Canadian Journal of Health Technologies

CADTH

July 2021 Volume 1 Issue 7

CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the first-line treatment of adult patients with metastatic microsatellite instability-high or mismatch repair-deficient colorectal cancer

Sponsor: Merck Canada Inc.

Final Recommendation: Reimburse with conditions

CADTH

ISSN: 2563-6596

Redactions: Confidential information in this document has been redacted at the request of the sponsor in accordance with the *CADTH Drug Reimbursement Review Confidentiality Guidelines.*

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Summary

CADTH

What Is the CADTH Reimbursement Recommendation for Keytruda?

CADTH recommends that Keytruda (pembrolizumab) should be reimbursed as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) colorectal cancer if certain conditions are met.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if prescribed by clinicians with experience in immuno-oncology and treating colorectal cancer, and if the price of the drug is reduced.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered to treat patients who have not received prior treatment for metastatic MSI-H/dMMR colorectal cancer and have a good performance status at the start of treatment with pembrolizumab.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that Keytruda extends survival, delays disease progression, and improves health-related quality of life compared with standard of care chemotherapy for metastatic MSI-H/dMMR colorectal cancer.
- Based on public list prices, Keytruda is not considered cost-effective at a willingness to pay of $50,000 per quality-adjusted life-year (QALY) for the indicated population, relative to currently reimbursed alternatives. A price reduction of at least 21% is required to ensure Keytruda is cost-effective at a $50,000 per QALY threshold.
- Based on public list prices, the 3-year budget impact is $67,056,712.

Additional Information

What Is Metastatic Colorectal Cancer?

Colorectal cancer is caused by cancerous cells that grow into and destroy tissues in the colon and/or rectum. In metastatic disease, the tumour spreads to and damages other parts of the body. Based on data from 2020, colorectal cancer accounts for 12% of new cancer cases and 12% of new cancer deaths, leading to an additional 26,900 Canadians being diagnosed with colorectal cancer and 9,700 additional deaths due to the disease that year. Approximately 20% to 25% of newly diagnosed colorectal cancers are metastatic at time of diagnosis. The MSI-H/dMMR subtype may be present in 15% of patients with colorectal cancer.

Unmet Needs in Metastatic Colorectal Cancer

Patients with metastatic MSI-H/dMMR colorectal cancer have poor prognosis and poor responses to standard chemotherapy.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $11,733 per 28 days.

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab should be reimbursed as monotherapy for the first-line treatment of metastatic microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) colorectal cancer only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 open-label, randomized controlled trial (RCT), Keynote-177 (N = 307), showed that pembrolizumab 200 mg IV every 3 weeks up to 2 years (35 doses) was associated with longer median progression-free survival (PFS) (median = 16.5 months; 95% confidence interval [CI], 5.4 to 32.4) compared with standard of care (SOC) chemotherapy (median = 8.2 months; 95% CI, 6.1 to 10.2). The restricted mean survival times (which were considered because the proportional hazards assumption for the PFS analysis was violated) were 13.7 months (95% CI, 12.0 to 15.4) for pembrolizumab and 10.8 months (95% CI, 9.4 to 12.2) for SOC for a between-group difference of 2.9 months (95% CI, 0.7 to 5.1) after 24 months of follow-up. Exploratory analyses indicated that health-related quality of life from baseline to week 18 improved with pembrolizumab and decreased for patients treated with SOC. The percentage of patients with serious adverse events reported was lower in the pembrolizumab group (40.5%) than in the SOC group (52.4%). Given the totality of the evidence, pERC concluded that pembrolizumab met the following needs: prolonging life by a substantial amount of time, maintaining good quality of life, delaying the need for chemotherapy, improving symptoms, providing an alternative treatment option, and an easier administration in comparison to the SOC.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, CADTH estimated the incremental cost-effectiveness ratio (ICER) for pembrolizumab was $62,090 per quality-adjusted life-year (QALY) compared with SOC chemotherapy. At this ICER, pembrolizumab is not cost-effective at a $50,000 per QALY willingness-to-pay (WTP) threshold for adult patients with metastatic MSI-H/dMMR colorectal cancer. A price reduction would be needed for pembrolizumab to be cost-effective at this threshold. Given uncertainty within the clinical evidence, including whether there is a statistically significant overall survival (OS) benefit with pembrolizumab, the price reduction estimated by CADTH (21%) is likely an underestimate.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason
Initiation	
1. Patient has not received prior treatment for metastatic MSI-H/dMMR colorectal cancer.	The Keynote-177 study excluded patients who had received prior treatment for metastatic MSI-H/dMMR colorectal cancer. Patients enrolled in the Keynote-177 study were still eligible to participate if they had received prior adjuvant chemotherapy for colorectal cancer.
2. Patient must have a good performance status.	The Keynote-177 study excluded patients who had an ECOG PS of greater than 1 at baseline.

Reimbursement condition	Reason
Discontinuation	
1. Reimbursement of treatment should be discontinued for disease progression based on immune-modified RECIST criteria, or uncontrollable or serious immunotherapy-associated toxicity.	Criteria used for treatment discontinuation in the Keynote-177 study.
2. The maximum duration of reimbursement is for up to 24 months or 35 doses in patients without disease progression.	Criteria used in the Keynote-177 study and as per the product monograph.
Prescribing	
1. The prescribing of pembrolizumab should be restricted to clinicians and centres with experience in immuno-oncology and treating colorectal cancer.	To ensure the appropriate patients receive treatment with pembrolizumab and to optimize toxicity management.
Pricing	
1. A reduction in price.	Pembrolizumab is more costly than SOC chemotherapy. A price reduction of at least 21% would be required for pembrolizumab to be considered cost-effective at a WTP threshold of $50,000 per QALY.

dMMR = mismatch repair deficient; ECOG PS = Eastern Cooperative Oncology Group Performance Status; MSI-H = metastatic microsatellite instability-high; QALY = quality-adjusted life-year; RECIST = Response Evaluation Criteria in Solid Tumours; SOC = standard of care; WTP = willingness to pay.

Implementation Guidance

1. Patients in the Keynote-177 study who stopped treatment (either prematurely or at the end of the 2-year study period) with stable disease or better could receive up to 17 more doses of pembrolizumab (approximately 1 year) if they subsequently experienced disease progression. The re-treatment protocol was consistent with other trials of pembrolizumab. pERC agreed with clinical expert input that re-treatment with pembrolizumab would be reasonable if treatment had been discontinued after a good response or prolonged disease stability and for reasons other than disease progression (e.g., toxicity or completion of the recommended 2-year or 35-dose treatment duration).
2. At the time of implementing a funding recommendation, jurisdictions may want to consider addressing the time-limited need for offering pembrolizumab to patients who are currently receiving chemotherapy as first-line treatment of metastatic MSI-H/dMMR colorectal cancer and have not progressed.
3. pERC noted that the clinical and economic evidence submitted to CADTH by the sponsor was restricted to use of pembrolizumab in patients who had not received prior treatment for metastatic MSI-H/dMMR colorectal cancer (i.e., as first-line therapy), which was the patient population enrolled in the Keynote-177 study. The Keynote-164 study that evaluated the efficacy of pembrolizumab in patients previously treated for metastatic MSI-H/dMMR colorectal cancer was considered out of scope for the review because this population represents a separate Health Canada–approved indication and the sponsor submitted for reimbursement in line with the first-line indication. Therefore, pERC could not extrapolate the evidence beyond the patient population included in the current submission for pembrolizumab.
4. Although Keynote-177 assessed pembrolizumab at a dosage of 200 mg IV every 3 weeks up to 2 years (35 doses), pERC noted there is no evidence to suggest that

the dosing amount of 200 mg IV is superior to 2 mg/kg IV (the dose used in initial pembrolizumab trials). For many patients, the flat dose may result in a larger dose and greater cost. Therefore, jurisdictions will need to choose between funding administration of pembrolizumab as a weight-based dose of 2 mg/kg IV up to a total dose of 200 mg IV (dose capped at 200 mg IV) or as a flat dose of 200 mg IV every 3 weeks for metastatic MSI-H/dMMR colorectal cancer. A similar consideration is needed for the other Health Canada–approved dosage of pembrolizumab 400 mg IV every 6 weeks up to 2 years (18 doses).

Discussion Points

- Patient group and clinician input to CADTH highlighted that metastatic MSI-H/dMMR colorectal cancer is an aggressive cancer with a poor prognosis that also responds poorly to standard therapy for metastatic colorectal cancer.
- Median OS for patients receiving pembrolizumab had not been reached by month 24 of Keynote-177. The hazard ratio (HR) for OS numerically favoured pembrolizumab compared with SOC (HR = 0.77; 95% CI, 0.54 to 1.09), although this difference did not reach statistical significance. Sensitivity analyses were conducted to adjust for bias introduced by treatment crossovers or subsequent use of anti-PD1/PDL1 treatment (but not subsequent use of other anticancer medications). The analyses showed a wide range of HR estimates, suggesting that the primary analysis was sensitive to the assumptions made. Although each HR estimate suggested pembrolizumab may improve OS relative to SOC chemotherapy, due to variable point estimates and wide confidence intervals, the exact magnitude of any OS benefit is uncertain.
- The SOC chemotherapies in the Keynote-177 study included FOLFOX or mFOLFOX, FOLFOX plus bevacizumab, FOLFOX plus cetuximab, FOLFIRI, FOLFIRI plus bevacizumab, or FOLFIRI plus cetuximab. pERC heard clinician expert input that the chosen SOC regimens were similar to those used in clinical settings in Canada, except that cetuximab is not used as a first-line treatment. As well, some combinations of chemotherapies that are used in Canadian practice — FOLFOX or FOLFIRI plus panitumumab, FOLFOXIRI with or without bevacizumab, CAPOX with or without bevacizumab, capecitabine with or without bevacizumab, 5-fluorouracil plus leucovorin with or without bevacizumab, and irinotecan monotherapy — were not included in the trial and not modelled as comparators in the sponsor-provided economic analysis. pERC noted that although these comparators were missing from the pharmacoeconomic analysis, the exclusion of these comparators likely does not impact the overall findings around the cost-effectiveness of pembrolizumab, as the SOC regimens were considered to reflect current clinical practice in Canada.
- The sponsor provided an indirect treatment comparison (ITC) that included the SOC chemotherapy regimens used in Keynote-177 as comparators and FOLFOX or FOLFIRI plus panitumumab, and CAPOX. Limitations associated with the structure of the sparsely populated networks and considerable clinical and methodological heterogeneity that could not be fully accounted for made the results of the ITC difficult to interpret. It could not be concluded whether pembrolizumab was favoured, not favoured, or similar to the comparators included in the ITC.
- pERC noted that although the frequency of overall adverse events was similar in the pembrolizumab (97%) and SOC (99%) groups in Keynote-177, patients in the pembrolizumab group reported fewer serious adverse events (41% versus 52%). The

reported immunotherapy-associated adverse events were similar to the documented ones typically associated with pembrolizumab treatment.

- The sponsor's economic model was sensitive to the assumptions made regarding the OS benefit, as well as the duration of PFS benefit beyond the observed trial period, of pembrolizumab versus SOC. pERC concluded that the 21% price reduction needed to achieve a $50,000 per QALY ICER is likely conservative and an underestimate.

Background

Pembrolizumab has a Health Canada indication as monotherapy for the first-line treatment of adult patients with metastatic MSI-H/dMMR colorectal cancer. Pembrolizumab is a PD-1 immune-checkpoint inhibitor. It is available as an IV solution for infusion; the Health Canada–approved dose for this indication is 200 mg IV every 3 weeks or 400 mg IV every 6 weeks until disease progression or unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer, in patients without disease progression.

Sources of Information Used by the Committee

To make their recommendation, pERC considered the following information:

- a review of 1 RCT in adult patients with metastatic MSI-H/dMMR colorectal cancer and 1 sponsor-provided ITC
- patients' perspectives gathered by 2 patient groups: Colorectal Cancer Canada and Colorectal Cancer Resource & Action Network
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 3 clinical specialists with expertise diagnosing and treating patients with colorectal cancer
- input from clinician groups, including the Cancer Care Ontario Gastrointestinal Cancer Drug Advisory Committee, the Canadian Gastrointestinal Oncology Evidence Network, the Medical Advisory Board of Colorectal Cancer Canada, and other gastrointestinal cancer–treating clinicians
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Patient Input

Two patient groups, Colorectal Cancer Canada and Colorectal Cancer Resource & Action Network, provided input for this submission. Patient perspectives were obtained from online surveys, focus groups, and telephone interviews with patients. The following is a summary of key input from the perspective of the patient groups:

- Respondents indicated fatigue and pain as key symptoms, as well as bloody stools, diarrhea, and abdominal cramping. Colorectal cancer impacts their ability to work, fulfill

family obligations, and engage in other daily activities. Patients reported experiencing poor mental health and quality of life, as do their caregivers.

- Patients expect new therapies will provide a cure, prolong life, relieve symptoms, promote good quality of life, delay need for chemotherapy, have limited side effects, have simpler administration, and provide another treatment option.
- Patients identified the adverse effects associated with chemotherapy as particularly problematic, especially fatigue and nausea, but also vomiting, pain, rash, neuropathy, hair loss, and low platelet counts. Therefore, any treatments that would offer alternatives to chemotherapy, have fewer side effects than chemotherapy, or delay the need for chemotherapy are important to patients.

Drug Plan Input

Input was obtained from all 9 provinces (Ministries of Health and/or cancer agencies) participating in CADTH reimbursement reviews. The Provincial Advisory Group identified the following as factors that could impact the implementation:

- numerous clinical eligibility criteria, including whether patients with metastatic MSI-H/dMMR colorectal cancer who received other systemic therapies for first-line treatment and experienced disease progression should be eligible to receive funding for treatment with pembrolizumab in later lines of therapy
- barriers to diagnosing metastatic MSI-H/dMMR colorectal cancer and monitoring treatment effects
- whether re-treatment for an additional 17 doses (1 year) or until disease progression, whichever occurs first, is reasonable.

Clinical Evidence

Clinical Trials

One open-label RCT (Keynote-177) was included in the CADTH review, which compared pembrolizumab 200 mg IV every 3 weeks to SOC chemotherapy to assess the efficacy and safety in adult patients with unresectable or metastatic MSI-H/dMMR colorectal cancer. The study randomized 307 patients across 120 sites from 23 countries. Notably, patients in the SOC group were permitted to cross over to the pembrolizumab group on disease progression, and all patients were permitted to receive subsequent anticancer medications.

Keynote-177 recruited adults with locally confirmed MSI-H/dMMR stage IV colorectal cancer. Eligible patients had to be 18 years or older, with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 established 10 days before initiation of therapy, and a life expectancy greater than 3 months. Patients were previously untreated but were still eligible to participate if they had received adjuvant chemotherapy for colorectal cancer if completed at least 6 months before randomization.

Baseline patient characteristics between the pembrolizumab and SOC groups were generally similar. There were numerical differences between the pembrolizumab and SOC groups in the percentage of female patients (53.6% versus 46.8%), percentage of patients with ECOG PS of 0 (49.0% versus 54.5%), the percentage of patients with hepatic or pulmonary metastases (56.2% versus 47.4%), and the percentage of patients with other metastases (43.8% versus 52.6%).

The major limitations on internal validity of Keynote-177 were the open-label study design and crossover of patients in the SOC group to the pembrolizumab group. As well, patients in either group could receive subsequent anticancer medications, including other anti-PD1/PDL1 medications, following disease progression. Although no patients crossed over from the pembrolizumab to SOC group, 56 patients (36.4%) in the SOC group crossed over to the pembrolizumab group. Furthermore, 44 (28.6%) patients in the SOC group and 44 (28.8%) patients in the pembrolizumab group received subsequent anticancer therapy. The differential crossover and subsequent use of anticancer medications could introduce bias that would impact survival analyses.

The generalizability of the study was mainly limited by excluding patients with an ECOG PS of 2 or greater and including cetuximab-containing regimens as SOC, which are not typically used in Canadian clinical practice.

Outcomes

Outcomes were defined a priori in CADTH's systematic review protocol. Of these, pERC discussed the following:

- PFS
- OS
- response rate
- health-related quality of life
- duration of disease control
- adverse events.

PFS and OS were co-primary outcomes in Keynote-177. PFS was defined as the time from randomization to the first of either disease progression per Response Evaluation Criteria in Solid Tumours (RECIST) based on a blinded central imaging vendor or death due to any cause.

Objective response rate and adverse events were listed as secondary outcomes. All other efficacy outcomes were exploratory.

Efficacy

Median PFS was longer in the pembrolizumab group (median = 16.5 months; 95% CI, 5.4 to 32.4) than in the SOC group (median = 8.2 months; 95% CI, 6.1 to 10.2) group, resulting in a HR of 0.60 (95% CI, 0.45 to 0.80). However, the restricted mean survival time was calculated because the HR may be biased because the proportional hazards assumption was not met. The restricted mean survival time after 24 months of follow-up was longer with pembrolizumab treatment (mean = 13.7 months; 95% CI, 12.0 to 15.4) than with SOC

(mean = 10.8 months; 95% CI, 9.4 to 12.2; between-group difference = 2.9 months; 95% CI, 0.7 to 5.1).

Median OS was not reached by month 24; however, the HR for OS was calculated to be 0.77 (95% CI, 0.54 to 1.09) in favour of pembrolizumab, but the comparison to SOC was not statistically significant. Sensitivity analyses generated a wide range of estimates for the HR and wide confidence intervals, indicating the OS analyses were sensitive to the assumptions made and associated with limited precision. The exact magnitude of the treatment effect with pembrolizumab on OS is uncertain.

Overall response rate was a secondary outcome and was higher in the pembrolizumab group (overall response rate = 43.8%; 95% CI, 35.8% to 52.0%) relative to the SOC group (overall response rate = 33.1%; 95% CI, 25.8% to 41.4%). The between-group difference of 10.7% (95% CI, −0.2% to 21.3%) was not statistically significant after adjusting for multiplicity. It was notable that 11.1% of patients in the pembrolizumab group and 3.9% in the SOC group had a complete response.

Other outcomes in Keynote 177 were evaluated as exploratory. The median time to response was similar in the pembrolizumab and SOC groups (2.2 and 2.1 months, respectively). The median duration of response could not be compared because there was no reported value in the pembrolizumab arm; however, the percentage of patients with an extended response duration was numerically higher in the pembrolizumab group compared with the SOC group at 6, 9, 12, 18, and 24 months. Health-related quality of life was measured using the changes from baseline to week 18 on the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and the EQ-5D-3L. Scores on the EORTC QLQ-C30 improved from baseline to week 18 in the pembrolizumab group by 3.33 points (95% CI, −0.05 to 6.72) whereas scores decreased by 5.63 points (95% CI, −9.32 to −1.94) in the SOC group (between-group difference = 8.96 points; 95% CI, 4.24 to 13.69). The minimal importance difference (MID) for colorectal cancer patients is 5 points. Scores on the EQ-5D-3L visual analogue scale and utility score from baseline to 18 weeks also improved with pembrolizumab treatment. The visual analogue scale scores in the pembrolizumab group increased from baseline by 4.50 points (95% CI, 1.16 to 7.83) and decreased by 2.88 points (95% CI, −6.46 to 0.69) in the SOC group, for a difference of 7.38 points (95% CI, 2.82 to 11.93) points in favour of pembrolizumab (the MID is 6 points for cancer patients). The EQ-5D-3L utility scores in the pembrolizumab group increased from baseline by 0.04 points (95% CI, 0.00 to 0.08) and decreased by 0.01 points (95% CI, −0.05 to 0.02) in the SOC group for a difference of 0.05 points (95% CI, 0.00 to 0.10) in favour of pembrolizumab, meeting the MID of 0.05 for cancer patients.

Harms (Safety)

The percentage of patients experiencing an adverse event was 97.4% in the pembrolizumab group and 99.3% in the SOC group. The most common adverse events in both groups were gastrointestinal events and fatigue. The percentage of patients with serious adverse events reported was lower in the pembrolizumab group (40.5%) than in the SOC group (52.4%). The frequency of adverse events resulting in treatment discontinuation, death, or death due to an adverse event were similar between both groups (pembrolizumab: 17.6%; SOC: 16.8%). The frequency of immune-mediated adverse events (identified as harms of interest for the CADTH review) was higher in the pembrolizumab group (30.7%) than in the SOC group (12.6%), which is not surprising given the differences in mechanisms of action. The most common immune-mediated adverse events were hypothyroidism, colitis, hyperthyroidism, pneumonitis, adrenal

insufficiency, hepatitis, and infusion reactions. However, the frequency of infusion-related reactions was higher in the SOC group (7.7% versus 2.0% with pembrolizumab).

Indirect Evidence

The sponsor-submitted ITC evaluated the comparative efficacy and safety of pembrolizumab versus competing interventions for the treatment of patients with metastatic MSI-H/dMMR colorectal cancer. Pembrolizumab was compared with CAPOX, panitumumab plus FOLFOX, and the SOC chemotherapies as administered in Keynote-177. The outcomes were OS, PFS, objective response rate, and safety outcomes. Bayesian network meta-analysis (NMA) methods were used for the comparisons. The base-case NMA for OS and PFS consisted of all included studies and used a subgroup of patients from the Keynote-177 trial who did not receive treatment with bevacizumab.

Five studies (mostly phase II or III, open-label RCTs) were included in the NMA, including Keynote-177. The base-case analysis of OS showed no difference between pembrolizumab and SOC or other interventions. Results from other analyses of OS (e.g., time-varying analysis, adjustment for different crossover methods) generally showed similar results. The base-case analysis for PFS indicated that pembrolizumab was favoured over all other treatments. Pembrolizumab was favoured over CAPOX for objective response rate. Pembrolizumab was favoured over comparator treatments with lower odds of grade 3 or higher adverse events, treatment-related grade 3 or higher adverse events, and serious treatment-related adverse events. No treatments were favoured over the others for discontinuations due to adverse events.

Key limitations of the NMA were the exclusion of bevacizumab as a comparator, the small and sparsely populated networks, and the considerable clinical and methodological heterogeneity that was not adequately addressed. These limitations precluded drawing definitive conclusions on the comparative efficacy and safety of pembrolizumab.

Economic Evidence

Cost and Cost-Effectiveness

Pembrolizumab is available as a 100 mg/4 mL vial, priced at $4,400 per vial. The recommended dosage is 200 mg every 3 weeks, at a cost of $11,733 per 28 days ($8,800 per cycle).

The sponsor submitted a cost-utility analysis of pembrolizumab, using partitioned survival model comprised of 3 health states: PFS (time to the first documented tumour progression, unacceptable toxicity, or to death from any cause), progressed disease, and death. Incremental costs and QALYs were estimated for pembrolizumab compared with 3 comparators: SOC; oxaliplatin plus leucovorin plus 5-fluorouracil (mFOLFOX6) plus panitumumab (mFOLFOX6-PAN); and irinotecan plus leucovorin plus 5-FU (FOLFIRI) plus panitumumab (FOLFIRI-PAN). The sponsor-assumed SOC included 6 regimens: mFOLFOX6, FOLFIRI, mFOLFOX6 plus cetuximab, FOLFIRI plus cetuximab, mFOLFOX6 plus bevacizumab, and FOLFIRI plus bevacizumab. The data used to characterize PFS, OS, the duration on treatment, and the risk of adverse events within the pembrolizumab and SOC comparators

were obtained from the Keynote-177 trial. To model PFS, OS, duration of treatment, and the probability of adverse events for the indirect comparators (i.e., FOLFIRI-PAN and mFOLFOX6-PAN), the sponsor used results from an NMA. The perspective of the analysis was the public health payer, and the time horizon of the analysis was 15 years.

CADTH noted the following limitations in the sponsor's analysis:

- The sponsor incorporated treatment-specific utilities, which does not reflect CADTH Guidelines. Furthermore, the EQ-5D-3L values applied to the "pre-progression" and "progressed disease" health states lacked face validity because they closely approximated population norms among people without metastatic disease.
- According to feedback from the clinical experts consulted by CADTH for this review, assumptions about whether patients received brand name bevacizumab (i.e., Avastin) (86%) versus the biosimilar equivalent (14%), and the degree of drug wastage associated with the administration of bevacizumab and panitumumab did not reflect clinical practice.
- The sponsor's approach for defining the comparator treatments limited their comparability to Canadian clinical practice. Comparators included cetuximab-based regimens that are not funded in Canada for this indication and included regimens relevant exclusively to a narrow subset of all patients with MSI-high/dMMR metastatic or unresectable colorectal cancer. Several relevant comparators that represent current SOC in Canada were also excluded.
- The sponsor incorporated an estimate of the cost of administering IV drugs that does not align with Canadian clinical practice based on feedback from the clinical experts consulted by CADTH for this review.
- The modelled time horizon of 15 years is not long enough to reflect all relevant costs and outcomes for the decision.

CADTH undertook reanalyses to address limitations with the sponsor's submission, including revised utility weights for the PFS and progressed disease health states, revised assumptions about how bevacizumab and panitumumab are administered in clinical practice (i.e., use of bevacizumab biosimilar and price, magnitude of drug wastage), revised assumption that 0% in the SOC comparator are treated with cetuximab-based regimens, revised resource use cost estimate for the administration of IV drugs, and extended the length of the model time horizon. In the CADTH base case, pembrolizumab and SOC were considered optimal treatments (i.e., on the efficiency frontier), whereas mFOLFOX6-PAN and FOLFIRI-PAN were not. Pembrolizumab was more costly (incremental cost = $173,843) and more effective (incremental QALYS = 2.80) than SOC, generating an ICER of $62,090 per QALY for pembrolizumab compared with SOC. Pembrolizumab had a 1% chance of being cost-effective at a WTP threshold of $50,000 per QALY. A price reduction of at least 21% is needed for pembrolizumab to be cost-effective compared with a WTP threshold of $50,000 per QALY when compared with SOC. The estimated QALY benefit associated with pembrolizumab was based on the assumed relationship between PFS and OS. CADTH's Clinical Review found that there was insufficient evidence within the trial data of an OS benefit. The cost-effectiveness analysis was sensitive to this assumption and the time horizon of the analysis.

CADTH was unable to address the cost-effectiveness of relevant treatment comparators (capecitabine, capecitabine plus bevacizumab, fluorouracil, fluorouracil plus bevacizumab, FOLFIRI, single-agent CAPOX, and single-agent irinotecan); the cost-effectiveness of pembrolizumab compared with these comparators is unknown. Additionally, 91% of the incremental QALYs estimated for pembrolizumab compared with SOC occurred during

the extrapolated period. In a scenario analysis in which no additional survival benefit for pembrolizumab was assumed beyond the trial period compared with SOC, the ICER for pembrolizumab versus SOC increased to $113,674 per QALY gained. Combined, these findings suggest that the cost-effectiveness results were driven primarily by assumptions about the relationship between PFS and OS, which was uncertain within the trial data.

Budget Impact

The sponsor estimated the incremental budget impact of reimbursing pembrolizumab to be $45,395,210 over 3 years. CADTH identified limitations with the submitted budget impact analysis and undertook reanalyses that estimated the incremental budget impact to be $67,056,712 over 3 years. CADTH noted the budget impact is sensitive to changes in the frequency of MSI-H/dMMR testing, and the rate of uptake for pembrolizumab in the indicated population.

Members of the pCODR Expert Review Committee

Dr. Maureen Trudeau (Chair), Dr. Catherine Moltzan (Vice-Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Kelvin Chan, Dr. Matthew Cheung, Dr. Winson Cheung, Dr. Michael Crump, Dr. Avram Denburg, Dr. Leela John, Dr. Christine Kennedy, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Ms. Valerie McDonald, Dr. Marianne Taylor, and Dr. Dominika Wranik.

Meeting Date: May 13, 2021

Regrets: None

Conflicts of Interest: None