in agreement with the analysis of Bayle et al.[16]

De Lemos et al.[17] has also pointed out that the 240 mg every two weeks and 480 mg every four weeks fixed dosing schedules may lead to increased drug usage and cost, depending on the pricing and availability of different size vials (40 mg, 100 mg, 240 mg). In Canada, where the 240 mg vial is not available, some jurisdictions have adopted a hybrid dosing strategy, using a 3 mg/kg dose in patients who weigh less than 80 kg, and a 240 mg fixed dose for patients who weigh 80 kg or more (i.e., a capped weight-based regimen). De Lemos et al.[18] has also suggested that a hybrid dosing strategy should also minimize the exposure of endotoxin from nivolumab infusion in smaller patients receiving fixed dosing, as cautioned by the manufacturer. No published literature supporting this statement was identified.

Ogungbenro et al.[19] evaluated four different dosing strategies in 42 patients based on UK drug costs: 3 mg/kg body weight; dosing banding using body weight (± 10% of calculated body weight) doses so that individual doses fit into one of 17 different bands (see Table 3 for details); fixed dosing of 240 mg every two weeks; and kinetic derived dose based on six body weight ranges. In this study, the cost of 10 cycles in 24 patients was greatest for weight-based dosing and least for dose banding. Significant wastage was associated with mg/kg dosing, largely because sharing the residual drug in a vial is not possible where the dose does not match the vial size. Dose banding is a strategy where the bands are based on vial sizes, which aims to minimize wastage. Relative to fixed mg/kg doses, the median concentration–time exposures were –3.1% for banding, +11.9% for fixed 240 mg dosing, and +11.4% for PK-derived strategies.

Conclusion

A fixed dose of 240 mg every two weeks was proposed by BMS to improve the ease of nivolumab use and administration, as well as to reduce prescription errors.[12] Justification of the 480 mg every four weeks dose was evaluated by Long et al.,[13] who indicated that less frequent fixed dosing was convenient, flexible, and was also likely to reduce the scheduling burden on cancer care institutions, dosage preparation time compared with body weight-based dosing, and the overall burden on pharmacy staff. A study supporting these claims has not been published.

Given the established safety profile of nivolumab up to the 10-mg/kg dose level, and well-characterized and relatively flat exposure-response relationships between 1 mg/kg and 10 mg/kg[4] allowed Zhao et al.[12] and Long et al.[13] to judge the 240 mg every two weeks and the 480 mg every four weeks regimens to be safe and effective. However, these analyses were potentially biased and while exposure, response, and adverse events have been balanced, these publications did not consider the relative cost or wastage of each regimen or the effect of vial size on cost and wastage.

Ogungbenro et al.[19] evaluated four different dosing strategies in 42 patients based on UK drug costs. In this study, using 40 mg and 100 mg vials, the cost of 10 cycles in 24 patients was greatest for weight-based dosing and least for dose banding. These results disagree with Giuliani,[15] where a fixed 240 mg every two weeks dosing regimen was more expensive than 3 mg/kg dosing, although only 100 mg vials were used. In Canada, 40 mg and 100 mg vials are available, vial rationalization can occur, but given that best available practice only allows one drug in the sterile hood at a time, rationalization requires the use of a closed system transfer device,[20] which may not be available at all centres. Therefore, wastage and cost savings may vary from site to site based on patient numbers, sterile program procedures, and purchasing practices.

The relatively wide efficacy and safety profile of nivolumab between 1 mg/kg and 10 mg/kg allow several possible dosing strategies to be considered. Based on the product monograph, a base dose of 3 mg/kg seems to be a reasonable standard regimen. One alternative option is the rather extensive dose banding option presented by Ogungbenro et al.[19] According to this scheme, all patients would receive approximately a 3 mg/kg dose and would achieve a nivolumab exposure that has been proven safe and effective across numerous clinical trials, achieving maximal savings based on reduced drug wastage calculated through simulation.[19]

Table 3: Nivolumab Dose Banding Proposed by Ogungbenro et al.[19]

Body Weight Range (kg)	Dose Range (mg)	Banded Dose (mg)
< 45	120 to 133	120
45 to 51	134 to 155	140
52 to 58	156 to177	160
59 to 66	178 to 199	180
67 to 73	200 to 219	200
74 to 79	220 to 239	220
80 to 86	240 to 259	240
87 to 93	260 to 279	260
94 to 99	280 to 299	280
100 to 106	300 to 319	300

Body Weight Range (kg)	Dose Range (mg)	Banded Dose (mg)
107 to 113	320 to 339	320
114 to 119	340 to 359	340
120 to 126	360 to 379	360
127 to 133	380 to 399	380
134 to 139	400 to 419	400
140 to 146	420 to 439	420
> 147	440 to 479	440

Use of a fixed 240 mg every two weeks dose would be less cost-effective for patients who weigh less than 80 kg, where their treatment could approach and even exceed twice the cost of a 3 mg/kg dose. An option would be to cap dosing at 240 mg for patients weighing more than 80 kg. This option would deliver the proven 3 mg/kg dosing to patients who weigh less than 80 kg and deliver a dose for patients who weigh more than 80 mg as recommended in the product monograph. This dosing option is acknowledged by de Lemos et al.[18] It would also reduce drug costs, although depending on vial sizes used, there would be some wastage for patients weighing between 80 kg and 100 kg (unless a 40 mg vial is used to compound the 240 mg dose).

All of these regimens would deliver exposures that have been justified by Zhao et al.[12] and would not place a patient at risk (as the dosage would never exceed 10 mg/kg), nor reduce efficacy (as all dosages would exceed 1 mg/kg).

Pembrolizumab Dosing (Research Question 2)

Pembrolizumab (Keytruda) Product Monographs

Pembrolizumab was first approved in Canada in 2015. In the 2017[21] and 2018[22] revisions of the product monographs, the recommended dose for melanoma and previously treated NSCLC was 2 mg/kg. In the most recent product monograph,[2] pembrolizumab is indicated for the treatment of unresectable or metastatic melanoma, primary mediastinal large B-cell lymphoma, urothelial cancer, and high microsatellite instability tumours at a dose of 200 mg administered as an infusion over 30 minutes three times weekly for up to 24 weeks. Justification or rationale for this change were not provided and were not identified in the published literature.

Pembrolizumab Exposure-Response Relationships

Several studies[3,17,23-26] have evaluated exposure-response relationships at doses between 2 mg/kg every two weeks or every three weeks and 10 mg/kg every two weeks or every three weeks. Robert et al.[25] completed one of the earliest evaluations of dose in an open-label, phase I trial, where patients (aged 18 years or older) with advanced melanoma whose disease had progressed after at least two ipilimumab doses were randomly assigned to IV pembrolizumab at 2 mg/kg every three weeks or 10 mg/kg every three weeks until disease progression, intolerable toxicity, or consent withdrawal. Body weight was not identified as a covariate in the final exposure-response model. The primary end point was overall response rate. One hundred and seventy-three patients received pembrolizumab; of those, 89 received 2 mg/kg and 84 received 10 mg/kg. The median follow-up duration was eight months (range of 23 to 48 weeks). The overall response rate was 26% at both doses — 21

of 81 patients in the 2 mg/kg group and 20 of 76 in the 10 mg/kg group (difference, 0%; 95% CI, –14 to 13; *P* = 0.96).

In 2016, Chen et al.[23] completed a systematic review to evaluate the overall efficacy, safety, and effective dose. However, only the study by Robert et al.[25] was available for evaluation. As a result, Chen et al.[23] reported that at the tested doses, 2 mg/kg to 10 mg/kg every three weeks, were statistically similar and had significant advantages over the 0.3 mg/kg every three weeks dose.

In 2016, Chatterjee et al.[17] completed an analysis of the KEYNOTE-001 study, where 55 patients received pembrolizumab 2 mg/kg every three weeks, 238 patients received 10 mg/kg every three weeks, and 156 patients received 10 mg/kg every two weeks. Response was assessed every nine weeks. The relationship between the estimated pembrolizumab area under the concentration–time curve at steady state over six weeks and the longitudinal change in tumour size (sum of longest diameters) was analyzed by regression and non-linear mixed-effects modelling.

Overall response rates are shown in Table 4. Regression analyses of percentage change from baseline in tumour size versus area under the concentration–time curve at steady state over six indicated a flat relationship (regression slope *P* > 0.05). Simulations showed the exposure-response relationship to be similarly flat, thus indicating that the lowest evaluated dose of 2 mg/kg every three weeks was likely at or near the efficacy plateau.

Table 4: Pembrolizumab Dose Response

Dose	2 mg/kg Q3W n = 55	10 mg/kg Q3W n = 238	10 mg/kg Q2W n = 156
Overall response rate (90% confidence interval)	15% (7% to 28%)	25% (18% to 33%)	21% (14% to 30%)

Q2W = every two weeks; Q3W = every three weeks.

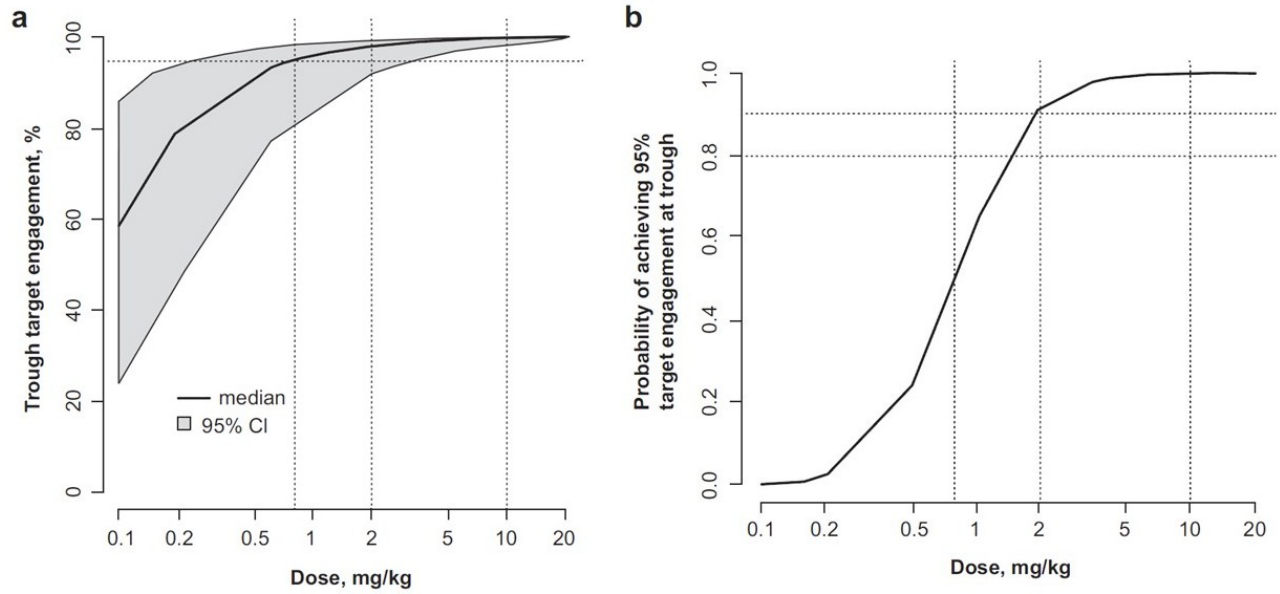
An exposure-safety analysis showed the adverse event incidence to be similar among the clinically tested doses. No significant exposure dependency on efficacy or safety was identified for pembrolizumab across doses. These results support the use of a 2 mg/kg every three weeks dosage in patients with previously treated advanced NSCLC.

In 2017, Chatterjee et al.[3] extended the 2016 modelling dose/exposure response (based on the change in tumour size from baseline through summation of the longest diameters) evaluation to include 1,366 patients in KEYNOTE-001, -002, and -006 receiving pembrolizumab at doses of 2 mg/kg every three weeks (n = 301), 10 mg/kg every three weeks (n = 668), or 10 mg/kg every two weeks (n = 397). Body weight was explored as a covariate, but it is not explicitly stated that it was included in the final model. Models indicated that pembrolizumab exposure was not a significant predictor of tumour size response, demonstrating that the dose range evaluated (2 mg/kg and 10 mg/kg every three weeks) is likely near or at the plateau of maximal response.

Elassaiss-Schaap et al.[24] used data from KEYNOTE-001 and studied 40 patients receiving doses of 0.005 mg/kg, 0.02 mg/kg, 0.06 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 2 mg/kg, and 10 mg/kg every three weeks. Modelling of the data demonstrated that pembrolizumab kinetics are non-linear at doses of less than 0.3 mg/kg every three weeks, but linear at doses above 0.3 mg/kg every three weeks. Body weight was not used as a covariate for either clearance or volume. The concentration of pembrolizumab required to cause 50% inhibition of the interleukin-2 stimulation ratio (IC50) values was estimated in the model.

Saturation of target engagement in blood based on the interleukin-2 bioassay began at doses equal to or greater than 1 mg/kg every three weeks and a steady state dose of 2 mg/kg every three weeks was needed to reach 95% target engagement, as shown in Figure 4. In panel a (on the left), target engagement is shown as a function of the concentration at steady state versus the percentage of target engagement, with a shaded band denoting the 95% CI for an every three weeks dosing regimen, based on simulations taking into account the uncertainty in the pharmacodynamic parameter estimates. In panel b (on the right), the probability (percentage of subjects within a simulated population) of achieving 95% target engagement at trough for different doses given every three weeks. Note that a dose of 2 mg/kg every three weeks achieves at least 95% target engagement and a dose of 1 mg/kg every three weeks achieves a 50% to 60% probability of 95% target engagement.

Figure 4: Pembrolizumab Target Engagement

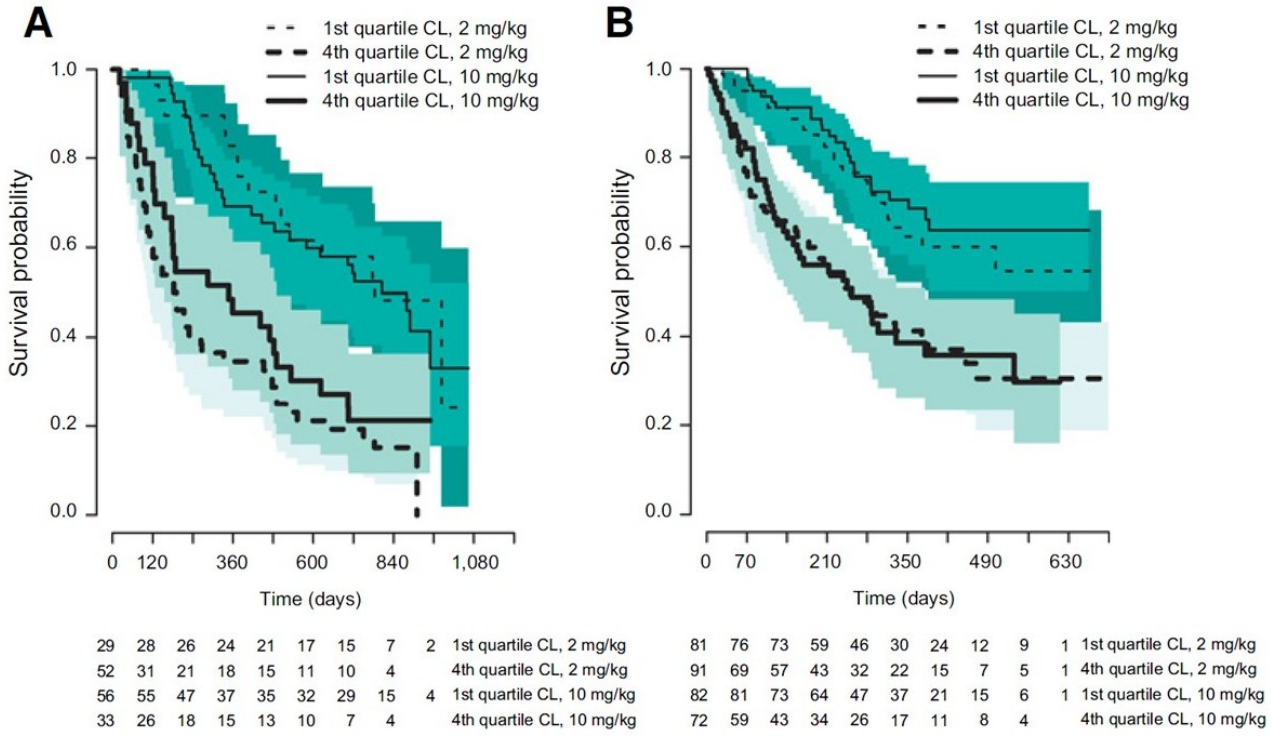


Source: Figure 5 from Elassaiss-Schaap J, Rossenu S, Lindauer A, et al. Using Model-Based "Learn and Confirm" to Reveal the Pharmacokinetics-Pharmacodynamics Relationship of Pembrolizumab in the KEYNOTE-001 Trial. CPT: Pharmacometrics & Systems Pharmacology. 2017 01;6(1):21-28. Distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC 4.0). https://creativecommons.org/licenses/by-nc/4.0/.

The largest evaluation identified in the literature was completed by Turner et al.[26]. In this study, 1,435 patients were taken from the KEYNOTE studies of patients with melanoma and NSCLC to investigate pembrolizumab exposure–survival relationships. In KEYNOTE-002, patients with melanoma received 2 mg/kg of pembrolizumab intravenously every three weeks (n = 180) and 10 mg/kg intravenously every three weeks (n = 181). In KEYNOTE-010, patients with NSCLC received pembrolizumab 2 mg/kg intravenously every three weeks (n = 344) or 10 mg/kg intravenously every three weeks (n = 346). In KEYNOTE-024, patients received pembrolizumab 200 mg intravenously every three weeks (n = 154). Full details of the PK model methods were published separately by Li et al.[27] Overall survival was independent of dose from 2 mg/kg to 10 mg/kg OS but patients with a slower elimination had improved survival.

Exposure-response trends were further explored by comparing the relationships of overall survival and pembrolizumab clearance between doses of 2 mg/kg and 10 mg/kg. In this analysis, as shown in Figure 5, the outer quartiles of each dose are shown. These data reveal a considerable difference in median overall survival for pembrolizumab-treated NSCLC (panel B) between subjects with rapid clearance (fourth quartile, 8.4 months; 95% CI, 6.4 to 11.0) and slow pembrolizumab clearance (first quartile, more than 23 months; lower 95% CI not reached). Figure 5 presents Kaplan–Meier plots of overall survival from 2 mg/kg and 10 mg/kg doses by within-dose baseline clearance quartiles demonstrating a strong association of clearance and overall survival in both (A) intradose first and fourth quartiles in advanced ipilimumab-refractory melanoma (KEYNOTE-002) and (B) intradose first and fourth quartiles in previously treated PD-L1–positive NSCLC (KEYNOTE-010).

Figure 5: Overall Survival With Various Pembrolizumab Doses



CL = clearance.

Source: Reprinted from Clinical Cancer Research, 2018, Dec 01;24(23):5841-5849, Turner et al, Pembrolizumab Exposure-Response Assessments Challenged by Association of Cancer Cachexia and Catabolic Clearance, with permission from AACR.

It is noteworthy that despite the confirmation of the fixed dose–exposure-response relationship, the analyses described here also reveal a prominent association of pembrolizumab clearance and overall survival, whereby subjects with slower clearance have a more than doubled life expectancy. The overall lack of influence of pembrolizumab dose and considerable within-dose clearance and exposure–overall survival trends signify latent confounding between pembrolizumab elimination and disease status.[26]

All of these evaluations demonstrate that, on average, the lowest effective dose is 2 mg/kg and that doses greater than 2 mg/kg every three weeks provide no survival advantage. These studies also suggest that doses up to 10 mg/kg every three weeks are safe and

effective; therefore, clinical studies have demonstrated that exposures between these two doses are safe and effective.

Interpretation

All studies[3,17,23-26] have concluded that dosing schedules between 2 mg/kg every three weeks and 10 mg/kg every three weeks are safe and effective. Elassaiss-Schaap et al.[24] demonstrated that the concentration observed at the end of the dosing interval (trough concentration) for a 2 mg/kg every three weeks regimen was required to obtain 95% of target engagement in blood.

Numerous dosing schedules have been proposed, used, or evaluated. These include:

- 200 mg every two weeks
- 200 mg every three weeks
- 400 mg every four weeks
- 400 mg every six weeks
- 2 mg/kg ± 200 mg cap every two weeks
- 2 mg/kg ± 200 mg cap every three weeks
- 4 mg/kg ± 400 mg cap every four weeks
- 4 mg/kg ± 400 mg cap every six weeks.

To compare these dosing regimens, concentration–time profiles have been simulated in a patient weighing 70 kg. These profiles were simulated using an average volume of distribution (6.5 L) and an average time-stationary clearance, which results in a half-life of 23.71 days.[27] The peak concentration following the dose at steady state and the average concentration were calculated based on the concentration at the midpoint of the dosage interval and the trough concentration at steady state (concentration at the end of the dosage interval) are provided in Table 5. For each dosage regimen, the average dose per day has been calculated. This average dose per day will translate into a relative drug procurement cost. This should not be construed as a cost-minimization surrogate, as every two week regimens will have greater clinic costs, nursing patient-care costs, and pharmacy preparation costs than every three week or every four week regimens. Target engagement for each regimen was estimated using the observed steady state trough concentration and the non-linear relationship between target attainment and trough concentration reported by Elassaiss-Schaap et al.[24]

Table 5: Peak, Average, and Trough Concentrations at Steady State in a Patient Weighing 70 kg

Dosing Regimen	Average Dose per Day (mg)	C_{max} at SS[a] (mg/L)	C_{avg} at SS[a] (mg/L)	Trough at SS[a] (mg/L)	Trough Target Engagement %[b] (90% CI)
1 mg/kg Q3W	3.33	23.38	17.20	12.75	96.8% (80% to98.8%)
2 mg/kg Q2W	10.00	63.82	51.64	43.01	Estimated 99.95%
2 mg/kg Q3W	6.66	46.77	34.41	25.50	98.0% (90% to 100%)
4 mg/kg Q4W	10.00	76.83	51.03	34.14	Estimated 99.11%
4 mg/kg Q6W	6.66	60.80	32.91	17.94	Estimated 97.00%
5 mg/kg Q3W	16.66	116.92	86.02	63.75	100% (96.7% to 100%)
200 mg Q2W	14.29	91.18	73.77	61.45	Estimated 99.99%

Dosing Regimen	Average Dose per Day (mg)	C_{max} at SS[a] (mg/L)	C_{avg} at SS[a] (mg/L)	Trough at SS[a] (mg/L)	Trough Target Engagement %[b] (90% CI)
200 mg Q3W	9.52	66.81	49.15	36.43	Estimated 99.31%
400 mg Q4W	14.29	109.76	72.90	48.77	Estimated 99.98%
400 mg Q6W	9.52	86.85	47.01	25.63	Estimated 98.16%

C_{avg} = time-averaged concentration after the first dose; CI = confidence interval; C_{max} = maximum concentration; Q2W = every two weeks; Q3W = every three weeks; Q4W = every four weeks; Q6W = every six weeks; SS = steady state.

[a] Dose at 168 days, ninth dose for Q3W, seventh dose for Q4W, or fifth dose for Q6W.

[b] Based on Elassaiss-Schaap et al.[24] using data from KEYNOTE-001. Target engagement for each regimen was estimated using the observed steady state trough concentration and the non-linear relationship between target attainment and trough concentration reported by Elassaiss-Schaap et al.[24]

Therefore, for a 70 kg patient, a 2 mg/kg dose every three weeks provides 98% trough target engagement using a dose of 6.66 mg/day. The other dosage regimen of 6.66 mg/day (4 mg/kg every six weeks) achieves a lower target engagement (97%) and the only other dosage regimen with similar target engagement (400 mg every six weeks) requires 9.52 mg/day. This would indicate that 2.0 mg/day every three weeks is the most efficient dosage regimen.

As the body weight increases to 100 kg, dosage caps begin. The 2 mg/kg every three weeks dose provides 98% trough target engagement using a dose of 9.52mg/day (Table 6). Other dosage regimens of 9.52 mg/day (4 mg/kg every six weeks and 400 mg every six weeks) achieve a lower target engagement. Therefore, this would again indicate that 2.0 mg/day every three weeks is the most efficient dosage regimen.

Table 6: Peak, Average, and Trough Concentrations at Steady State in a Patient Weighing 100 kg

Dosing Regimen	Average Dose per Day[a] (mg)	C_{max} at SS[a] (mg/L)	C_{avg} at SS[a] (mg/L)	Trough at SS[a] (mg/L)	Trough Target Engagement %[b] (90% CI)
1 mg/kg Q3W	4.76	33.41	24.58	18.21	96.8% (80% to 98.8%)
2 mg/kg Q2W	14.29	91.77	74.31	61.00	Estimated 99.56%
2 mg/kg Q3W	9.52	66.81	49.15	36.43	98.0% (90% to 100%)
4 mg/kg Q4W	14.29	109.58	72.90	48.77	Estimated 99.01%
4 mg/kg Q6W	9.52	86.85	47.01	25.63	Estimated 97.14%
5 mg/kg Q3W	23.81	167.03	122.89	91.07	100% (96.7% to 100%)
200 mg Q2W[c]	14.29	91.18	74.31	61.45	Estimated 99.56%
200 mg Q3W[c]	9.52	66.81	49.15	36.43	Estimated 98.14%
400 mg Q4W[d]	14.29	109.58	72.90	48.77	Estimated 99.01%
400 mg Q6W[d]	9.52	86.85	47.01	25.63	Estimated 97.14%

C_{avg} = time-averaged concentration after the first dose; CI = confidence interval; C_{max} = maximum concentration; Q2W = every two weeks; Q3W = every three weeks; Q4W = every four weeks; Q6W = every six weeks; SS = steady state.

[a] Dose at 168 days, ninth dose for Q3W, seventh dose for Q4W, or fifth dose for Q6W.

[b] Based on Elassaiss-Schaap et al.[24] using data from KEYNOTE-001. Target engagement for each regimen was estimated using the observed steady state trough concentration and the non-linear relationship between target attainment and trough concentration reported by Elassaiss-Schaap et al.[24]

[c] Values applicable to a 200 mg cap scenario under a 2 mg/kg or greater regimen.

[d] Values applicable to a 400 mg cap scenario under a 4 mg/kg or greater regimen.

As the body weight increases to 150 kg, dosage caps are in place and limit the daily dose of a number of regimens. Based on the explicit statement in Elassaiss-Schaap,[24] the 2 mg/kg dose every three weeks provides 98% trough target engagement using a dose of 14.29 mg/day (Table 7). The capped 2 mg/kg every three weeks regimen that is capped at 200 mg utilizes 9.52 mg/day but achieves a lower target engagement of 96.90%. Numerous other regimens achieve similar or higher target engagements, but all require a higher daily dose, indicating that the 2.0 mg/kg every three weeks dosage with a 200 mg dosage cap is still an efficient dosage regimen.

Table 7: Peak, Average, and Trough Concentrations at Steady State in a Patient Weighing 150 kg

Dosing Regimen	Average Dose per Day (mg)	C_{max} at SS[a] (mg/L)	C_{avg} at SS[a] (mg/L)	Trough at SS[a] (mg/L)	Trough Target Engagement %[b] (90% CI)
1 mg/kg Q3W	7.14	50.11	36.87	27.32	96.8% (80% to 98.8%)
2 mg/kg Q2W	21.43	136.77	110.65	92.17	Estimated 98.47%
2 mg/kg Q3W	14.29	100.22	73.73	54.64	98.0% (90% to100%)
4 mg/kg Q4W	21.43	109.76	72.90	48.77	Estimated 97.62%
4 mg/kg Q6W	14.29	130.28	70.52	38.52	Estimated 96.94%
5 mg/kg Q3W	35.71	250.54	184.33	136.61	100% (96.7% to 100%)
200 mg Q2W[c]	14.28	91.17	73.77	61.45	Estimated 98.29%
200 mg Q3W[c]	9.52	66.81	49.15	36.43	Estimated 96.90%
400 mg Q4W[d]	14.28	109.76	72.90	48.77	Estimated 97.62%
400 mg Q6W[d]	9.52	86.85	47.01	25.63	Estimated 95.88%

C_{avg} = time-averaged concentration after the first dose; CI = confidence interval; C_{max} = maximum concentration; Q2W = every two weeks; Q3W = every three weeks; Q4W = every four weeks; Q6W = every six weeks; SS = steady state.

[a] Dose at 168 days, ninth dose for Q3W, seventh dose for Q4W, or fifth dose for Q6W.

[b] Based on Elassaiss-Schaap et al.[24] using data from KEYNOTE-001. Target engagement for each regimen was estimated using the observed steady state trough concentration and the non-linear relationship between target attainment and trough concentration reported by Elassaiss-Schaap et al.[24]

[c] Values applicable to a 200 mg cap scenario under a 2 mg/kg or greater regimen.

[d] Values applicable to a 400 mg cap scenario under a 4 mg/kg or greater regimen.

Again, a target engagement of 98% based on the trough concentration achieved at the end of the dosage interval with a 2 mg/kg every three weeks dosage would indicate that throughout the dosing interval, the minimum target engagement is 98%.

Conclusion

Evaluation of exposure-response relationships and multiple dosing regimens of pembrolizumab indicates that 2 mg/kg every three weeks, with a 200 mg upper dose cap, is the most efficient dosage to deliver target engagement of 95% based on the trough or end of dosage interval concentration. This dose is the most efficient at body weights below or at the capped dosage weight (100 kg), and above the capped dosage weight. Using such a dosage regimen is both efficient from a mg/day metric and achieves target engagement 95% or higher through the dosing interval. Keytruda is available as a 50 mg powder for solution and 100 mg/4 mL solution for infusion. Capping the dosing regimen at 200 mg will limit wastage for patients weighing more than 100 kg.

Ogungbenro et al.[19] evaluated four different dosing strategies in 42 patients based on UK drug costs. In this study, only a 50 mg vial of pembrolizumab was available and dosing

across nine bands was shown to be the most cost-effective.[19] In Canada, the 50 mg vial is being discontinued[28] and only the 100 mg vial is available. As the latter is already reconstituted, the applicability of this study within the Canadian health care system is questionable. Nevertheless, vial rationalization can occur, but as best available practice only allows one drug in the sterile hood at a time, rationalization requires the use of a close system transfer device,[20] which may not be available at all centres. Therefore, wastage and cost savings may vary from site to site based on patient numbers, sterile program procedures, and purchasing practices.

Nivolumab Elimination (Research Question 3a)

Nivolumab (Opdivo) Product Monograph

Nivolumab was first approved in Canada in September 2015 with a NOC/c. PK data, reported in the product monograph, is based on a population-based kinetic analysis in an unspecified number of patients receiving doses between 0.1 mg/kg and 20 mg/kg. The reported geometric mean clearance is 9.5 mL/hr (0.228 L/day), the steady state volume of distribution is 8.0 L, and the terminal half-life is 26.7 days.

A summary of the PK metrics reported in the current monograph shown in Table 8.

Table 8: Health Canada–Approved Product Monograph Pharmacokinetics Information

Year of Monograph	Sample Size	Volume Central (L)	Variability CV (%)	Clearance First Dose (L/day)	Variability CV (%)	Clearance at SS (mL/hr)	Variability CV (%)	Half-Life (Days)	Variability CV (%)
2019[1]	Not reported	8.0	Not reported	Not reported[a]	Not reported	9.5 mL/hr 0.228 L/day[a]	Not reported	26.7	Not reported

CV = coefficient of variation; SS = steady state.

[a] Clearance for first dose versus steady state doses are not differentiated.

Summary of the Published Literature

Six publications were identified that report a population-based PK analysis of data in patients from a total of 25 different studies.[14,29-33] Except for Lee et al.,[30] which reports the kinetics of nivolumab in a unique study, each population PK evaluation utilizes multiple clinical trials with a good degree of overlap of multiple clinical trials between the evaluations.[14,29,31-33] The reported sample size, data source, and final model parameter estimates for volume terms and clearance are reported in Table 9. Five of the six studies[14,29-31,32] produce calculated half-lives that are very similar (between 17.47 and 21.3 days). Only the study by Zhang et al.[33] reports a half-life that is somewhat different (25.2 days) from all other population PK reports, although similar to the 26.7 days reported in the product monograph.[1] Pooling all studies would allow calculation of a mean published half-life, but because of considerable overlap (some clinical trials appear in five of the six studies [identified in Table 9 in italics]), the data from some patients would be overrepresented. Nevertheless, the calculated weighted mean (published) half-life is 20.09 days (utilizing the beta half-life of 25.2 days from Zhang et al.[33]).

Bajaj et al.[14]

The abstract for this publication indicates a dose range from 0.3 mg/kg to 10 mg/kg. The text indicates otherwise, in that some of the patients in ONO-4538-01 received a 20 mg/kg dose.

The nivolumab PK model was developed using data from 1,895 patients who received 0.3mg/kg to 20.0 mg/kg nivolumab in 11 clinical trials. In the data set, 1,264 males and 631 females had an average age of 61.12 years and a mean body weight of 79.09 kg.

The PK of nivolumab was determined to be linear, such that clearance is independent of dose (demonstrated no change) within the dose range of 0.1 mg/kg to 20.0 mg/kg. Analysis of dose proportionality during base-model development indicated that models describing the elimination of nivolumab by a non-linear model incorporating a Michaelis–Menten elimination term representing target-mediated drug disposition did not improve the goodness-of-fit compared with a linear model. The base model is a two-compartment model with zero-order IV infusion and first-order elimination with final parameter estimates (shown in Table 9).

Lee et al.[30]

Eighteen patients from Korea received a single dose of nivolumab (six patients at each dose of 1 mg/kg, 3 mg/kg, and 10 mg/kg in study ONO-4538-13) and were followed up for three weeks. Eight patients were male and ten were female, ranging in age from 27 to 84 years with a mean of 56 years. Body weight was not specified.

The authors do not specify how the PK parameters (specifically half-life) were calculated, although it appears that no modelling was involved, and the half-life was determined on the basis of nine samples drawn over 21 days following a one-hour infusion. The mean elimination half-life of nivolumab among the groups ranged from 15.0 (10 mg/kg) to 19.1 days (3 mg/kg). When the maximum concentration and area under the curve of day 21 in patients from Korea were compared with patients from Japan and the US, the authors reported that the PK parameters of nivolumab were similar among patients from Korea, Japan, and the US.

Zhang et al.[33]

This evaluation used data from 1,209 patients across several studies that included patients who were Chinese (314), non-Chinese Asians (21), and non-Asian (865) who received doses of 0.1 mg/kg (n = 17); 0.3 mg/kg (n = 24); 1 mg/kg (n = 92); 3 mg/kg (n = 896), 10 mg/kg (n = 151), and 240 mg (n = 20). Exposure with nivolumab monotherapy was evaluated based on a total data set of 1,200 patients, of whom 959 had previously treated advanced or metastatic NSCLC (non-squamous, n = 544; squamous, n = 415) and 23 had nasopharyngeal cancer.

Individual baseline clearance and time-dependent clearance were assessed and compared across patients who were Chinese, non-Chinese Asian, and non-Asian. Nivolumab PKs were linear and dose-proportional and were well-characterized with a two-compartment model with zero-order infusion in patients who were Chinese, non-Chinese Asian, and non-Asian. The magnitude of the effects of baseline covariates on nivolumab clearance and volume of the central compartment, assessed using the population PK model, was within ± 20% of the reference values as assessed by 95% CI, with the exception of body weight. Importantly, neither race nor tumour type had a clinically relevant effect on nivolumab clearance (less than 20%). Baseline clearance was 9% lower in the Asian versus the global population, but this is not considered clinically relevant. However, in this study, volume and clearance are not clearly reported. Only half-life in patients who were Chinese is explicitly reported as 605.5 hours (25.2 days).

This analysis also compared exposure of a fixed dose (240 mg every two weeks) with the approved body weight-based nivolumab regimen of 3 mg/kg every two weeks. Despite the

fixed dose of 240 mg every two weeks showing approximately 25% higher nivolumab exposure versus the 3 mg/kg every two weeks regimen in patients from China, the predicted exposure of this same fixed regimen in Chinese patients was approximately 62% lower than that of the well-tolerated nivolumab 10 mg/kg every two weeks regimen in the global population. Based on the predicted exposures and the finding that race and ethnicity was not a clinically meaningful covariate of nivolumab population PK, it is anticipated that nivolumab fixed dosing would be a suitable approach for Chinese patients.

Table 9: Nivolumab Pharmacokinetic Summary

Reference	Sample Size	Source	Volume Central (L)	Variability	Volume Peripheral (L)	Variability	Clearance (L/day)	Half-Life (Days)
Bajaj et al., 2017,[14] time-stationary clearance	1,895 patients, 11,572 samples	MDX1106-01, MDX1106-03 CA209-010, CA209-017, CA209-025, CA209-037, CA209-057, CA209-063, CA209-066 ONO-4538-01, ONO-4538-02	3.63	3.5 to 3.75[a]	2.78	2.58 to 3.04[a]	9.4 mL/h 0.225 L/day	19.75[b]
Lee et al., 2018,[30] time-stationary clearance	18	ONO-4538-13	81.16 mL/kg[c] 5.68 L				0.162 mL/h/kg 0.272 L/day	17.47 days 15.0 to 19.1[d]
Zhang et al., 2019,[33] time-stationary clearance	1,209 patients, 6,945 samples	MDX1106-01, CA209-003, CheckMate 017, 057, 063, 077, and 078	Not reported		Not reported		Chinese: 10.2 mL/h Asian: 9.2 mL/h Non-Asian: 11.6 mL/h	Chinese patients T-half beta 25.2 days[d] T-half beta steady state 35.9 days[d]
Osawa et al., 2019,[31] time-stationary clearance	1,302 patients 8,585 samples	CheckMate 017, 032, and 057, CA209-001, CA209-003, CA209-063, ONO-4538-01, ONO-4538-02, ATTRACTION-2	4.46	4.35 to 4.57[a]	2.52	2.27 to 2.79[a]	0.011 L/hr (0.264 L/d)	18.33[b]
Wang et al., 2019,[34] time-varying clearance	1,074	MDX-1106-01, MDX-1106-03, CA209-017, CA209-039, CA209-063, CA209-057, CA209-205 ONO-4538-01, ONO-4538-02	4.13	14.1[e]	2.50	14.2[e]	0.0108 L/hr 0.259 L/day	17.88[3]
Hamuro et al., 2019,[29] time-varying clearance	1,773 patients, 11,664 samples	CA209-001, CA209-003, CA209-005, CA209-063, CA209-051, CA209-017, CA209-057, CA209-037, CA209-066, CA209-238	4.01	1.24[e]	2.78	3.07[e]	10.4 mL/hour 0.250 L/day	21.29[b]

Reference	Sample Size	Source	Volume Central (L)	Variability	Volume Peripheral (L)	Variability	Clearance (L/day)	Half-Life (Days)
Total	5,498							20.09

[a] 95% confidence interval provided.

[b] Half-life was not reported. It has been calculated based on total volume. Variability for these estimates was not calculated.

[c] In this study only total steady state volume of distribution is reported. Steady state volume of distribution is the sum of the volume of the central compartment and peripheral volume.

[d] Range of means for each dosage reported.

[e] Per cent relative standard error reported.

Osawa et al.31

The analysis population consisted of patients who are Asian and non-Asian and have gastric and gastro-esophageal junction cancers. The study included 1,302 patients with various recurrent or metastatic solid tumours (including colorectal cancer, melanoma, castration-resistant prostate cancer, squamous and non-squamous NSCLC, and RCC), and included 387 patients with gastric cancer or gastro-esophageal cancer who had received nivolumab 0.1 mg/kg to 10 mg/kg (single dose or every two weeks) in nine studies. Patient demographics such as weight and age were not included in the publication.

In addition, nivolumab exposures for patients receiving the fixed 240 mg every two weeks dosage regimen were simulated and compared with the weight-based 3 mg/kg every two weeks dosage regimen in 387 patients with gastric cancer or gastro-esophageal cancer.

In the present analyses, nivolumab concentration data from patients were described by a linear, two-compartment, zero-order input IV infusion model with first-order elimination and time-varying clearance. The model was the same as a previously developed model by Bajaj et al.,[14] except for the incorporation of additional covariate-parameter effects. The additional covariate-parameter relationships included in the present analysis were the effect of gastrectomy on clearance and the effect of tumour type on maximal effect at high drug concentrations (E_{max}) as it affected clearance.

Nivolumab PK was described using a compartment, zero-order IV infusion and time-varying clearance model. Baseline clearance in patients with gastric cancer or gastro-esophageal cancer was approximately 33% greater than in patients with NSCLC in second-line or subsequent lines of treatment. The effect of race was not deemed clinically relevant (less than a 20% difference).

Nivolumab exposures following 240 mg every two weeks were similar to 3 mg/kg every two weeks in patients who are non-Asian and 46% higher in patients who are Asian due to lower body weight. However, the simulated concentrations following 240 mg every two weeks produced an average serum concentration following the first dose of 31.0 mcg/mL in patients who are Asian. This concentration is below the previously reported exposure of 86.5 mcg/mL achieved for a well-tolerated dose of 10 mg/kg every two weeks.[34] Osawa et al. suggest that because of this safety margin, the use of a fixed 240 mg every two weeks dose is an option in these patient populations.

Wang et al.[34]

The analysis population consisted of 1,074 patients from nine studies. Four hundred and fifteen female patients and 659 male patients ranged in age from 27 to 78 years (mean, 61 years) and in weight from 49 kg to 109.5 kg (mean, 73 kg).

In this analysis, nivolumab concentration data were analyzed using a kinetic model identical to the previously reported two-compartment model with zero-order IV infusion and first-order elimination, with time-varying clearance according to a sigmoid E_{max} function, identical to that of Bajaj et al.,[14] except for the addition of variables to focus on tumour type. The final model was used to simulate exposures for a 3 mg/kg every two weeks regimen and a fixed dose of 240 mg every two weeks (equivalent to 3 mg/kg every two weeks given to patients with a body weight of 80 kg).

Based on the simulation using the final model, the distribution of nivolumab exposures in the simulated population with cHL after 3 mg/kg or 240 mg every two weeks was similar. The

percentage difference in geometric mean of all summary measures of exposures after weight-based dosing and fixed dosing was less than 11.3% across a body weight range of 40 kg to 168 kg. The exposure of patients with lower weights receiving a fixed 240 mg dose was obviously greater than weight-based dosing. However, Wang reported that the 95th percentile of simulated nivolumab exposures was lower than exposures produced by nivolumab 10 mg/kg given every two weeks, which was considered a clinically safe dose.

Hamuro et al.[29]

The analysis population consisted of 1,773 patients with 11,644 observations from multiple clinical trials and many different tumour types (melanoma, NSCLC, colorectal, prostrate, and RCC). In addition, nivolumab exposures for patients receiving the fixed 240 mg every two weeks dosage regimen were simulated and compared with the weight-based 3 mg/kg every two weeks dosage regimen in 387 patients with gastric cancer or gastro-esophageal cancer.

In this analysis, nivolumab concentration data from patients were described by a linear, two-compartment, zero-order input IV infusion model with first-order elimination and time-varying clearance. The model was the same as a previously developed model by Bajaj et al.,[14] and included all covariates except tumour type, as adjuvant therapy for patients with melanoma was not assessed previously, and other tumour types from the earlier assessment were not included in this analysis.

This study demonstrated that patients with melanoma receiving adjuvant therapy following surgical removal of the tumour had a baseline nivolumab clearance that was 40% lower and did not change during treatment compared with patients with melanoma. The clearance in melanoma patients started higher, but with a reduction in clearance during therapy, was only 20% lower at steady state.

Interpretation

Population-based PK evaluations have produced similar PK results, reporting mean volumes between 5.7 L and 7.68 L, clearance between 0.225 L/day and 0.272 L/day, resulting in estimated half-lives between 17.9 and 25.2 days (see Table 9). Five of these studies[14,29,31-33] have sample sizes between 1,074 and 1,895 patients. A weighted mean half-life, based on sample size in each study, is 20.09 days (Table 9).

Bajaj et al.[14] evaluated a time-varying clearance, and while a 25% reduction in clearance was observed with repeated doses, the data were well described by a time-stationary clearance model. Zhang et al.[33] report a change in clearance over several months of nivolumab therapy, but the clearance was also well described by a fixed, unchanging rate. The goal of at least two of the evaluations[31,34] was not PK parameter description but rather a comparison of race[31] and mean nivolumab exposures following 240 mg every two weeks and 3 mg/kg every two weeks using the same population kinetic model as Bajaj et al.[14] Exposure was similar in patients who are non-Asian, but 46% higher in patients who are Asian due to a lower body weight, resulting in an average serum concentration following the first dose of 31.0 mcg/mL in patients who are Asian. This concentration is below the previously reported exposure of 86.5 mcg/mL achieved for a well-tolerated dose of 10 mg/kg every two weeks.[29] Both Osawa et al.[31] and Wang et al.[34] suggest that because of this safety margin, the use of fixed 240 mg every two weeks dose is an option in these patient populations. However, it should be understood that for every patient weighing less than 80 kg, regardless of race, a 240 mg dose will produce greater exposure than a 3 mg/kg dose.

Other Considerations

Minimum Dose or Concentration Response

In the evaluation of time between treatments, a washout period of 10 half-lives (used in bioequivalence studies[35]) will produce a concentration less than 0.01% of the peak concentration on average. While such a concentration might reasonably be expected to be well below the minimum effective concentration, consideration of dose response is important.

In classic linear dose response, all doses have some response, but in E_{max} and sigmoid E_{max} dose response, a threshold concentration or dose is required before response can be detected. Once the concentration drops below this threshold, residual malignant cells could begin to multiply, and tumour doubling time would determine when the tumour became visible again. Therefore, it would be pertinent to also consider the minimum effective dose or concentration and tumour growth in the washout evaluation.

While a number of publications have evaluated nivolumab dose or exposure response,[32,36,37] these evaluations have focused on achieving complete response rather than determining the minimum dose that generates any response. For example, in a study of 168 patients with metastatic RCC, Motzer et al.[37] randomly assigned patients to receive 0.3 mg/kg, 2 mg/kg, or 10 mg/kg of nivolumab intravenously once every three weeks3W. No dose-response relationship was detected as measured by progression-free survival. Median progression-free survival was 2.7, 4.0, and 4.2 months, respectively (P = 0.9). Similarly, Gettinger et al.[36] evaluated 129 patients with heavily pre-treated advanced NSCLC who received nivolumab 1 mg/kg, 3 mg/kg, or 10 mg/kg IV once every two weeks in eight-week cycles for up to 96 weeks. Median overall survival was similar (9.2, 14.9, and 9.2 months) across all three doses (1 mg/kg, 3 mg/kg, or 10 mg/kg, respectively), making the response rather flat at these doses. Therefore, available evidence does not allow to ascertain the residual biological or clinical activity of 0.1% peak drug concentration or to identify any minimum concentration where nivolumab exerts its effect on malignancies. With these limitations in mind, if ten half-lives are used to estimate the washout period before a second treatment should begin, a period of 201 days (approximately 6.7 months) is calculated based on the median published half-life (20.09 days) reported in Table 9.

Conclusions

Population-based PK evaluations have produced similar PK results, reporting mean volumes between 5.7 L and 7.7 L, clearance between 0.225 L/day and 0.272 L/day, resulting in estimated half-lives between 17.9 and 25.2 days. Five of these studies[14,29,31,33,34] have sample sizes between 1,074 and 1,895 patients. A weighted mean half-life, based on sample size in each study, is 20.1 days (Table 9).

In bioequivalence studies, the washout period is generally ten half-lives.[35] Using the latter as a reasonable washout period and the half-life of 20.01 days for nivolumab, a washout of 201 days (approximately 6.7 months) is calculated.

Pembrolizumab Elimination (Research Question 3b)

Pembrolizumab (Keytruda) Product Monograph

Pembrolizumab was first initially approved in Canada in 2015. PK data reported in the product monograph are the result of analysis of patient data from the KEYNOTE studies. In the 2019 Health Canada–approved product monograph, time-dependant clearance was acknowledged and volume and clearance for first and steady state doses was provided: "Pembrolizumab clearance (CV%) is approximately 23% lower [geometric mean, 195 mL/day (40%)] after achieving maximal change at steady state compared with the first dose (252 mL/day [CV%: 37%]); this decrease in clearance with time is not considered clinically important."[2]

A summary of the PK metrics reported in the 2019 product monograph is shown in Table 10. This summary agrees closely with published reports,[5,24,27,38,39] primarily because the data source is similar (KEYNOTE studies) and summaries were published by the FDA, Merck employees,[5,24] both,[27] or was abstracted from the product monograph without new or unique analysis.[39]

Pembrolizumab model evaluations published in 2017 or later report a shorter half-life (23.7 days)[5,27,38] as the result of the reduction in clearance following multiple doses. Clearance declines by 23%, from a mean of 252 mL/day, following the first dose, to 195 mL/day at steady state. It is stated in publications and the 2019 product monograph that this reduction in clearance is not clinically significant.

Table 10: Health Canada–Approved Product Monograph Pharmacokinetics Information

Year of Monograph	Sample Size	Volume Central (L)	Variability CV (%)[a]	Clearance First Dose (L/day)	Variability CV (%)[a]	Clearance at SS (L/day)	Variability CV (%)[a]	Half-Life (Days)	Variability CV (%)[a]
2019[2]	2,993	6.0	20	0.195	40	0.252	37	22	32

CV = coefficient of variation; SS = steady state.

[a] Variability expressed as CV (calculated as 100 × standard deviation/mean).

Summary of the Published Literature

Based on the literature search results, at least five publications report PK data.[5,24,27,38,39]The first report was published in 2016.[39] This report is effectively a review article. The authors cite the May 2, 2016, US product monograph utilizing data from 2,195 patients and report, as does the 2016 US product monograph, a half-life of 27 days. The authors do not offer new or unique insights or analysis and cite no other publications.

Four population-based PK modelling studies have been completed based on patients in clinical studies who have received doses between 0.005 mg/kg and 10 mg/kg.[5,24,27,38] These studies range in patient sample sizes from 40[24] to 2,841.[27] The most complete data set is that of Li et al.[27] This evaluation presents data from 1,691 males and 1,150 female patients from the KEYNOTE 001, 002, 006, and 010 studies. All other analyses[5,24,38] used data from one or more of these same clinical studies and, therefore, differ in sample size and in the inclusion of variables in the PK model. The reported sample size, data source, and final model parameter estimates for volume terms and clearance are reported in Table 11. Half-life is not reported but has been calculated by CADTH based on final estimates and is also shown in Table 11.

Table 11: Pembrolizumab Pharmacokinetic Metric Summary of Full Publications Arranged by Date of Publication

Reference	Sample Size	Source	Volume Central (L)	Variability	Volume Peripheral (L)	Variability	Clearance (L/Day)	Variability	Half-Life (Days)
Longoria[39 a]	2,195	2016 US PM[b]	7.4[c]	19%[c]	NA	NA	0.2	37[d]	27
Elassaiss-Schaap [24]	40	KEYNOTE 001	2.88	5.90	2.85	16.5[f]	0.168	11.1	21[e]
Li,[27] Time-Dependent Clearance Model (M_3)	2,841	KEYNOTE 001, 002, 006, and 010	3.47	0.70	2.96	11.5	0.249	5.87	17.9[e]
Li,[27] Time-Stationary Clearance Model (M_1)	2,841	KEYNOTE 001, 002, 006, and 010	3.49	0.71	4.00	1.81	0.219	1.43	23.71[e]
Ahamadi,[5] Time-Stationary Clearance Model	2,195	KEYNOTE 001, 002, and 006	3.48	0.891[f]	4.06	2.01	0.22	2.14[f]	23.75[e]
Li,[38] Time-Dependent Clearance Model	644	KEYNOTE 010	3.34	NA	3.62	NA	0.238	NA	21[e]
Li,[38] Time-Stationary Clearance Model	644	KEYNOTE 010	3.15	1.28[f]	3.54	4.40[f]	0.221	2.63[f]	23.7[e]

NA = not available; PM = product monograph.

[a] The authors have abstracted the pharmacokinetic data from the prescribing information and no other references are cited.

[b] In the Canadian product monograph of July 2017,[21] 2,188 patients were evaluated for pharmacokinetics. Volume is reported as 7.5 L with a coefficient of variation (%) of 21%. The half-life is reported as 26 days. An updated product monograph dated July 4th, 2019,[2] 2,993 patients were evaluated and the volume of distribution is 6 L and half-life is 22 days.

[c] Only "volume" reported. Likely, central volume + peripheral volume = total volume.

[d] Coefficient of variation (100x std/mean).

[e] Half-life was not reported. It has been calculated based on the relationship between volume and clearance where clearance = rate constant (k) × volume of distribution at steady state; total volume is the sum of central volume and peripheral volume; half-life = ln(2) / k; variability for these estimates was not calculated.

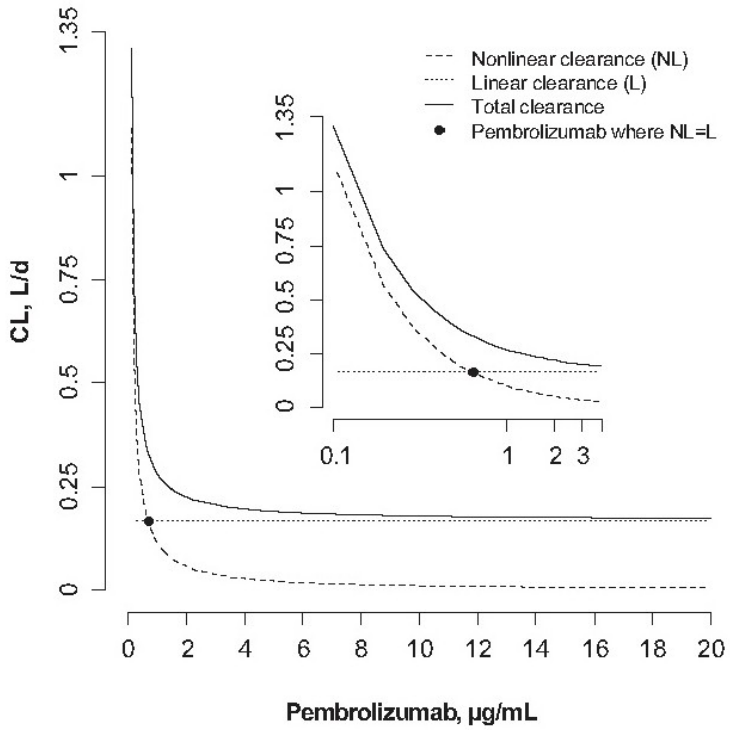
[f] Per cent relative standard error.

Review of Population Pharmacokinetic Models

All population-based PK models have utilized the same series of clinical trials (KEYNOTE) and have a reported mean volume between 5.7 L and 7.5 L, clearance between 0.168 L/day and 0.249 L/day, resulting in estimated half-lives between 17.9 and 27 days. The first population-based analysis of pembrolizumab kinetics utilized data from KEYNOTE-001 and evaluated doses as low as 0.005 mg/kg.[24] In this evaluation, Elassaiss-Schaap et al.[24] reported reductions in clearance with increasing concentrations as a sigmoidal function, suggesting non-linear elimination with a mean Michaelis–Menten constant (K_m) of 0.0784 mcg/mL (equivalent to 78 ng/mL) and a maximum elimination rate (V_{max}) of 0.114 mg/day. However, above a concentration of 3 mcg/mL, or doses greater than 0.3 mg/kg every three weeks, total clearance was observed to be fairly constant at 0.2 L/day (Figure 6) with a volume of distribution of approximately 6 L. Figure 6 illustrates the dependence of total

clearance (solid line), linear clearance (broken line), and non-linear clearance (dashed line) on pembrolizumab concentrations. The inset shows the same graph versus log concentration versus clearance. Note that above a concentration of 3 mcg/mL, total clearance is constant.

Figure 6: Pembrolizumab Clearance Depending on Concentration

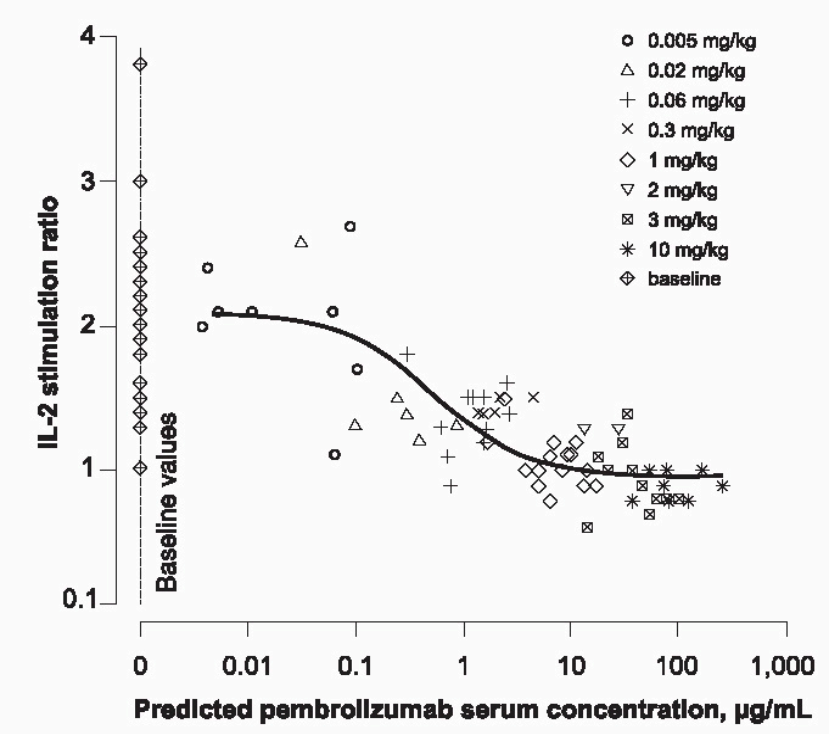


Source: Figure 4 from Elassaiss-Schaap J et al. Using Model-Based "Learn and Confirm" to Reveal the Pharmacokinetics-Pharmacodynamics Relationship of Pembrolizumab in the KEYNOTE-001 Trial. CPT Pharmacometrics Syst Pharmacol. 2017 Jan;6(1):21-28. Distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC 4.0). https://creativecommons.org/licenses/by-nc/4.0/.

Elassaiss-Schaap et al.[24] also report that a steady state dose of 2 mg/kg every three weeks was needed to reach 95% target engagement. Target engagement pharmacodynamics was assessed using the interleukin-2 stimulation assay ratio, which leverages the inhibitory effect of pembrolizumab on the interaction between PD-1 and interleukin-2 to infer the level of antibody-target binding. Figure 7 displays pharmacodynamic observations (symbols separate different doses) and population-predicted (solid line) PD-1 receptor modulation as a function of pembrolizumab exposure.

As Elassaiss-Schaap et al.[24] published the first population-based PK analysis and reported a time-dependent clearance, subsequent evaluations also addressed a changing clearance with multiple doses.[5,27,38] Li et al.[27] evaluated 2,841 patients from KEYNOTE-001, -002, -006, and -010. In this data set, patients between 15 and 94 years of age who weighed between 35.7 kg and 209.5 kg received between 1 mg/kg every three weeks and 10 mg/kg every two weeks. A summary of the number of patients by dose and study is provided in Table 13. It would appear that doses of 0.005 mg/kg, 0.02 mg/kg, 0.06 mg/kg, 0.1 mg/kg, and 0.3 mg/kg included in KEYNOTE-001, that were part of the analysis by Elassaiss-Schaap et al.,[24] were not included in the evaluation by Li et al.[27]

Figure 7: Programmed Cell Death Protein 1 Modulation



IL-2 = interleukin-2.

Source: Figure 4 from Elassaiss-Schaap J et al. Using Model-Based "Learn and Confirm" to Reveal the Pharmacokinetics-Pharmacodynamics Relationship of Pembrolizumab in the KEYNOTE-001 Trial. CPT Pharmacometrics Syst Pharmacol. 2017 Jan;6(1):21-28. Distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC 4.0). https://creativecommons.org/licenses/by-nc/4.0/.

Table 12: Patient and Pharmacokinetic Observation Summary of NONMEM Data Set

Study	Dose	Number of Subjects	Number of Observations
KEYNOTE-001	1 mg/kg Q2W	4	48
	1 mg/kg Q3W	1	10
	2 mg/kg Q3W	228	1,407
	3 mg/kg Q2W	3	58
	10 mg/kg Q2W	385	2,585
	10 mg/kg Q3W	600	3,648
KEYNOTE-002	2 mg/kg Q3W	207	1,143
	10 mg/kg Q3W	212	1,200
KEYNOTE-006	10 mg/kg Q2W	275	2,194
	10 mg/kg Q2W	273	2,140
KEYNOTE-010	2 mg/kg Q3W	327	2,296
	10 mg/kg Q3W	326	2,312

Q2W = every two weeks; Q3W = every three weeks.

The final population PK model utilized a two-compartment PK model, scaled based on body weight, with a time-dependent change on clearance. Covariates for clearance included gender, glomerular filtration rate, baseline albumin, baseline tumour size and type, bilirubin, and performance scale at baseline. Baseline albumin and gender were covariates for

volume. The final values for the time-dependent clearance model (M_3) and the time-stationary model (M_4) for volume and clearance and calculated half-life are shown in Table 11. The time-dependent model (M_3) performed better with less bias than other models and was better correlated with best overall response.

Decreasing clearance with time was described by a sigmoidal function of on-study treatment time. Covariates accounting for inter-individual variation in time-varying clearance were explored. A relationship between the clearance change and patients' response was identified, likely reflecting the influence of disease severity on drug clearance rather than a typical PK/pharmacodynamic relationship with exposure driving outcome.

Ahamadi et al.[5] also evaluated pembrolizumab concentration–time data obtained from patients receiving doses of 1 mg/kg to 10 mg/kg administered every two weeks or every three weeks. Ahamadi et al.[5] fitted the data with a two-compartment model with linear (or time-stationary) clearance. Ahamadi et al.[5] indicated that while nonlinearity in pembrolizumab PKs had been observed at doses below 1 mg/kg, citing Elassaiss-Schaap et al.[24], as their analysis was restricted to data above1 mg/kg, the results did not indicate nonlinearity of clearance in the range of clinical doses.

The fourth population-based pembrolizumab PK evaluation was completed by Li et al.[38] utilizing 644 patients from KEYNOTE-010 with NSCLC. This paper was published in 2019, and although data from more than 2,841 patients was likely available, this evaluation focused on using the longitudinal effect (mathematically describing the time courses) of tumour size, lymphocyte count, albumin, and lactate dehydrogenase (LDH) on pembrolizumab clearance. The requirement for the need for serial measurements of these four variables limited sample size. Therefore, this evaluation was completed not to describe the PKs of pembrolizumab, but in an attempt to determine why clearance changed with time.

Pharmacology Related to Change in Clearance

There appear to be two different time or dose dependencies to clearance. Elassaiss-Schaap et al.[24] reported reductions in clearance with increasing concentrations as a sigmoidal function, suggesting non-linear elimination with a mean K_m of 0.0784 mcg/mL (equivalent to 78 ng/mL) and a maximum elimination rate of 0.114 mg/day. However, above a concentration of 3 mcg/mL, or doses greater than 0.3 mg/kg given every three weeks, clearance was observed to be fairly constant at 0.2 L/day.

The second time-dependent clearance has been noted with multiple doses greater than 1 mg/kg. Li et al.[27] excluded doses of less than 1 mg/kg but did observe a 20% reduction in clearance from the first dose to the 20th week. This was observed with a sample size of 2,841 patients. However, Ahamadi et al.[5] also evaluated pembrolizumab concentration–time data obtained from patients receiving doses of 1 mg/kg to 10 mg/kg administered every two weeks or every three weeks in 2,195 patients. Ahamadi et al.[5] fitted the data with a two-compartment model with linear (or time-stationary) clearance but did not observe a change in clearance following the first dose to steady state.

Li et al.[27] acknowledge that the direction and magnitude of change in clearance varies between patients.[27] Li et al.[27] observed that the population median clearance of pembrolizumab was 20% lower at the steady state compared with the clearance observed following the first dose.[27] However, as there was also a five times dose or exposure range observed in patients in the clinical trial,[27] the 20% change was not regarded as clinically significant.

Li et al. also describe a previously reported relationship between biologic drug clearance and disease severity in cancers[40,41] and evaluated this in a restricted cohort of patients.[38] It is suggested that the reduction in clearance with time may be viewed as a proxy for reversal of disease severity by an effective treatment. The observation by Li et al.[27] of the association between pembrolizumab best overall response, baseline tumour size, and initial albumin were all found to be associated with the magnitude of the time-varying clearance, where a larger change in clearance was associated with the better response status.

The 2019 report of Li et al.[38] focused on evaluating the relationship between biological markers tumour size, lymphocyte count, albumin, LDH, and changing pembrolizumab clearance. Of the four longitudinal covariates, larger baseline tumour size and lower albumin concentration contributed to higher clearance. A relationship between the change in clearance and the patient's response was observed such that in responders there was a larger decrease in clearance, contributing to increased drug exposure.

Interpretation

All population-based PK models have utilized the same series of clinical trials (KEYNOTE) and have reported mean volume between 5.7 L and 7.5 L, clearance between 0.168 L/day and 0.249 L/day, resulting in estimated half-lives between 17.9 and 27 days.

The largest data set is that of Li et al.,[5] representing data from 1,691 males and 1,150 female patients receiving between 1 mg/kg and 10 mg/kg doses in KEYNOTE 001, 002, 006 and 010 studies. This study is judged as the most complete data set. All other analyses[24,27,38] used data from one or more of these same clinical studies and, therefore, differ in sample size and in the inclusion of covariates in the PK model. While Li et al.[27,38] are proponents of a changing clearance model, Ahamadi et al.[5] analyzed a similar data set and did not observe time-dependant clearance changes. Therefore, while there may be some value to the time-dependant clearance models reported by Li et al.,[27,38] the time-stationary model of Li et al.[27] generates an estimated half-life of 23.71 days, which is also the median half-life reported in Table 11.

Other Considerations

Minimum Dose or Concentration Response

As mentioned for nivolumab, a washout period of 10 half-lives (used in bioequivalence studies[35]) will produce a concentration of less than 0.01% of the peak concentration on average, but limitations of this approach call for considering the minimum effective dose or concentration and tumour growth in the washout evaluation. However, such information was not identified in the literature.

If a washout period of 10 half-lives is used to estimate the time before a second treatment should begin, using the median half-life of 23.7 days (as reported in Table 11), a washout of 237 days is calculated (approximately eight months).

Conclusions

All population-based PK models have utilized the same series of clinical trials (KEYNOTE) and have a reported mean volume between 5.7 L and 7.5 L, clearance between 0.168 L/day and 0.249 L/day, resulting in estimated half-lives between 17.9 and 27 days.

Based on the full publications, and in an effort to avoid data duplication, the results of 2,841 patients reported by Li et al.[5] are judged as the best estimate of pembrolizumab PKs. The calculated half-life of 23.71 days, using the time-stationary clearance model is in agreement with all other reports and is in fact the median of reported half-lives in Table 11.

In bioequivalence studies, the washout period is generally 10 half-lives.[35] Using the latter as a reasonable washout period and a half-life of 23.71 days for pembrolizumab, a washout of 237 days (approximately eight months) is calculated.

Durvalumab Elimination (Research Question 3c)

Durvalumab (Imfinzi) Product Monograph

Durvalumab was first approved in Canada in November 2017 with a NOC/c. PK data, reported in the product monograph, is based on a population PK analysis that included 1,310 patients receiving doses of 10 mg/kg or greater. The reported mean steady state clearance is 8.24 mL/h (0.198 L/day), the steady state volume of distribution is 5.6 L, and the terminal half-life is 17 days. The product monograph also reports that following multiple doses: there is a 2.6-times increase in systemic accumulation in area under the curve, a 1.9 times increase in maximum concentration, and a 3.2 times increase in the trough concentration.

Durvalumab clearance decreases over time, with a mean maximal reduction (per cent coefficient of variation) from baseline values of approximately 22.9% (46.3%). The decrease in clearance was not considered clinically relevant. A summary of the PK metrics reported in the current monograph are shown in Table 13.

Table 13: Health Canada–Approved Product Monograph Pharmacokinetics Information

Year of Monograph	Sample Size	Volume Central (L)	Variability CV (%)	Clearance First Dose (L/day)	Variability CV (%)	Clearance at SS (mL/hr)	Variability CV (%)	Half-Life (Days)[a]	Variability CV (%)
2019[42]	1,310	5.6	Not reported	Not reported[b]	Not reported	8.24 mL/hr 0.198 L/day[b]	Not reported	17	Not reported

CV = coefficient of variation.

[a] Half-life was calculated.

[b] Text indicates that the mean maximal reduction is 22.9% at steady state.

Summary of Published Literature

Two publications report a population-based PK analysis of data in patients with hematologic malignancies[43] and solid tumours.[44] These reports have been completed based on patients in six different clinical trials who have received doses of 1,500 mg by one-hour infusion administered every four weeks[43] or between 0.1 mg/kg every two weeks and 20 mg/kg every four weeks.[44] The reported sample size, data source, and final model parameter estimates for volume terms and clearance are reported in Table 14. Modelling did not generate a half-life in either study,[43,44] but has been calculated based on final estimates and is shown in Table 14. Baverel et al.[44] reported that the terminal half-life was estimated to be approximately 21 days, which is in close agreement with calculations.

Table 14: Durvalumab Pharmacokinetic Metric Summary

Reference	Sample Size	Source	Volume Central (L)	Variability	Volume Peripheral (L)	Variability	Clearance (L/Day)	Variability	Half-Life (Days)
Ogasawara et al., 2019,[43] Time-Stationary	267 patients; 1,812 samples	MDS-001 [NCT02775903], MM-002 [NCT02685826], MM-005 [NCT03000452], NHL-001 [NCT02733042]	4.63	2.1[a]	2.68	6.3[a]	0.0107 L/hr 0.2568 L/day	3.1[a]	19.7[b]
Beverel et al., 2018,[44] Time-Stationary	1,409 patients; 7,407 samples	1108 [NCT01693562], ATLANTIC [NCT02087423]	3.51	3.44 to 3.58[c]	3.56	3.36 to 3.78[c]	0.232	0.221 to 0.240[c]	21.1[b]
Beverel et al., 2018,[44] Time-Varying	1,409 patients; 7,407 samples	1108 [NCT01693562], ATLANTIC [NCT02087423]	3.51	3.44 to 3.59[2]	3.45	3.26 to 3.66[c]	0.232	0.224 to 0.238[c]	20.8[b]
Total/Weighted Mean	1,676								20.87

[a] Per cent relative standard error) reported.

[b] Half-life was not reported. It has been calculated based on total volume, where central volume + peripheral volume = total volume. Variability for these estimates was not calculated.

[c] 95% confidence interval provided.

Review of Population Pharmacokinetics Models

Ogasawara et al.[43] evaluated a total of 1,812 serum durvalumab concentrations from 267 patients in the population PK analyses. Models were developed using a non-linear mixed-effect modelling approach. The study included 173 male (64.8%) and 94 female (35.2%) patients with various hematologic malignancies who ranged in age from 21 to 89 years (median age, 71 years) and in weight from 37.7 kg to 121 kg (median, 74.7 kg). All patients received a 1,500 mg dose by one-hour infusion administered every four weeks. Samples were drawn differently in each study ranging from pre and post infusion over six cycles to multiple samples following cycles 1 and 2.

Ogasawara et al. reported that the PKs of durvalumab were adequately described by a two-compartment model with first-order elimination and no change to clearance with time. Inter-individual variability was estimated for clearance and the volume of distribution of central compartment. Non-linear (Michaelis–Menten) clearance was not included in the base model as a result of poor precision of Michaelis–Menten parameter estimates (K_m and V_{max}) and poor stability of the model. Similarly, the empirical time-varying clearance model was not implemented in the base model because the time-varying clearance parameter was estimated with poor precision. The final equation describing clearance utilized serum albumin, immunoglobulin G (IgG), LDH, soluble PD-L1, weight, and gender. The final equation describing volume utilized serum albumin, weight, and gender.

In this population PK model, durvalumab PK was well described by a two-compartment model with first-order clearance. Serum albumin, IgG, soluble PD-L1, LDH, weight, sex, and some malignancy type (myelodysplastic syndromes, acute myeloid leukemia, and multiple myeloma [MM]) were incorporated in the final model as covariates on clearance and central

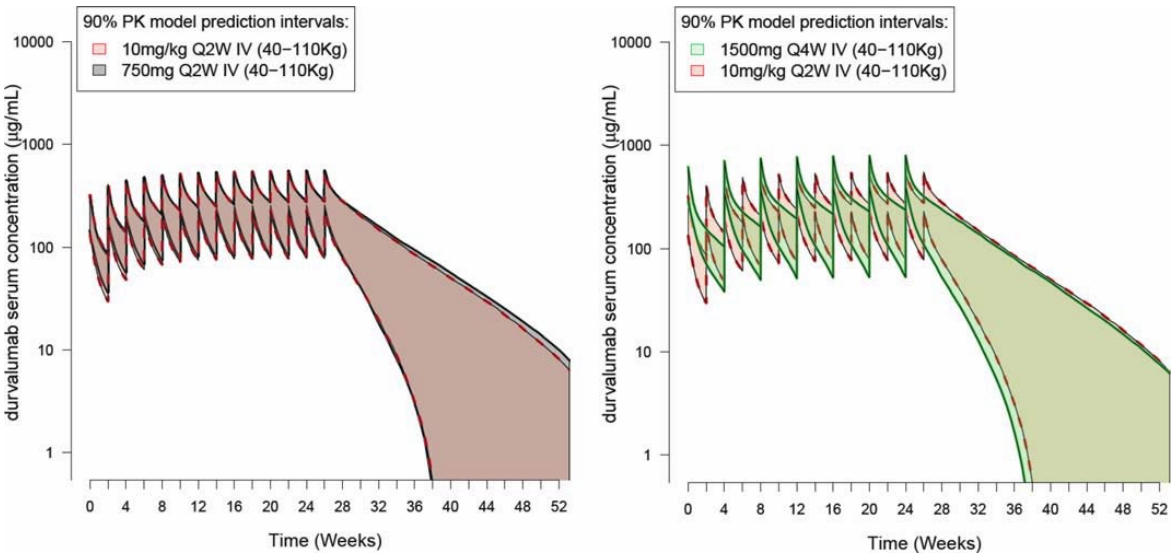
volume. Change in albumin (in all patients) and IgG (in patients with MM) over time adequately accounts for the time-dependent decrease in durvalumab clearance. For MM, patients with an IgG of 20 g/L or greater showed a 30% lower area under the curve compared with patients with an IgG of lower than 20 g/L.

The type of hematologic malignancy had a relatively small impact on durvalumab PKs. The differences in durvalumab exposure (median and 90% CI) were within 20% among myelodysplastic syndromes or acute myeloid leukemia, MM, and non-Hodgkin lymphoma or Hodgkin lymphoma. In addition, there was no apparent difference in durvalumab exposure among various non-Hodgkin lymphoma sub-types. For MM, hyper-gammaglobulinemia was a key determinant of durvalumab exposure.

A total of 7,407 serum durvalumab concentrations from 1,409 patients were used in the population PK analyses by Baverel et al.[44] Population PK models were developed using a non-linear mixed-effect modelling approach. Included were 799 male (56.7%) and 610 female (43.3%) patients with various solid tumours with a median age of 62 years (range, 19 to 96 years) and median weight of 69.8 kg (range, 34 kg to 149.1 kg). Dose levels in Study 1108 (NCT01693562) ranged from 0.1 mg/kg to 10 mg/kg IV every two weeks and from 15 mg/kg IV every three weeks to 20 mg/kg IV every four weeks, whereas ATLANTIC (NCT02087423) used a dose of 10 mg/kg IV every two weeks.

A two-compartment PK model, including both linear and non-linear (Michaelis–Menten) clearance, described the data. Durvalumab exhibited non-linear PKs with saturable target-mediated clearance at doses less than 3 mg/kg and linearity was approached at doses equal to or greater than 3 mg/kg. In the final model, covariates for clearance included creatinine clearance, gender, tumour size, and the albumin concentration. Covariates for volume included gender and body weight.

Figure 8: Simulated Pharmacokinetic Profiles of Durvalumab



PK = pharmacokinetic; Q2W = every two weeks; Q4W = every four weeks.

Source: Figure 4 from Baverel et al. Population pharmacokinetics of durvalumab in cancer patients and association with longitudinal biomarkers of disease status. Clin Pharmacol Ther. 2018 Apr;103(4):631-642. Distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC 4.0). https://creativecommons.org/licenses/by-nc/4.0/.

Figure 8 displays the simulated PK profiles of durvalumab following weight-based dosing regimens (10 mg/kg IV every two weeks) compared with fixed dosing (left panel: 750 mg IV every two weeks; right panel: 1,500 mg IV every four weeks). The area (pink, grey, and green) represents the 90% prediction interval from the semi-mechanistic time-varying clearance model according to three different dosing schemes; they are delimited by the fifth and 95th percentiles of the simulated PK data obtained from a pool of virtual patients (n = 1,000). Only the body weight covariate effect was investigated (no time-varying covariate were used for simulations). Both simulations show that concentrations decline to less than 1 mcg/mL between week 37 and 62 (11 to 36 weeks after the last dose).

As reported in Table 14, durvalumab clearance was 0.232 L/day, central volume was 3.51 L, peripheral volume was 3.45 L, and K_m was 0.344 mg/L. The estimated half-life was about 21 days. Although population PK analysis identified statistically significant covariates (body weight, sex, post-baseline anti-drug antibody, creatinine clearance, Eastern Cooperative Oncology Group performance status, soluble PD-L1 levels, tumour size, and albumin), none were found to be clinically relevant (impact on kinetic parameters was less than 30%). Age, race, tumour type, LDH, neutrophils-to-lymphocytes ratio, renal function (mild to moderate), and hepatic function (mild) had no impact on PKs.

Therefore, these results indicate that the change in clearance over time was not clinically relevant and there is no need for dose adjustment based on baseline patient characteristics. Furthermore, population modelling of durvalumab supports the potential switch to a flat-dosing regimen of 750 mg IV every two weeks or a regimen of 1,500 mg IV every four weeks. The fixed-dose regimen of durvalumab of 1,500 mg IV every four weeks is currently pursued in multiple confirmatory trials across several indications.

Interpretation

Evaluations in hematologic and solid tumours have produced similar PK results, reporting mean volumes between 6.96 L and 7.31 L, clearance between 0.0.232 L/day and 0.257 L/day, resulting in estimated half-lives between 19.73 and 21.1 days. A weighted mean half-life, based on sample size, in 1,676 patients is 20.87 days (Table 14). Baverel et al.[44] generated concentration–time simulations showing that concentrations decline to less than 1 mcg/mL between weeks 37 and 62 (11 to 36 weeks after the last dose).

The PK of durvalumab in hematologic malignancies was generally consistent between hematologic and solid tumours and both evaluations support the switch to a flat-dosing regimen of 750 mg IV every two weeks or a regimen of 1,500 mg IV every four weeks.

Other Considerations

Minimum Dose or Concentration Response

As mentioned previously, a washout period of 10 half-lives (used in bioequivalence studies[35]) will produce a concentration of less than 0.01% of the peak concentration on average. As with the other drugs under review, it would be pertinent to also consider the minimum effective dose or concentration and tumour growth in the washout evaluation. However, such information was not identified in the literature.

If a washout period of 10 half-lives is used to estimate the time before a second treatment begins, using the median half-life of 20.87 days (as reported in Table 14), a washout of 209 days is calculated (approximately seven months). This is in agreement with the concentration–time simulation generated by Baverel et al.[44] that demonstrated that

concentrations decline to less than 1 mcg/mL between weeks 37 and 62 (77 to 252 days after the last dose).

Conclusions

Evaluations in hematologic and solid tumours have produced similar PK results, reporting mean volumes between 6.96 L and 7.31 L, clearance between 0.0.232 L/day and 0.257 L/day, resulting in estimated half-lives between 19.73 and 21.1 days. A weighted mean half-life, based on a sample size of 1,676 patients, is 20.87 days (Table 14).

In bioequivalence studies, the washout period is generally 10 half-lives.[35] Using the latter as a reasonable washout period and the half-life of 20.87 days for durvalumab, a washout of 209 days (approximately seven months) is calculated.

Clinical Review

A Rapid Response Reference List entitled *Cancer Immunotherapy After Adjuvant Immunotherapy: Clinical Effectiveness and Guidelines* was prepared by CADTH.[45] Detailed methods can be found in the full report.

The review was meant to address research questions 4 to 6, as stated previously. The inclusion criteria used for the selection of relevant studies are reproduced in Table 15.

Table 15: Selection Criteria

Population	Q1: Patients with metastatic melanoma who completed and have progressed after adjuvant therapy with nivolumab or pembrolizumab Q2: Patients with recurrent/metastatic non–small cell lung cancer who completed and have progressed after consolidation therapy with durvalumab
Intervention	Q1: Nivolumab, pembrolizumab, ipilimumab combined with nivolumab Q2: Atezolizumab, nivolumab, pembrolizumab
Comparator	Q1 to Q2: Any comparator (e.g., placebo, immunotherapy, chemotherapy, targeted therapy) No treatment (i.e., single-arm studies) Q3: Evidence-based guidelines
Outcomes	Q1 to Q2: Progression-free survival, overall survival, response rate, quality of life Adverse events, discontinuation Length of treatment-free period prior to intervention Q3: Evidence-based guidelines
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, evidence-based guidelines

Results (Research Questions 4 to 6)

No relevant clinical evidence was identified regarding the clinical effectiveness of nivolumab, pembrolizumab, or ipilimumab-nivolumab in patients with melanoma who progressed after adjuvant therapy with nivolumab or pembrolizumab. No relevant clinical evidence was identified regarding the clinical effectiveness of atezolizumab, nivolumab, or pembrolizumab in patients with recurrent or metastatic NSCLC who progressed after consolidation therapy with durvalumab. Additionally, no relevant evidence-based guidelines were identified regarding the timing of re-treatment with immune checkpoint inhibitors.

A conference abstract by Owen et al.[46] matching the pre-specified criteria was identified and listed in the report's appendix. It should be noted that conference abstracts are not an

acceptable publication format for inclusion in the body of CADTH Rapid Response reports and cannot be the subject of further appraisal. The abstract reported an observational study of 137 melanoma patients from 15 cancer centres who recurred after adjuvant anti-PD1 and underwent subsequent anti-PD1 or ipilimumab (anti-CTLA-4) therapy. In patients who recurred during adjuvant anti-PD1 therapy, none responded to subsequent anti-PD1 and 33% responded to ipilimumab therapy. In patients who recurred off treatment, 40% responded to a second course of IO therapy. The authors concluded that "these data suggest minimal activity of further anti-PD1 monotherapy in those who recur while on adjuvant anti-PD1, but possible activity in those who recur off treatment." The findings should be seen as exploratory given the inherent limitations of the observational study and the lack of detailed information about methodology and results (owing to the abstract format).

Implications for Decision-Making

PQ1: Are there any potential issues with implementing a consistent dosing schedule (i.e., weight-based dosing with a cap) of nivolumab and pembrolizumab for all oncology indications?

Various dosing schedules and resulting patient exposures and clinical responses to IO drugs were compared in the literature. The main finding from these studies is that the relationship between drug exposure and clinical response is relatively flat for both nivolumab and pembrolizumab over a broad range that encompassed most if not all dosing scenarios. Fixed doses of IO drugs are recommended in many instances by CADTH or Health Canada, either for convenience or because the clinical trials underpinning the evidence base made use of such doses. However, the Health Canada–approved product monographs of Opdivo and Keytruda clearly state that there are no clinically significant differences in safety and efficacy between weight-based and fixed doses of both drugs.[1,2] The present Technology Review report finds that these statements are supported by convincing literature, including clinical, PK, and modelling studies. Such conclusions are also echoed in other reviews.[6,47] As both dosing strategies are appropriate, their combination (i.e., weight-based up to a pre-specified fixed maximum dose) would also be appropriate. The latter strategy would be at least as cost-effective, if not more, than other strategies in all situations, without jeopardizing patient safety or clinical response. To more directly answer the policy question, the review and interpretation of the literature in this CADTH Technology Review did not identify any potential issues with capped weight-based dosing of nivolumab and pembrolizumab as an extension of currently accepted dosing regimens.

One argument for use of fixed doses is that they can be administered using exact multiples of commercial vial sizes, allowing for simpler manipulations with no residual drug in vials. While this advantage may be evident, it must be weighed against the equally obvious and potentially more impactful wastage of drugs given to patients in excess of what is needed for an optimal exposure and therapeutic response. For example, pembrolizumab given at the 200 mg fixed dose would exceed the conventional, well-evidenced 2 mg/kg dose for any patient weighing less than 100 kg. For a person weighing 70 kg, 60 mg would be "wasted" for each dose, as it would not have been needed for therapeutic response. In facilities that are equipped with the proper transfer devices, vial rationalization can extend the use of partial vials to serve multiple patients. From an implementation perspective, it would be advisable that sterile procedures be established and optimized at the institutional level to allow vial rationalization for pembrolizumab, nivolumab, and potentially other drugs with

variable dosing. In support of this strategy, cost analyses have underscored the economic rationale for preferring weight-based dosing in resource-constrained health care systems.[7,19,48] It remains to be seen whether an actual reduction in pharmacy burden from fixed dosing can be translated into reduced costs and how these would compare with the savings afforded by weight-based dosing. Following any policy changes regarding IO dosing, ongoing assessment of clinical and economic outcomes in the real-world setting may help validate decisions and refine implementation.

Dose banding is a refinement of the weight-based approach that proposes the use of round doses, often multiples of vial sizes, for pre-defined weight ranges in order to simplify calculations and preparations. Banding of both pembrolizumab and nivolumab was explored in the literature and was found to be cost-effective.[19] A recent systematic review by the Institut national d'excellence en santé et services sociaux (INESSS) found that dose banding of anticancer drugs (including IO drugs) can lead to reductions in waste and costs, although its impact on PK and clinical outcomes was uncertain due to scarce evidence.[49] Authorities regulating the provision of cancer care, such as the National Health Service in England,[50,51] have proposed dose banding for nivolumab and pembrolizumab. Canadian cancer agencies may want to explore standardizing dose banding for these drugs and other anticancer drugs.

PQ2: Is Immuno-Oncology (IO) drug re-treatment after adjuvant IO therapy effective? How long after end of adjuvant IO therapy can patients with progressing melanoma or non–small cell lung cancer be considered eligible for a second IO treatment?

A review of the clinical literature was conducted to address the first part of the second policy question, which relates to effectiveness of re-treatment. No evidence was identified that could precisely clarify this issue. As adjuvant immunotherapy is a relatively new concept in oncology, it is possible that informative studies — either randomized controlled trials or observational — are underway. As a case in point, the ongoing KEYNOTE-054 study[52] on adjuvant pembrolizumab includes reinitiation with the drug for subsequent disease recurrence that occurs more than six months after completion of one year of adjuvant treatment. Furthermore, a multi-centre analysis[46] presented in abstract form suggests that reinitiation or switching to a different IO drug is potentially effective if the patient recurs while off treatment after adjuvant immunotherapy. Unfortunately, the time allotted to consider a patient off treatment and therefore eligible for repeat therapy was not specified in the publication. Reports of patients being re-treated with IO drugs have been published,[53-55] but none included patients treated in the adjuvant setting.

With the effectiveness question unresolved, it can be assumed that a patient with no exposure to an IO drug for a sufficient amount of time can be considered eligible for the same or similar treatment upon relapse, given that the tumour would have grown in the absence of drug pressure and may not necessarily be refractory to it. Consequently, a simplified re-treatment question can be addressed by identifying the time needed for an appropriate washout of the IO drugs when no significant residual biological activity should be exerted on the target cells.

Substantive PK literature on pembrolizumab, nivolumab, and durvalumab was identified to help answer this question. Washout periods were calculated by multiplying the half-lives by ten, in accordance with Canadian regulatory guidance.[35] (Results are summarized in Table 16.) For all three drugs, a caveat is noted in that partial biological activity cannot be ruled out

after ten half-lives due to an absence of clinical evidence at such low concentrations. Additionally, it is possible that drug-refractory tumour cells may start multiplying during the specified washout period, but only become detectable after that period has ended and eligibility is effective. Finally, serum clearance may not parallel loss of antibody-receptor binding and thus biological activity. For instance, pharmacodynamic data from a phase I clinical study[56] showed that receptor (PD-1) occupancy on circulating T cells exceeded 70% two months after nivolumab infusion, despite an observed serum half-life of 12 to 20 days in the study. Therefore, suggested washout values should be viewed as theoretical and somewhat arbitrary from a policy and practice perspective. More evidence from well-conducted clinical studies is needed to confirm the effectiveness of a new course of IO drugs in patients who progressed both while on adjuvant IO therapy and after it was terminated and allowed to clear out of the system.

Table 16: Summary of Immuno-Oncology Drug Half-Lives and Washout Periods

Drug	Half-Life	Washout[a]
Nivolumab	20.1 days	201 days (6.7 months)
Pembrolizumab	23.7 days	237 days (8 months)
Durvalumab	20.9 days	209 days (7 months)

[a] Calculated as ten half-lives.

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Appendix 1: Recent CADTH Recommendations Regarding Immuno-Oncology Dosing

Table 17: Pembrolizumab Dosing by Jurisdiction

Indication[a]	Pembrolizumab for NSCLC — First-Line	Pembrolizumab for Classical Hodgkin Lymphoma	Pembrolizumab for mUC	Pembrolizumab for Non-Squamous NSCLC
Provincial funding summary	pCODR 10101	pCODR 10109	pCODR 10117	pCODR 10153
Potential next steps for stakeholders in pCODR recommendation	pERC acknowledged the KN-024 assessed dose of 200 mg every three weeks up to 35 cycles, and felt it reasonable that pembrolizumab be administered at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg).	pERC acknowledged that a weight-based dose of 2 mg/kg every three weeks has been approved for other indications; however, there is currently no evidence for the 2 mg/kg dose for the current indication.	pERC felt it would be reasonable that pembrolizumab be administered at 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg).	pERC recognized that jurisdictions will need to choose between administering pembrolizumab as a fixed dose of 200 mg, as in the KEYNOTE189 trial, or at a dose of 2 mg/kg up to a total dose of 200 mg (dose capped at 200 mg), as is used in clinical practice for other indications.
Dosing requirements[b]				
BC	No requirement	Under negotiation with manufacturer	Under negotiation with manufacturer	Under negotiation with manufacturer
AB	Weight-based with cap			
SK	No requirement			
MB				
ON				
NB				
NS				
NL	Weight-based with cap			
PEI	No requirement			

AB = Alberta; BC = British Columbia; NSCLC = non–small cell lung carcinoma; MB = Manitoba; mUC = metastatic urothelial carcinoma; NB = New Brunswick; NL = Newfoundland; NS = Nova Scotia; ON = Ontario; pCODR = CADTH pan-Canadian Oncology Drug Review; PEI = Prince Edward Island; SK = Saskatchewan.

[a] Earlier pembrolizumab recommendations (2016) did not identify different dosing schedules as next steps for stakeholders.

[b] Based on funding criteria shared with CADTH as of November 7, 2019.

Table 18: Nivolumab Dosing by Jurisdiction

Indication[a]	Nivolumab for Adjuvant Melanoma	Nivolumab in Combination With Ipilimumab for Renal Cell Carcinoma	Nivolumab for Classical Hodgkin Lymphoma	Nivolumab in Combination With Ipilimumab for Metastatic Melanoma	Nivolumab for Squamous Cell Carcinoma of the Head and Neck
Provincial Funding Summary	pCODR 10147	pCODR 10132	pCODR 10120	pCODR 10098	pCODR 10095
Potential Next Steps for Stakeholders in pCODR Recommendation	Although less frequent treatment dosage schedules have been adopted in other indications, pERC noted that clinicians may choose to adhere to the trial protocol of biweekly doses given that treatment with nivolumab in this setting is for curative intent.	pERC agreed that it is reasonable to administer nivolumab as a 3 mg/kg dose up to a maximum of 240 mg every two weeks or 6 mg/kg up to a maximum of 480 mg every four weeks.	pERC acknowledged that while fixed dosing is widely used in solid tumour treatment, there is currently insufficient evidence available to recommend using cost-saving dosing strategies of 3 mg/kg up to a dose cap of 240 mg every two weeks and 6 mg/kg up to a dose cap of 480 mg every four weeks.	pERC felt it would be reasonable that nivolumab be administered at 3 mg/kg up to a total dose of 240 mg (dose capped at 240 mg).	pERC acknowledged that a fixed dose of nivolumab has also been approved for other indications; however, there is currently no evidence for fixed dosing for the current indication.
Dosing Requirements[b]					
BC	No requirement	No requirement	Under negotiation with manufacturer	No requirement	No requirement
AB	Under negotiation with manufacturer				Weight-based with cap
SK					No requirement
MB					
ON					
NB					
NS					
NL					Weight-based no cap
PEI		Under provincial consideration		Not applicable	Under provincial consideration

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland; NS = Nova Scotia; ON = Ontario; pCODR = CADTH pan-Canadian Oncology Drug Review; PEI = Prince Edward Island; SK = Saskatchewan.

[a] Earlier nivolumab recommendations (2016) did not identify different dosing schedules as next steps for stakeholders; concerns of fixed duration of treatment.

[b] Based on funding criteria shared with CADTH as of November 7, 2019.