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CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: In combination with chemotherapy, for the treatment of adult patients with locally recurrent unresectable or metastatic triple-negative breast cancer who have not received prior chemotherapy for metastatic disease and whose tumours express programmed cell death-ligand 1 (combined positive score ≥ 10) as determined by a validated test

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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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 Keytruda?

CADTH recommends that Keytruda be reimbursed by public drug plans, in combination with chemotherapy, for the treatment of adult patients with locally recurrent unresectable or metastatic triple-negative breast cancer (TNBC) who have not received prior chemotherapy for metastatic disease and whose tumours express programmed death-ligand 1 (PD-L1) (combined positive score [CPS] ≥ 10) as determined by a validated test if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered for adult patients with centrally confirmed TNBC who have PD-L1–positive tumours (CPS ≥ 10), have not received treatment for locally recurrent or metastatic TNBC, and are in relatively good health (i.e., have a good performance status, as determined by a specialist). Patients with unstable central nervous system (CNS) metastases or those who have clinical contraindications to immunotherapy are not eligible for reimbursement.

What Are the Conditions for Reimbursement?

Keytruda should only be reimbursed if prescribed in combination with chemotherapy and given by a clinician who is experienced in treating breast cancer and the cost of Keytruda is reduced.

Why Did CADTH Make This Recommendation?

- Clinical trial evidence demonstrated that patients treated with Keytruda and chemotherapy experienced a delay in the spread of cancer and lived longer.
- Keytruda with chemotherapy met patients' needs of delaying disease progression and prolonging survival; it was unlikely to worsen health-related quality of life (HRQoL).
- Based on CADTH's assessment of the evidence, Keytruda does not represent good value to the health care system at the public list price. A price reduction is therefore required.
- Based on public list prices, Keytruda is estimated to cost the public drug plans approximately $33 million over the next 3 years.

Additional Information

What Is TNBC?

Breast cancer can be classified by proteins (receptors) expressed by the cancer cell. TNBC is a cancer that does not have estrogen and progesterone hormone receptors and has little epidermal growth factor receptor 2 (HER2) expression.

Unmet Needs in Patients With TNBC

Patients with locally recurrent unresectable or metastatic TNBC have fewer treatment options and tend to have a worse prognosis than patients with other types of invasive breast cancer. About 12% of patients with metastatic TNBC survive 5 years or less.

How Much Does Keytruda Cost?

Treatment with Keytruda is expected to cost approximately $11,733 per patient per 28-day cycle. When in combination with chemotherapy, the per-patient 28-day cycle cost ranges from $14,107 to $17,133.

Recommendation

The CADTH pan-Canadian Oncology Drug Review Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed in combination with chemotherapy for the treatment of adult patients with locally recurrent unresectable or metastatic TNBC who have not received prior chemotherapy for metastatic disease and whose tumours express PD-L1 (CPS ≥ 10) as determined by a validated test only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One multicentre, randomized, placebo-controlled, phase III study (KEYNOTE-355; N = 323 for patients with PD-L1–positive tumours [CPS ≥ 10]) demonstrated that treatment with pembrolizumab in combination with chemotherapy resulted in added clinical benefit for adult patients with locally recurrent unresectable or metastatic TNBC who had not received prior chemotherapy for metastatic disease and whose tumours expressed a CPS of 10 or greater. KEYNOTE-355 showed that, compared with chemotherapy plus placebo, pembrolizumab in combination with chemotherapy was associated with statistically significant and clinically meaningful improvements in overall survival (OS) at a 20.2-month median follow-up time (hazard ratio [HR] = 0.73; 95% confidence interval [CI]: 0.55 to 0.95; P = 0.0093). The addition of pembrolizumab also demonstrated a statistically significant improvement in progression-free survival (PFS) (HR = 0.65; 95% CI, 0.49 to 0.86; P = 0.0012) compared with placebo. Although exploratory, the addition of pembrolizumab to chemotherapy did not suggest a detriment in HRQoL from baseline to week 15. pERC considered the safety profile of pembrolizumab in combination with chemotherapy to be manageable and consistent with the known safety profile of pembrolizumab.

Patients identified a need for treatments that prolong survival, achieve disease control, have minimal side effects, and maintain quality of life. pERC concluded that pembrolizumab in combination with chemotherapy met some of the patients' needs as it prolongs survival, delays disease progression, and likely does not have detrimental effects of HRQoL versus chemotherapy alone.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pembrolizumab, using a fixed dose, in combination with chemotherapy was $198,317 per quality-adjusted life-year (QALY) gained compared with chemotherapy alone. At this ICER, pembrolizumab is not cost-effective at a $50,000 per QALY gained willingness-to-pay threshold. A price reduction is required for pembrolizumab to be considered cost-effective at a threshold of $50,000 per QALY gained.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pembrolizumab in combination with chemotherapy should be reimbursed when initiated in patients who	Evidence from the KEYNOTE-355 trial demonstrated a statistically significant	PD-L1 status must be determined before initiating treatment to ensure tumours express PD-L1 (CPS ≥ 10).

Reimbursement condition	Reason	Implementation guidance
have all of the following: 1.1. metastatic breast cancer or locally recurrent inoperable breast cancer that cannot be treated with curative intent 1.2. not previously treated with chemotherapy in the metastatic or incurable locally advanced setting 1.3. centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines[a] 1.4. PD-L1–positive tumours (CPS ≥ 10) 1.5. at least 6 months' time interval between the completion of treatment with curative intent and the first documented local or distant disease recurrence.	clinical benefit in patients who fulfilled these characteristics.	
2. Patients must not have: 2.1. unstable CNS metastases 2.2. a clinical contraindication to immunotherapy.	The KEYNOTE-355 trial excluded patients with active CNS metastases and with active autoimmune disease. There is no evidence to suggest these patients will benefit from treatment with pembrolizumab in combination with chemotherapy.	Patients with treated or stable CNS metastases should be eligible for treatment and were included in the Keynote-355 trial. Treatment of patients with autoimmune disease may be at the discretion of the treating physician.
3. Patients should have good performance status.	Patients with an ECOG performance status of 0 or 1 were included in the KEYNOTE-355 trial.	Patients with an ECOG performance status of 2 may be treated at the discretion of the treating clinician.
Discontinuation		
4. Treatment should be discontinued upon the occurrence of any of the following: 4.1. clinical disease progression 4.2. unacceptable toxicity.	Consistent with clinical practice, patients from the KEYNOTE-355 trial discontinued treatment upon progression or unacceptable toxicity.	—
5. Pembrolizumab should be reimbursed for a maximum of 35 cycles (200 mg every 3 weeks), 18 cycles (400 mg every 6 weeks), or 2 years, whichever is longer. Chemotherapy can be continued beyond this time.	Patients in the KEYNOTE-355 trial were treated with pembrolizumab for a maximum of 35 cycles. In the presence of clinical benefit, patients who completed 35 cycles of treatment with pembrolizumab (approximately 2 years) could continue chemotherapy alone beyond this time point at the investigators' discretion.	It would be reasonable to re-administer pembrolizumab at the time of relapse (up to 17 additional every-3-week doses or 1 year), with or without chemotherapy, at the discretion of the treating physician for patients who have discontinued pembrolizumab before any disease progression or if disease progression occurred during a treatment break.

Reimbursement condition	Reason	Implementation guidance
6. Patients are allowed to discontinue 1 or more components of the study treatment at the discretion of the treating clinician in case of serious adverse events.	According to the protocol of the KEYNOTE-355 study, patients were allowed to discontinue chemotherapy due to toxicity and continue pembrolizumab alone or vice versa.	Pembrolizumab may be continued as monotherapy if a patient has experienced toxicity with the chemotherapy regimen.
Prescribing		
7. Pembrolizumab in combination with chemotherapy should be prescribed by clinicians with expertise and experience in treating breast cancer; treatment should be delivered in institutions with expertise in immunotherapy drug delivery.	This helps to ensure that pembrolizumab in combination with chemotherapy is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	Pembrolizumab may be given at a dose of 400 mg IV every 6 weeks instead of 200 mg IV every 3 weeks. It can be given based on weight at 2 mg/kg up to 200 mg every 3 weeks or 4 mg/kg up to 400 mg every 6 weeks.
8. Pembrolizumab in combination with chemotherapy (i.e., paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin) should only be reimbursed when administered in combination.	In the KEYNOTE-355 trial, pembrolizumab was administered in combination with either paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin.	Chemotherapy can continue after 35 cycles of pembrolizumab.
Pricing		
9. A reduction in price	The ICER for the pembrolizumab combination with chemotherapy is $198,317 when compared with chemotherapy alone. A price reduction of 81% would be required for pembrolizumab to achieve an ICER of $50,000 per QALY gained compared to chemotherapy.	—

ASCO = American Society of Clinical Oncology; CAP = College of American Pathologists; CNS = central nervous system; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; ICER = incremental cost-effectiveness ratio; PD-L1 = programmed death-ligand 1; QALY = quality-adjusted life-year; TNBC = triple-negative breast cancer.

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Discussion Points

- pERC acknowledged that there is an unmet need for effective and safe therapy options in this patient population, which is aligned with patient and clinician group inputs that noted that metastatic TNBC is an aggressive disease and patients who relapse on first-line chemotherapy have a poor prognosis.
- pERC discussed the results of the KEYNOTE-355 trial and noted that OS and PFS were identified as clinically relevant outcomes by patients and clinicians and were statistically significant in favour of pembrolizumab in combination with chemotherapy. Given that the prognosis of patients with metastatic TNBC is poor, with a median survival of fewer than 2

years on first-line chemotherapy, the benefits observed with the addition of pembrolizumab to chemotherapy were considered clinically meaningful.

- pERC discussed the toxicity profile observed in the KEYNOTE-355 trial and agreed with the clinical experts and the clinician group inputs that incidence and severity of adverse reactions appeared consistent with the known safety profile of pembrolizumab. The most frequently reported adverse events (AEs) of any grade with pembrolizumab in combination with chemotherapy included anemia, nausea, neutropenia, alopecia, and fatigue. No new safety signals were reported with regards to immune-mediated AEs.
- The Health Canada–recommended dose for pembrolizumab in the patient population under review is 200 mg every 3 weeks or 400 mg every 6 weeks until disease recurrence or unacceptable toxicity or for a total treatment duration of 2 years (up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg), whichever is longer. pERC discussed that, although the pivotal trial used a 200 mg every 3 weeks dosing schedule, the 400 mg every 6 weeks and weight-based dosing schedules may be adopted by some clinicians in clinical practice to reduce burden on clinic resources and patients.
- The pharmacoeconomic analysis primarily informing pERC's economic rationale for the recommendation considered pembrolizumab as a fixed dose, per the product monograph. pERC discussed the results of the scenario analysis conducted by CADTH where pembrolizumab was assumed to be administered using a weight-based dose. In this analysis, the ICER decreased to $170,139 per QALY gained; a price reduction of 77% would be required for pembrolizumab to achieve an ICER of $50,000 per QALY gained in such a scenario. pERC noted that this analysis is associated with additional uncertainty given that the treatment was not evaluated as a weight-based dose; this may influence efficacy, compliance, and AEs.

Background

TNBC is an invasive form of breast cancer that affects 10% to 20% of patients with breast cancer. TNBC is distinguished by the absence of an estrogen receptor, progesterone receptor, and little to no expression of the HER2 gene. It is most common in women who are younger than 40 years; women who are Black; and women with a BRCA-1 mutation. Metastatic TNBC differs from other types of invasive breast cancer in that it tends to grow and spread faster, has fewer treatment options, and tends to have a worse prognosis. The predicted 5-year survival is 12% for metastatic TNBC compared to 77% for all TNBC and 89% for all breast cancer.

The standard approach for metastatic TNBC is treatment with single-drug chemotherapies such as taxanes, and gemcitabine with carboplatin. The median OS for patients with metastatic TNBC treated with conventional chemotherapy is 9 to 13 months. Combination chemotherapy may be used in patients with progressive or higher burden of disease, such as rapidly progressive visceral disease. There are currently no approved targeted treatments available for metastatic TNBC. According to the experts consulted by CADTH, patients who have higher PD-L1–positive CPS expression may be more likely to benefit from treatment regimens that use immunotherapies in combination with chemotherapy versus chemotherapy alone.

Pembrolizumab in combination with chemotherapy has been approved by Health Canada for the treatment of adult patients with locally recurrent unresectable or metastatic TNBC who have not received prior chemotherapy for metastatic disease and whose tumours express PD-L1 (CPS ≥ 10) as determined by a validated test. The dosage recommended in the product monograph is 200 mg IV every 3 weeks, or 400 mg IV every 6 weeks.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 1 phase III clinical study in adult patients with locally recurrent unresectable or metastatic TNBC who have not received prior chemotherapy for metastatic disease
- patients' perspectives gathered by patient groups, the Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (RBC)
- input from the public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with metastatic TNBC
- input from 3 clinician groups, including Ontario Health-Cancer Care Ontario (OH-CCO) Breast Cancer Drug Advisory Committee, Canadian breast cancer medical oncologists led by The Ottawa Hospital Cancer Centre (TOHCC), and the Provincial Breast Tumour Group (Alberta)
- a review of the pharmacoeconomic model and report submitted by the sponsor.

Stakeholder Perspectives

Patient Input

Two patient groups, CBCN and RBC, provided input for this review. CBCN collected patient input via 2 online surveys in patients from Canada with metastatic TNBC (survey 1, 2017, n = 14; survey 2, 2012, n = 87 [71 patients and 16 caregivers]) and a grey literature search. None of the respondents from the CBCN surveys had direct experience with pembrolizumab. The RBC input was based on general observations and insights gathered through various ongoing initiatives (including patients' blogs, virtual support groups, working groups, patient advisory boards, peer-support networks, Instagram, and scientific advisory committees) as well as online surveys (N = 78), Zoom interviews (n = 7), 1 to 1 meetings (n = 2; 1 had experience with pembrolizumab), and 2 testimonials from patients in Canada with metastatic TNBC.

In the CBCN submission, patients highlighted the negative impacts of metastatic breast cancer symptoms such as fatigue (54%), insomnia (39%), and pain (37%). The majority of respondents experienced metastases to their lungs (N = 10), followed by metastases to other parts of their bodies (e.g., bones, liver, and brain). These symptoms and metastases impose a heavy physical, emotional, psychosocial, and financial toll as well as negatively impacting HRQoL. Respondents from the CBCN surveys acknowledged that currently available treatments for metastatic TNBC have only shown to prolong the progression-free period and highlighted the decreasing response rates in later lines of therapy; while the

disease will eventually progress, patients seek to live their remaining months and years with the best possible HRQoL. The input provided by RBC indicated that especially for patients who are diagnosed at a young age, TNBC may have detrimental effects on patients' wellbeing in terms of fertility, childcare, relationships, body image, social activities, employment, and mental health.

Patients from both groups identified that the unmet needs for new treatments were prolonging survival, controlling disease, and maintaining quality of life. The RBC submission suggested that patients value long-term health outcomes over immediate concerns such as reducing symptoms or managing side effects. Patient respondents from CBCN expected new treatments to improve disease control and quality of life, delay disease progression, have minimal side effects, and be affordable and easy to access.

One patient with metastatic TNBC from RBC who had direct experience with pembrolizumab treatment stated that the drug had contributed to controlling the disease, shrinking tumour size, and improving HRQoL.

Clinician Input

Input From the Clinical Experts Consulted by CADTH

According to the clinical experts, improvement in survival and quality of life remain the most important unmet needs in patients with metastatic TNBC. The clinical experts agreed that pembrolizumab would be used in the first-line setting for the treatment of metastatic TNBC. In the opinion of the clinical experts, pembrolizumab with chemotherapy would be the new standard of care and would replace current treatment (e.g., chemotherapy alone), rather than being reserved for patients who are intolerant to existing treatments. The clinical experts advised that patients best suited for treatment with pembrolizumab combined with chemotherapy are those who meet the inclusion criteria of the KEYNOTE-355 study. In particular, patients with a CPS of 10 or more would be eligible for pembrolizumab. The clinical experts advised that patients least suitable for pembrolizumab included those who are unfit, frail, have a poor Eastern Cooperative Oncology Group (ECOG) performance status, or have active autoimmune disease. The experts indicated that radiological and clinical investigations are used to evaluate response on a regular basis. The experts also noted that PD-L1 status has been predictive of benefit in metastatic cases. The most common assessment modality is the shrinkage of tumour on clinical and/or radiological tests. The clinical experts stated that disease progression (tumour enlargement unless pseudoprogression is suspected) and the occurrence of intolerable AEs would be considered when deciding treatment discontinuation. The clinical experts stated that prescribing depends on the comfort level of the centre with administration of the drug and management of side effects.

Clinician Group Input

Three clinician group inputs were provided: OH-CCO Breast Cancer Drug Advisory Committee (based on input from 1 clinician), Canadian breast cancer medical oncologists led by TOHCC (based on input from 6 medical oncologists), and the Provincial Breast Tumour Group (Alberta) (based on input from 2 medical oncologists). The OH-CCO's Drug Advisory Committee provides timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. The TOHCC group consists of medical oncologists throughout Canada with an expertise in breast oncology and in particular

systemic therapies in advanced TNBC. The Provincial Breast Tumour Group (Alberta) is responsible for treating patients with TNBC in Alberta.

The clinician groups indicated that the current first-line treatment for metastatic TNBC, cytotoxic chemotherapy (taxane, platinum, and anthracycline), showed limited benefit in fulfilling the treatment goal of delaying disease progression and improving both duration and quality of life. The clinician groups identified the unmet need of more effective and tolerable treatment options in the metastatic setting. The OH-CCO highlighted that the lack of CPS testing within the province may delay the delivery of test results and thus delay the diagnosis of TNBC. The clinician groups all mentioned that pembrolizumab would fit in the fist-line metastatic setting in combination with chemotherapy in treating patients with TNBC. The clinician groups highlighted that pembrolizumab with chemotherapy would be expected to shift the current treatment paradigm by replacing chemotherapy alone. The suitable patients for pembrolizumab with chemotherapy identified by the clinician groups were those whose tumours expressed PD-L1(CPS ≥ 10), who had an ECOG performance status of 0 to 2, and for whom time from completion of adjuvant treatment was greater than 6 months, which aligned with the KEYNOTE-355 trial inclusion criteria. Patients identified as least suitable were those whose tumours do not express PD-L1 (CPS ≥ 10), who require other lines of therapy or had received neoadjuvant or adjuvant pembrolizumab for early-stage disease within 12 months, and with high risk of adverse toxicity related to immunotherapy.

The clinician groups agreed that treatment response should be measured using assessments based on symptoms, laboratory markers, radiographic scans, and tumour measurements. The appropriate interval for assessments is 3 months. Improvement of organ function (bone, liver, lung) and severity of symptoms, maintenance or improvement of performance status, and tumour radiographic response with either stabilization of disease or response by Response Evaluation Criteria in Solid Tumours (RECIST) criteria were considered clinically meaningful responses. When deciding to discontinue pembrolizumab with chemotherapy treatment, disease progression, intolerable or dangerous toxicity (grade 3 or higher immune-mediated toxicity), and patient preference or refusal should be considered. The clinician groups agreed that outpatient settings, such as hospital or a specialty clinic, that have oncology specialist (e.g., medical oncologists, chemotherapy nurses, oncology pharmacists) would be appropriate to administer systemic cancer therapies and monitor and manage treatment-related toxicities. In addition, the clinician groups highlighted that the pembrolizumab with chemotherapy combination has been considered as a new standard of care by internationally accepted guidelines, has shown to be well tolerated with a manageable toxicity profile, and to be highly accepted and valued by patients in Canadian clinical practice; thus, it is imperative that people living in Canada have access to this treatment.

The views of the clinician groups were overall consistent with the clinical experts consulted by CADTH.

Drug Program Input

The clinical experts consulted by CADTH provided advice on the potential implementation issues raised by the drug programs.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
For first-line treatment of metastatic TNBC, cytotoxic chemotherapy is administered either as a single drug or in combination, particularly for rapidly progressive disease or those with visceral disease. The most commonly used chemotherapy agents in Canada include taxanes (paclitaxel, docetaxel, nab-paclitaxel), anthracyclines (doxorubicin or epirubicin), carboplatin or cisplatin plus gemcitabine, vinorelbine, and capecitabine. In some jurisdictions, nab-paclitaxel is only funded if the patient is not able to use a taxane due to a contraindication to the standard pre-medications or due to severe toxicity or a hypersensitivity reaction to the taxane.	This was a comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
What is the specific definition of TNBC (i.e., cut-offs for determining ER or PR negativity and HER2 negativity) for eligibility for pembrolizumab?	pERC agreed with the clinical experts that TNBC is defined by the most recent ASCO/CAP guidelines.[a]
In the KEYNOTE-355 study, patients with TNBC cancer who previously completed treatment for stage I to III breast cancer were eligible if at least 6 months had elapsed between completion of treatment with curative intent (e.g., last dose of adjuvant chemotherapy administration if applicable) and documentation of local or distant disease recurrence. Would the same criteria be applicable for pembrolizumab eligibility in this group of patients at the time of diagnosis for advanced TNBC?	pERC agreed with the clinical experts that the KEYNOTE-355 trial criteria are applicable to Canadian clinical practice. Treatment with pembrolizumab in combination with chemotherapy is reasonable if at least 6 months have elapsed between completion of treatment with curative intent and local or distant disease recurrence.
If a patient received pembrolizumab in the neoadjuvant or adjuvant setting for early-stage TNBC, are they eligible to receive pembrolizumab again at the time of documented local or distant disease recurrence? If so, what time should elapse between completion of neoadjuvant or adjuvant pembrolizumab before being eligible for pembrolizumab again for metastatic TNBC?	In the KEYNOTE-355 trial, 59.8% of patients received prior neoadjuvant or adjuvant chemotherapy. No patient received pembrolizumab in the neoadjuvant or adjuvant setting for early-stage TNBC. The clinical experts noted that there is currently no evidence to inform this decision. pERC agreed that treatment with pembrolizumab in combination with chemotherapy may be reasonable if disease recurred at least 6 months post completion of neoadjuvant or adjuvant treatment with pembrolizumab.
Considerations for discontinuation of therapy	
Is there a minimum number of chemotherapy cycles that should be administered with pembrolizumab? If a patient experiences significant toxicity to chemotherapy, can chemotherapy be discontinued and pembrolizumab continued as monotherapy? Should chemotherapy be continued for the same duration of pembrolizumab in the absence of unacceptable toxicity?	pERC agreed with the clinical experts that given that no minimum number of chemotherapy cycles was specified in the KEYNOTE-355 trial, the same should apply in clinical practice. pERC agreed with the clinical experts that the KEYNOTE-355 protocol should be followed. According to the protocol of the KEYNOTE-355 study, patients were allowed to discontinue chemotherapy due to toxicity and continue pembrolizumab alone or vice versa.

Implementation issues	Response
	The protocol of the KEYNOTE-355 trial specified that if a patient completed 35 administrations of pembrolizumab, they could continue chemotherapy treatment at the discretion of the investigator. pERC agreed with the clinical experts that the decision to determine if chemotherapy should be continued in clinical practice should be at the discretion of the treating clinician.
The requested duration of treatment for pembrolizumab is until disease progression, unacceptable toxicity or up to 24 months (or 35 doses every 3 weeks or 18 doses every 6 weeks), whichever is longer, in patients without disease progression. If pembrolizumab is discontinued for reasons other than disease progression or intolerability after the initial 24 months of treatment, are patients eligible for an additional 12 months of treatment at the time of disease recurrence, similar to other indications for pembrolizumab? Should the same or different chemotherapy (if any) be administered in this situation?	pERC agreed with the clinical experts that it would be reasonable to re-administer pembrolizumab at the time of relapse (up to 17 additional every 3-week doses or 1 year) at the discretion of the treating physician for patients who discontinued pembrolizumab before any disease progression or experienced disease progression during a treatment break. These criteria align with the KEYNOTE-355 protocol criteria. According to the KEYNOTE-355 protocol, patients who started re-treatment with pembrolizumab were allowed to be given chemotherapy at the discretion of the treating physician. According to the KEYNOTE-355 protocol, patients had to receive the same type of chemotherapy drugs as used in their initial course. pERC agreed with the clinical experts that patients who start re-treatment with pembrolizumab may receive chemotherapy treatment at the discretion of the treating physician.
Considerations for prescribing of therapy	
PAG would like to inform pERC that, for consistency, jurisdictions would plan on implementing pembrolizumab as weight-based dosing up to a cap (e.g., 2 mg/kg every 3 weeks to a maximum dose of 200 mg or 4 mg/kg every 6 weeks to a maximum of 400 mg), similar to other indications.	This was a comment from the drug programs to inform pERC deliberations.
In the KEYNOTE-355 study, there was a choice of 3 chemotherapy regimens to be administered with pembrolizumab — nab-paclitaxel, paclitaxel, or gemcitabine plus carboplatin. Should the chemotherapy selection be at the discretion of the treating physician as per local institutional standards for metastatic TNBC? Is there a preferred chemotherapy?	pERC agreed with the clinical experts that the chemotherapies used in the KEYNOTE-355 trial (i.e., paclitaxel, nab-paclitaxel, or gemcitabine plus carboplatin) are commonly used and reflective of clinical practice. Other combinations are rare; however, if a patient is intolerant (e.g., side effects, allergies) to the chemotherapies used in the KEYNOTE-355 trial, it may be reasonable to use other chemotherapy drugs, chosen according to patient characteristics.
Generalizability	
Only patients with an ECOG performance status of 0 or 1 were eligible for the Keynote-355 study. Should patients with an ECOG performance status greater than 1 be eligible?	The KEYNOTE-355 trial included patients with an ECOG performance status of 0 to 1. pERC agreed with the clinical experts that it would be reasonable to generalize the KEYNOTE-355 trial results to patients with an ECOG performance status of up to 2 at the discretion of the treating physician.
If a patient starts with chemotherapy first, can pembrolizumab be added after, provided all other eligibility criteria are met and no disease progression has occurred? Please answer this question for 2 scenarios: • In the event of delays obtaining PD-L1 results or	The clinical experts noted that a short window of time (such as within 6 weeks from the initiation of chemotherapy to match a commonly used frequency of pembrolizumab) may be reasonable to add pembrolizumab after initiation of chemotherapy pERC noted that an opportunity to add pembrolizumab to

Implementation issues	Response
any other delay in accessing pembrolizumab, but where chemotherapy needs to be initiated before this information is available • Time-limited situation: at the time of public funding for patients who have started first-line chemotherapy and meet all eligibility criteria, but pembrolizumab was not yet funded when chemotherapy was initiated.	chemotherapy should be available in both scenarios described by PAG (i.e., in the event of delays initiating pembrolizumab and as a time-limited opportunity) as long as the patient is on chemotherapy with no progression of disease.
Should patients who are currently receiving chemotherapy for metastatic TNBC have pembrolizumab added to therapy (provided they have not previously been treated with immune checkpoint inhibitors), regardless of the line of therapy, provided they have a PD-L1 CPS of ≥ 10?	pERC agreed with the clinical experts that there is insufficient evidence to make a recommendation for pembrolizumab beyond the first-line metastatic TNBC setting, which was studied in the KEYNOTE-355 trial.
Care provision issues	
PD-L1 CPS testing for breast cancer needs to be operationalized and funded in some jurisdictions on or before pembrolizumab implementation.	This was a comment from the drug programs to inform pERC deliberations.
System and economic issues	
PAG is concerned about overall budget impact of pembrolizumab given the volume of patients with TNBC who may be eligible and the cost of pembrolizumab. All chemotherapy comparators with the exception of nab-paclitaxel currently have generic versions available.	This was a comment from the drug programs to inform pERC deliberations.

ASCO = American Society of Clinical Oncology; CAP = College of American Pathologists; CPS = combined positive score; ECOG = Eastern Cooperative Oncology Group; ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2; PAG = Provincial Advisory Group; PD-L1 = programmed cell death-ligand 1; pERC = CADTH pan-Canadian Oncology Drug Review Expert Review Committee; PR = progesterone receptor; TNBC = triple-negative breast cancer.

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Clinical Evidence

Pivotal Study

Description of Study

KEYNOTE-355 is an ongoing, phase III, randomized, multicentre, double-blind, 2-part placebo-controlled trial. The primary objective of the trial was to evaluate the efficacy and safety of pembrolizumab in combination with chemotherapy versus placebo plus chemotherapy for patients with locally recurrent inoperable or metastatic TNBC that has not been previously treated with chemotherapy for metastatic disease. The KEYNOTE-355 trial was initiated in August 2016 and has 251 participating centres across 29 countries in North America (5 sites in Canada, N = 34), South America, Europe, Asia, and Australia. The study was conducted in 2 parts. Part 1 was the safety run-in (N = 30), and part 2 was the efficacy evaluation (N = 847). Patients from part 1 were not included in part 2. For the purpose of this CADTH

review, only part 2 was evaluated. The 2 primary efficacy outcomes were OS and PFS in all patients and patients with PD-L1–positive tumours. Secondary outcomes included objective response rate (ORR), duration of response (DOR), disease control rate, and HRQoL in all patients and patients with PD-L1–positive tumours. The study was considered to have met its primary objective if the combination of pembrolizumab and chemotherapy was superior to placebo and chemotherapy in either PFS or OS in either all patients or in patients with PD-L1–positive tumours (CPS ≥ 1 or CPS ≥ 10) at either an interim analysis (IA) or the final analysis (FA)(OS only).Given that the indication for the sponsor-submitted reimbursement request was for patients with PD-L1 expression score of CPS ≥ 10, this review focused on patients with a PD-L1 CPS expression of 10 or greater. In total, 1,372 patients had been screened of which 847 patients were randomized in the intention-to-treat population in a 2:1 ratio between the pembrolizumab in combination with chemotherapy (N = 566) and the placebo plus chemotherapy group (N = 281). Randomization was stratified based on 3 stratification factors:

- type of chemotherapy on-study (paclitaxel or nab-paclitaxel or gemcitabine/carboplatin)
- PD-L1 expression at baseline (CPS ≥ 1 or < 1)
- prior treatment with the same class of chemotherapy in the neoadjuvant or adjuvant setting (yes or no).

Treatment was to continue until confirmation of progressive disease (PD) or death. Both patients and investigators were blinded to study treatments administered during the trial. In total, 75.1% and 38.1% had a tumour tissue PD-L1 expression score of CPS ≥ 1 and CPS ≥ 10, respectively. All patients enrolled were female. Majority of patients were < 65 years of age, White, post-menopausal, and had an ECOG performance status of 0. In the KEYNOTE-355 trial, in patients with CPS ≥ 10, the median number of study treatment administrations was 35.1 and 22.6 in the pembrolizumab and placebo groups, respectively. The median number of administrations with each individual study treatment component was (pembrolizumab + chemotherapy versus placebo + chemotherapy) pembrolizumab: 11.0 versus 8.8, nab-paclitaxel: 23.5 versus 15.0, paclitaxel: 19.0 versus 14.0, gemcitabine: 13.0 versus 14.0, and carboplatin: 13.0 versus 14.0)

There were 3 planned efficacy IAs and an FA for part 2 of the KEYNOTE-355 trial. The FA of the study (data cut-off date of June 15, 2021) was event and follow-up time driven and was to be conducted after approximately 500 OS events have been observed among all patients, or after approximately 23 months since last patient randomized, whichever occurred later. The FA of ORR results was conducted at IA1 and the FA of PFS was conducted at IA2.

The focus of this CADTH review is the FA, which is consistent with results from IA1 and IA2.

Efficacy

All efficacy results are reported for the subset of patients with PD-L1–positive tumours (CPS ≥ 10).

Overall Survival

At the FA data cut-off (June 15, 2021), KEYNOTE-355 met the success criterion for the primary hypothesis of OS in patients with locally recurrent inoperable or metastatic TNBC and PD-L1–positive tumours (CPS ≥ 10). The median OS was 23.0 months (95% CI, 19.0 to 26.3) in the pembrolizumab in combination with chemotherapy group and 16.1 months (95% CI, 12.6 to 18.8) in the placebo plus chemotherapy group. The HR for OS obtained between

pembrolizumab in combination with chemotherapy versus placebo plus chemotherapy was 0.73 (95% CI, 0.55 to 0.95; P = 0.0093). Overall, pembrolizumab in combination with chemotherapy demonstrated a statistically significant and clinically meaningful improvement in OS that represented a 27% reduction in the risk of death for patients with PD-L1–positive tumours (CPS ≥ 10).

Health-Related Quality of Life

The following questionnaires were used to assess HRQoL: the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the EORTC QLQ-Breast Module 23 (EORTC QLQ-BR23), and the EQ-5D visual analogue scale (EQ-5D VAS). Overall, there were no differences between groups in terms of HRQoL on any of the questionnaires between baseline and week 15.

Progression-Free Survival

At the IA2 data cut-off (December 11, 2019), the KEYNOTE-355 trial met the coprimary end point of PFS in patients with PD-L1–positive tumours (CPS ≥ 10). At IA2, median PFS was 9.7 months in the pembrolizumab in combination with chemotherapy group and 5.6 months in the placebo plus chemotherapy group. The HR for PFS was 0.65 (95% CI, 0.49 to 0.86; P = 0.0012). Based on the prespecified success criteria, pembrolizumab in combination with chemotherapy statistical significantly improved PFS compared with placebo plus chemotherapy in patients with tumours expressing a CPS of 10 or greater.

The findings on PFS from the FA were consistent with the results at IA2. At the FA data cut-off (June 15, 2021), a total of 144 (65.5%) PFS events had occurred in the pembrolizumab in combination with chemotherapy arm compared to 81 (78.6%) events in the placebo plus chemotherapy arm in patients with PD-L1–positive tumours with a CPS of 10 or greater. The HR for PFS at FA was 0.66 (95% CI, 0.50 to 0.88; P = 0.0018) in patients with a PD-L1 CPS of 10 or greater. Median PFS was 9.7 months (95% CI, 7.6 to 11.3) in the pembrolizumab in combination with chemotherapy group compared to 5.6 months (95% CI, 5.3 to 7.5) in the placebo plus chemotherapy group in patients with PD-L1–positive tumours with a CPS of 10 or greater. Overall, pembrolizumab in combination with chemotherapy continued to show a statistically significant improvement in PFS compared with placebo plus chemotherapy in patients with PD-L1–positive tumours (CPS ≥ 10).

Objective Response Rate

At the FA data cut-off, there were 116 (52.7%) objective responses (95% CI, 45.9 to 59.5%) in the pembrolizumab group compared to 42 (40.8%) objective responses (95% CI, 31.2 to 50.9%) in the placebo group in patients with a PD-L1 CPS of 10 or greater. The secondary hypotheses pertaining to ORR in all patients and in patients with a PD-L1 CPS of 1 or greater were tested at IA1 and not formally tested at the FA. ORR for patients with a PD-L1 CPS of 10 or greater was not included in the multiplicity strategy. These ORR results from the FA are consistent with the IA1 results.

Duration of Response

At the FA, the median DOR was greater in the pembrolizumab in combination with chemotherapy group at 12.8 months compared to the placebo plus chemotherapy group at 7.3 months in patients with a PD-L1 CPS of 10 or greater. Median time to response was 1.9 months in both groups. DOR results from the FA were consistent with the previously reported IA2 results and showed the sustained DOR benefit in the pembrolizumab in combination with chemotherapy group over a longer duration of follow-up. The proportion of patients with an

extended response at 6 months or more and 12 months or more by Kaplan-Meier estimation was 87.1% and 55.5% in the pembrolizumab in combination with chemotherapy group and 55.5% and 37.9% in the placebo plus chemotherapy group, respectively.

Harms

Overall, almost all patients in the pembrolizumab in combination with chemotherapy arm (99.6%) and in the placebo plus chemotherapy and placebo arm (98.2%) reported at least 1 AE by the June 15, 2021, data cut-off. AEs of grade 3 or higher were slightly more common in the pembrolizumab in combination with chemotherapy arm (77.9%) than in the placebo plus chemotherapy arm (73.7%). The most common AEs in both arms were neutropenia, decreased neutrophil count, anemia, thrombocytopenia, decreased white blood cell count, and leukopenia.

AEs of grade 3 to 5 reported in at least 5% of patients were also generally similar in both treatment arms, which included (for the pembrolizumab in combination with chemotherapy versus placebo plus chemotherapy arms), neutropenia (30.1% versus 30.2%), decreased neutrophil count (18% versus 20.3%, respectively), anemia (18% versus 16.4%, respectively), thrombocytopenia (11.2% versus 11.7%, respectively), and decreased white blood cell count (10.5% versus 10.3%, respectively). Overall, 3.0% and 1.8% of AEs resulted in death in the pembrolizumab in combination with chemotherapy and the placebo plus chemotherapy groups, respectively. AEs leading to discontinuation of any study intervention were higher in the pembrolizumab in combination with chemotherapy arm (10.7%) compared to the placebo plus chemotherapy arm (5.3%).

Notable harms were more common in the pembrolizumab in combination with chemotherapy arm compared to the placebo plus chemotherapy arm, except for infusion reactions. The most common notable harms in the pembrolizumab in combination with chemotherapy versus placebo plus chemotherapy group were hypothyroidism (15.8 versus 3.2%, respectively), hyperthyroidism (4.3% versus 1.1%, respectively), infusion reactions (3.7% versus 5.0%, respectively), and pneumonitis (2.5% versus 0, respectively).

Critical Appraisal

In KEYNOTE-355, the consistency between the interim results and final results helped strengthen the robustness of the findings at the FA. For example, PFS assessed at the FA was not formally tested based on the statistical hierarchy, yet the results were consistent with the results at IA2, in which the statistically significant result was demonstrated.

A potential concern in the KEYNOTE-355 study included the lack of stratification randomization conducted on patients with a PD-L1 CPS of 10 or greater or lower than 10, which was the primary focus of this reimbursement review (subpopulation of those whose tumours have a PD-L1 CPS of ≥ 10). This may have contributed to imbalances between the treatment arms, particularly potential unknown confounding covariates. In the Health Canada Reviewer Report, the same concern was raised and was addressed by the sponsor, who noted that an evaluation and sensitivity analysis of the potential for imbalance in the CPS of 10 or greater population was conducted. It was concluded that the impact of not having a CPS of 10 or greater as a stratification factor would be minimal, and the imbalances in baseline factors were limited and did not change the conclusion of the primary analysis. It was acknowledged in the Health Canada Reviewer Report that the sponsor's responses to this concern were deemed detailed and adequate. The HRQoL assessment were exploratory analyses; HRQoL results were reported up to week 15, though this time point might not

be able to capture an accurate picture of patients' experiences with pembrolizumab in combination with chemotherapy for a prolonged period of time. The assessment time point at week 15 was selected to ensure at least a 60% completion and 80% compliance with patient-reported outcome assessments to ensure validity of the longitudinal model of change in patient-reported outcome scores over time. Analyses performed on the patient-reported outcomes were noninferential.

The clinical experts consulted considered the inclusion and exclusion criteria of the KEYNOTE-355 study appropriate and the baseline and demographic characteristics to be generalizable to Canadian practice. The magnitude of benefit of pembrolizumab in patients who did not meet the inclusion criteria outlined in the KEYNOTE-355 study is uncertain. The choice of chemotherapy in the KEYNOTE-355 study was considered appropriate by the clinical experts consulted by CADTH, as was the duration of follow-up. The clinical experts noted that the concomitant medications allowed in the KEYNOTE-355 study were also commonly used in Canadian practice and were considered appropriate.

Indirect Treatment Comparison

Description and Methods of the Published Network Meta-Analysis

The sponsor-submitted indirect treatment comparison (ITC) conducted a systematic review and used a Bayesian network meta-analysis to evaluate the relative efficacy and safety of pembrolizumab in combination with chemotherapy compared to other treatments, including nab-paclitaxel or paclitaxel, atezolizumab plus nab-paclitaxel, bevacizumab plus paclitaxel, carboplatin, docetaxel, ixabepilone plus bevacizumab, bevacizumab plus nab-paclitaxel, and pembrolizumab plus nab-paclitaxel or paclitaxel for the first-line treatment of patients with previously untreated locally recurrent inoperable or metastatic TNBC. The efficacy outcomes of interest were PFS and OS.

Efficacy Results

The sponsor-submitted ITC reported that the results for OS favoured pembrolizumab in combination with chemotherapy over nab-paclitaxel or paclitaxel (HR = 0.54; 95% CrI, 0.36 to 0.82), carboplatin (HR = 0.36; 95% CrI, 0.19 to 0.68), and docetaxel (HR = 0.30; 95% CI, 0.17 to 0.55).

The sponsor-submitted ITC reported that the results for PFS favoured pembrolizumab in combination with chemotherapy over nab-paclitaxel or paclitaxel (HR = 0.51; 95% CI, 0.33 to 0.78). However, pembrolizumab in combination with chemotherapy was not favoured versus other comparators included in the ITC for PFS.

Critical Appraisal

Due to limited data availability, the sponsor-submitted ITC was not able to obtain and compare baseline patient characteristics between the included trials; it was also not able to estimate between-trial heterogeneity due to having only a small number of trials in the network. Consequentially, there is substantial uncertainty around the ITC results and firm conclusions cannot be drawn on the relative efficacy between pembrolizumab in combination with chemotherapy and relevant comparators aside from direct evidence provided by the KEYNOTE-355 study.

Other Relevant Evidence

No long-term extension studies or other relevant studies were included in the sponsor's submission to CADTH.

Conclusions

One pivotal study (KEYNOTE-355) and 1 sponsor-submitted ITC provided evidence for this CADTH review. The OS and PFS benefits observed in the KEYNOTE-355 trial with pembrolizumab in combination with chemotherapy versus placebo plus chemotherapy in patients with a PD-L1 CPS of 10 or greater were statistically significant, considered clinically meaningful by the clinical experts, and aligned with the outcomes important to patient groups. The secondary outcomes, ORR and DOR, were supportive of the observed OS and PFS results. There was no signal suggesting that the addition of pembrolizumab to chemotherapy resulted in a significant decrease in HRQoL from baseline to week 15. The submitted ITC compared the efficacy of pembrolizumab in combination with chemotherapy to other comparators and the results suggested that OS favoured pembrolizumab in combination with chemotherapy in the comparison to nab-paclitaxel or paclitaxel, carboplatin, and docetaxel. PFS favoured pembrolizumab in combination with chemotherapy in the comparison to nab-paclitaxel or paclitaxel but not to other treatments. However, no firm conclusions could be drawn from the ITC results based on several limitations. No new safety concerns were identified for the use of pembrolizumab in combination with chemotherapy for the treatment of locally recurrent inoperable or metastatic TNBC. The clinical experts stated that there is experience using pembrolizumab for other indications and oncologists are familiar with AEs due to pembrolizumab.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Partitioned survival model
Target population	Adults with locally recurrent inoperable or metastatic TNBC whose tumours expressed PD-L1 (CPS ≥ 10) and who have not received chemotherapy for recurrent inoperable or metastatic TNBC
Treatment	Pembrolizumab (200 mg every 3 weeks or 400 mg every 6 weeks until disease progression, unacceptable toxicity or up to 24 months or 35 doses for 200 mg or 18 doses for 400 mg, whichever is longer) in combination with chemotherapy (one of nab-paclitaxel, paclitaxel, or gemcitabine + carboplatin)
Submitted price	$4,400 per 100 mg/4 mL vial
Treatment cost	$11,733 per 28-day cycle. When in combination with chemotherapy, a 28-day cycle cost ranges from $14,107 to $17,133, depending on the chemotherapy used.
Comparator	Chemotherapy (1 of nab-paclitaxel, paclitaxel, or gemcitabine + carboplatin)
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs

Component	Description
Time horizon	Lifetime (20 years)
Key data source	KEYNOTE-355, a phase III randomized, placebo-controlled, double-blind trial, informed PFS, OS, time-on-treatment, and utility values
Submitted results	ICER = $175,414 per QALY (incremental costs = $124,946; QALYs = 0.71)
Key limitations	• The long-term clinical efficacy of pembrolizumab is uncertain. Approximately 37% of OS and 70% of PFS gains from pembrolizumab predicted in the model occur beyond the time frame of the KEYNOTE-355 trial, for which there is no observed data. • The sponsor modelled utilities based on how close a person was to death, an approach which is associated with uncertainty. It was unclear how the time points used to create time to death categories aligned with key clinical events like changes in treatment or disease progression. Furthermore, the sponsor used progression-based disease management costs, whereas the approach to health-state costs and utilities should be aligned. As such, this created uncertainty with whether the health benefits and costs have been adequately captured in the sponsor's model. • The sponsor adopted relative dose intensities to account for missed doses or treatment interruptions, which inappropriately reduced drug costs. • The distribution of chemotherapy, both in combination with pembrolizumab and alone, in the sponsor's base case does not reflect Canadian clinical practice.
CADTH reanalysis results	• CADTH made the following revisions to the sponsor's pharmacoeconomic model: reweighted the distribution of chemotherapy drugs to align with Canadian clinical practice, assumed a relative dose intensity of 100% for all treatments, and modelled health-state utilities based on disease progression status. • In the CADTH base case, compared with chemotherapy alone, pembrolizumab + chemotherapy was associated with an ICER of $198,317 per QALY gained (incremental costs = $142,093; incremental QALYs = 0.72). • A price reduction of at least 81% would be needed for pembrolizumab to be cost-effective at a WTP threshold of $50,000 per QALY gained.

CPS = combined positive score; ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival; PD-L1 = programmed cell death-ligand 1; PFS = progression-free survival; QALY = quality-adjusted life-year; WTP = willingness to pay.

Budget Impact

CADTH identified the following key limitations with the sponsor's analysis: The use of relative dose intensity to estimate actual drug costs is not appropriate; the weighted cost of chemotherapy, market share of comparators at baseline, and market displacement assumptions are not aligned with clinical practice; the market share and uptake of pembrolizumab is underestimated; the PD-L1 testing uptake is uncertain and its cost is not relevant to adopted perspective; the submitted budget impact model has limited transparency and flexibility.

CADTH reanalysis included adopting a relative dose intensity of 100%, aligning market share and displacement of comparators to reflect Canadian clinical practice, excluding PD-L1 testing costs, revising market share displacement assumptions, assuming a rapid increase in market share of pembrolizumab, and increasing the market share of pembrolizumab. Based on the CADTH reanalysis, the 3-year budget impact to the public drug plans of introducing pembrolizumab for adult patients with locally recurrent unresectable or metastatic TNBC with PD-L1 (CPS ≥ 10) expression, who have not received prior chemotherapy, is expected to be $33,132,736 (year 1 = $4,346,142; year 2 = $12,528,377; year 3 = $16,258,217).

CADTH

pERC Information

Members of the Committee

Dr. Maureen Trudeau (Chair), Mr. Daryl Bell, Dr. Jennifer Bell, Dr. Matthew Cheung; Dr. Winson Cheung, Dr. Michael Crump, Dr. Leela John, Dr. Christian Kollmannsberger, Mr. Cameron Lane, Dr. Christopher Longo, Dr. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: November 9, 2022

Regrets: Two expert committee members did not attend

Conflicts of interest: None