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CADTH Reimbursement Recommendation

Pembrolizumab (Keytruda)

Indication: For the treatment of adult patients with high-risk early-stage triple-negative breast cancer in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.

Sponsor: Merck Canada Inc.

Final recommendation: Reimburse with conditions

CADTH

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Summary

CADTH

What is the CADTH Reimbursement Recommendation for Keytruda?

CADTH recommends that Keytruda be reimbursed by public drug plans for the treatment of adult patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery only if certain conditions are met.

Which Patients Are Eligible for Coverage?

Keytruda should only be covered for adult (18 years of age or older) patients with early-stage TNBC who are at high risk for breast cancer coming back.

What Are the Conditions for Reimbursement?

Keytruda should only be used with chemotherapy before surgery, then alone after surgery. Keytruda should only be reimbursed if: prescribed by a specialist, if the patient is in relatively good health (i.e., have a good performance status, as determined by a specialist), the patient has not received prior systemic therapy for non-metastatic TNBC; and the patient has no clinical contraindication to immunotherapy.

Why Did CADTH Make This Recommendation?

- Evidence from a clinical trial demonstrated that cancer did not get worse or come back for patients who were treated with Keytruda with chemotherapy before surgery, then alone after surgery.
- Based on CADTH's assessment of the health economic evidence, Keytruda in combination with neoadjuvant chemotherapy and as adjuvant monotherapy does not represent good value to the health care system at the publicly listed price. A price reduction is therefore required.
- Over 3 years, Keytruda is expected to increase drug costs to the public plans by more than $138 million.

Additional Information

What Is TNBC?

Breast cancer can be classified by proteins (receptors) expressed by the cancer cell. Some breast cancers do not have estrogen and progesterone hormone receptors and do not have much human epidermal growth factor receptor 2 (HER2). This is called triple-negative breast cancer (TNBC).

Unmet Needs in Patients With TNBC

The intention of surgery for early-stage breast cancer is to cure patients. However, in some cases, for patients who are at high risk for breast cancer coming back, cancer may come back or worsen. Therefore, there is a need for treatment options that can prevent cancer from coming back or worsening for these patients.

How Much Does the Keytruda Neoadjuvant and Adjuvant Treatment Cost?

Treatment with Keytruda in the neoadjuvant and adjuvant setting is expected to cost approximately $11,733 per 28 days (based on a fixed dose of 200 mg every 21 days).

Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that pembrolizumab be reimbursed for the treatment of adult patients with high-risk early-stage triple-negative breast cancer (TNBC) in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

One phase III, randomized, double-blind, multi-centre, placebo-controlled study (KEYNOTE-522) demonstrated that the addition of pembrolizumab to neoadjuvant chemotherapy followed by adjuvant pembrolizumab monotherapy led to clinically meaningful improvements in event-free survival (EFS) compared to neoadjuvant chemotherapy in TNBC (EFS hazard ratio [HR] = 0.63; 95% CI, 0.48 to 0.82; P = 0.0003093). Although health-related quality of life (HRQoL) was an exploratory analysis in the KEYNOTE-522 study, results suggested no difference between the 2 groups. Pembrolizumab was associated with a manageable toxicity profile.

Pembrolizumab addresses unmet needs for this patient population who have a poor prognosis and high risk of disease recurrence. Patients expressed a need for access to effective treatments that reduce the risk of disease recurrence, delay disease progression, control disease, improve quality of life, and reduce the severity of side effects. Given the totality of the evidence, pERC concluded that pembrolizumab met some of the needs identified by patients in terms of reducing the risk of disease recurrence, controlling disease, and providing a manageable toxicity profile.

Using the sponsor-submitted price for pembrolizumab and publicly listed prices for all other drug costs, the incremental cost-effectiveness ratio (ICER) for pembrolizumab in combination with neoadjuvant chemotherapy and as adjuvant monotherapy, using a fixed-based dose, was $81,408 per quality-adjusted life-year (QALY) compared with chemotherapy as neoadjuvant therapy alone. At this ICER, pembrolizumab is not cost-effective at a $50,000 per QALY willingness to pay (WTP) threshold in the Health Canada indicated population. A reduction in price is therefore required for pembrolizumab to be considered cost-effective at a $50,000 per QALY threshold. If used as a weight-based dose, the ICER decreases to $67,657 per QALY. This analysis is associated with additional uncertainty given that the treatment was not evaluated as a weight-based dose, so this may influence efficacy, compliance, and adverse events. CADTH notes these estimates are contingent on an overall survival benefit being realized.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with pembrolizumab should be initiated only in non- metastatic estrogen	As per KEYNOTE-522 study inclusion criteria and clinical expert opinion.	—

Reimbursement condition	Reason	Implementation guidance
receptor (ER) negative, PR negative, HER2 negative breast cancer patients who are: 1.1. suitable for neoadjuvant chemotherapy 1.2. clinically node positive or cT1c, N1-2 or T2-4, N0-2 [per American Joint Committee on Cancer].		
2. Patients must have all of the following: 2.1. good performance status 2.2. no prior systemic therapy for non-metastatic TNBC 2.3. no clinical contraindication to immunotherapy.	As per KEYNOTE-522 study inclusion criteria and clinical expert opinion.	—
Renewal		
3. To continue in the adjuvant setting, pembrolizumab should be renewed for patients whose treatment is tolerable and whose disease has not progressed before surgery.	As per KEYNOTE-522 study.	—
4. Patients should be assessed for evidence of disease progression as per standard practice.	As per KEYNOTE-522 study and clinical expert opinion.	—
Discontinuation		
5. Treatment with pembrolizumab should be discontinued upon the occurrence of any of the following: 5.1. clinical disease progression 5.2. unacceptable toxicity.	As per KEYNOTE-522 study and clinical expert opinion.	—
6. The maximum duration of reimbursement in the neoadjuvant and adjuvant setting is for up to 1 year or 17 cycles in patients without disease progression.	As per KEYNOTE-522 study, the total duration of pembrolizumab-based therapy in KEYNOTE-522 was 1 year (combined 17 doses including 8 cycles in neoadjuvant setting and 9 cycles in adjuvant setting).	—
Prescribing		
7. Pembrolizumab should only be prescribed by clinicians with expertise and experience in treating breast cancer.	To ensure pembrolizumab is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	—
8. Pembrolizumab should be prescribed in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery.	Pembrolizumab was administered in combination with chemotherapy as neoadjuvant treatment.	Based on clinical expert opinion, any anthracycline and taxane-based protocol theoretically will be appropriate. If a patient had contraindications to anthracycline,

Reimbursement condition	Reason	Implementation guidance
		a taxane-based chemotherapy protocol could be used.
Pricing		
9. A reduction in price	The ICER for pembrolizumab using a fixed-based dose in the neoadjuvant/adjuvant setting is $81,408 when compared with chemotherapy as neoadjuvant therapy alone. A price reduction of 36% would be required for pembrolizumab to be able to achieve an ICER of $50,000 per QALY. If used as a weight-based dose, the ICER decreases to $67,657 per QALY. A price reduction of 24% would be required for pembrolizumab to achieve an ICER of $50,000 per QALY in this scenario analysis. Substantially higher price reductions would be required if no overall survival benefit is realized.	—
Feasibility of adoption		
10. The feasibility of adoption of pembrolizumab must be addressed	At the submitted price, the budget impact of pembrolizumab is expected to be greater than $40 million per year in year 2 onwards. The total budget impact for all eligible patients diagnosed in years 1 to 3 could exceed $200 million.	—

ER = estrogen receptor; ICER = incremental cost-effectiveness ratio; PR = progesterone receptor; QALY = quality-adjusted life-year; TNBC = triple-negative breast cancer.

Discussion Points

- pERC discussed the acceptability of pathologic complete response (pCR) and EFS as outcomes and ultimately their impact on overall survival (OS). pERC acknowledged that data immaturity may lead to uncertainty as the median OS and EFS could not be estimated at the fourth interim analysis. pERC agreed with the clinical experts that clinically meaningful improvement in EFS was observed and that there was a pCR advantage with pembrolizumab in the KEYNOTE-522 study.
- pERC acknowledged that standard of care now incorporates adjuvant capecitabine, which was not administered in the KEYNOTE-522 study, and recognized that clinicians may wish to prescribe capecitabine with pembrolizumab in the adjuvant setting. pERC cannot comment on the suitability of capecitabine with this therapy in the adjuvant setting as there is no available evidence to support this combination.
- pERC discussed the dose scheduling of chemotherapy and acknowledged the variations of scheduling in centres across Canada. As a result, pERC expressed that any taxane or anthracycline regimen is acceptable in combination with pembrolizumab in the neoadjuvant setting.

Background

Breast cancer is the most frequently diagnosed cancer in females in Canada, with projected estimates of about 27,700 new cases in 2021. It was estimated that 5,400 females would die from the disease in the same year. Fewer males are affected, with an estimated 290 new cases and 55 related deaths in 2021. TNBC is an invasive form of breast cancer (BC) affecting 10% to 20% of patients. It is most common in females under 40 years of age, African-American females, and females with a BRCA-1 mutation. It is well established that patients with the BRCA-1 mutation are more likely to develop TNBC compared to patients with other mutations. TNBC is distinguished by the absence of an estrogen receptor (ER), progesterone receptor, and no expression of the HER2 gene. The clinician groups consulted highlighted that patients with TNBC have a higher risk of recurrence and death compared to other types of BC. The clinician groups noted that patients with a pathologic complete response (pCR) have on average a 5-year disease-free survival of 85% to 90% for localized disease, while those with no pCR have a higher recurrence rate. Most patients with BC, including TNBC, present with no symptoms at early stages of the disease. Breast changes such as firm or hard lumps, a lump in the armpit, changes in breast size and shape, changes to the nipple, and discharge from the nipples are some common symptoms reported. Additional symptoms such as bone pain, weight loss, nausea, appetite loss, shortness of breath, cough, headache, double vision, and muscle weakness may manifest with tumour size increase or spread to other organs.

The standard approach for early-stage TNBC is neoadjuvant chemotherapy for cT1c or greater tumours. According to the experts consulted, this approach allows for clinical downstaging (better chance of clear margins, breast conservation surgery, and potential avoidance of completion axillary node dissection), and prognostication (patients achieving pCR having excellent long-term outcomes). Several neoadjuvant chemotherapy (NACT) regimens are available in practice. The clinical experts and clinician groups highlighted that the sequential use of anthracycline-taxane (or taxane-anthracycline) combination chemotherapy (standard dose every 3 weeks or every 2 weeks dose-dense) was standard of practice across jurisdictions in Canada. The clinical experts consulted also noted that dose-dense AC (doxorubicin, cyclophosphamide) every 2 weeks for 4 cycles followed by paclitaxel every 2 weeks for 4 cycles, with carboplatin often added, is the preferred NACT regimen in Canadian practice.

Pembrolizumab underwent a priority review at Health Canada and obtained a Notice of Compliance (NOC) on April 13, 2022, for the treatment of adult patients with high-risk early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery. Pembrolizumab is an immunoglobulin G4 (IgG4) monoclonal antibody against the programmed cell death protein 1 (PD-1). The Health Canada recommended dose of pembrolizumab for adults with early-stage TNBC is either 200 mg intravenously (IV) every 3 weeks or 400 mg IV every 6 weeks, for a total of 1 year of treatment. It is recommended that patients be treated with neoadjuvant pembrolizumab in combination with NACT for 8 doses of 200 mg IV every 3 weeks or 4 doses of 400 mg IV every 6 weeks, or until disease progression that precludes definitive surgery or unacceptable toxicity.

Sources of Information Used by the Committee

To make their recommendation, the Committee considered the following information:

- A review of 1 phase III randomized controlled trial in adult patients with early-stage TNBC (previously untreated, locally advanced non-metastatic TNBC)
- A review of 1 published indirect treatment comparison (ITC) identified by CADTH
- Patient perspectives gathered by 2 patient groups, the Canadian Breast Cancer Network (CBCN) and Rethink Breast Cancer (Rethink)
- Input from public drug plans and cancer agencies that participate in the CADTH review process
- Two clinical specialists with expertise in diagnosing and treating patients with TNBC
- Input from 2 clinician groups, the Ontario Health — Cancer Care Ontario (OH-CCO) Breast Cancer Drug Advisory Committee and the Ottawa Hospital Cancer Centre (TOHCC) Breast Disease Site Group
- A review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

Patient Input

Two patient groups, CBCN and Rethink Breast Cancer (Rethink), provided input for this review. The CBCN patient input was based on an online survey (CBCN's 2017 Lived Experience Breast Cancer Patient Survey), telephone interviews, and a literature review of current studies and grey literature. The Rethink input was based on general observations and insights gathered through various ongoing initiatives including patients' blogs, virtual support groups, working groups, and patient advisory boards, as well as telephone interviews with 2 patients and a caregiver to 1 patient, and a focus group with 7 patients from the TNBC Working Group.

Respondents from both patient groups highlighted that TNBC is a rare subtype of BC which is relatively more aggressive and has a higher rate of recurrence and poorer prognosis compared to other BCs. Respondents in both groups noted lack of access to effective treatment as an unmet need. Respondents from CBCN highlighted the need for treatment options that will reduce the risk of disease recurrence, delay disease progression, control disease, improve quality of life, and reduce severity of side effects from treatments. Respondents from Rethink indicated that they are willing to tolerate additional side effects and reduced quality of life in exchange for a treatment that can control TNBC.

Respondents in both patient groups who received pembrolizumab stated that the treatment was effective and improved their quality of life, with tolerable or minimal side effects. The most common adverse events (AEs) reported by patients that had experience with pembrolizumab included fatigue, colitis, and diarrhea. Respondents in both groups noted challenges in differentiating whether the side effects were due to pembrolizumab, or chemotherapy given that they received these treatments concurrently. One patient in the Rethink group reported that pembrolizumab had effectively reduced their tumour size but that they had experienced AEs such as hives, skin conditions, and thyroid issues, while other patients noted experiencing minimal side effects with pembrolizumab.

One caregiver mentioned that, overall, pembrolizumab treatment had been a positive experience, with side effects being "somewhat of a challenge." Patient respondents that had received pembrolizumab indicated that they would recommend pembrolizumab to other patients with TNBC.

Clinician Input

Input From Clinical Experts Consulted by CADTH

pCR, OS, and EFS were considered clinically meaningful outcomes by the clinical experts consulted during the CADTH review. The experts highlighted that the treatment goal for high-risk early-stage TNBC is to reduce the risk of BC recurrence and improve survival in patients. The clinical experts stated that pCR is associated with improvement in disease-free survival in TNBC, not all patients respond to current treatment options, and pCR rates are approximately 50% in patients receiving chemotherapy. The clinical experts indicated that staging approaches and routine breast tumour biopsy characterization of estrogen receptor (ER), progesterone receptor (PR), and HER2 (ER/PR/HER2) status are currently in place to identify patients in Canada.

The experts generally agreed that the use of immunotherapy will cause a paradigm shift in practice for the treatment of TNBC. The clinical experts advised that patients who meet the inclusion criteria outlined in the KEYNOTE-522 study will be best suited for treatment. In the opinion of the experts, patients with pre-existing serious autoimmune diseases may not be eligible for this regimen. The experts added that patients with T1a/T1bN0 (node 0) are also not eligible, due to the early-stage disease (regardless of coexisting autoimmune conditions), as these patients will likely have surgery upfront. In addition, the experts indicated that patients with less serious autoimmune conditions and patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 should weigh the pros and cons of the new regimen while considering older standard options in lower risk TNBC cases. The experts highlighted that there are currently no biomarkers to assess treatment response early on in patients with TNBC. The experts noted that in practice settings, patients will undergo a physical exam before each cycle in the neoadjuvant setting and imaging scans may be used to rule out disease progression and review the patient's fitness for surgery.

According to the clinical experts, disease progression (tumour enlargement unless pseudo-progression is suspected) and the occurrence of AEs — particularly autoimmune toxicities (any grade 4 treatment-related AE or grade 2 to 3 AE not improving to grade 1 with supportive care or dose modifications) — would be considered when deciding treatment discontinuation.

Clinician Group Input

Two clinician group inputs were provided, 1 from the OH-CCO Breast Cancer Drug Advisory Committee (based on input from 2 clinicians) and 1 from the TOHCC Breast Disease Site Group (based on input from 15 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 (PDRP) and the Systemic Treatment Program. The TOHCC aims to provide each person affected by cancer with world-class care, exceptional service, and compassion.

Both clinician groups identified NACT followed by adjuvant chemotherapy as the current Canadian treatment paradigm for patients with TNBC. Both groups considered achieving long-term cure, improved OS, EFS, and delaying disease progression as important treatment

goals. Both groups identified the lack of effective treatment options for patients with TNBC, limited pCR rates, and highest recurrence and death rates in patients with TNBC compared to other types of breast cancer as unmet needs. Both groups anticipated that pembrolizumab will fit into the current treatment paradigm as a new treatment standard for TNBC. Both groups agreed that it would not be appropriate to recommend that patients with TNBC try other treatments before initiating pembrolizumab. Both clinician groups considered tumour shrinkage (clinically or radiographically), improvement in pCR, and EFS as clinically meaningful outcomes when assessing treatment response.

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

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may impact their ability to implement a recommendation.

Table 2: Responses to Questions From the Drug Programs

Implementation issues	Response
Relevant comparators	
KEYNOTE-522 used chemotherapy with paclitaxel-carboplatin for 4 cycles (12 weeks), then doxorubicin-cyclophosphamide for 4 cycles (12 weeks). This regimen is one of many chemotherapy options available for neoadjuvant chemotherapy. Most chemotherapy regimens available in Canada for neoadjuvant use for early-stage TNBC are anthracycline- and taxane-based. What chemotherapy regimens are appropriate for neoadjuvant use in combination with pembrolizumab?	pERC acknowledged the clinical experts' response and agreed. pERC expressed that any taxane or anthracycline regimen is acceptable for the neoadjuvant portion of this therapy. According to the clinical experts, any anthracycline- and taxane-based protocol theoretically will be appropriate. The expert did note that dose-dense (dd) protocols have evidence supporting greater efficacy in TNBC and therefore improved survival. In the opinion of the experts, if a patient had contraindications to anthracycline, a taxane-based chemotherapy protocol could be used. The clinical experts highlighted that most clinicians will likely use the anthracycline cyclophosphamide combined with taxane (ACT) regimen. The experts noted that oncologists may switch the sequence to taxane and carboplatin first, and then anthracycline to correspond to administration with KEYNOTE-522. According to the experts, some clinicians may elect to give the ACT in a dd manner. Another alternative could be weekly paclitaxel with carboplatin for 12 weeks, then anthracycline with cyclophosphamide (AC), as AC with weekly paclitaxel is superior to ACT. The clinical experts noted that although epirubicin and docetaxel could be administered interchangeably with doxorubicin and paclitaxel, it is not clear if the protocol could be interchanged and offer the same pCR rates.
Many chemotherapy regimens for neoadjuvant chemotherapy use dd scheduling (in cycles occurring every 14 days for anthracycline-based treatments, instead of every 21 days). • KEYNOTE-522 used dosing every 21 days for anthracycline-based cycles. Is the 21-day cycle length for	pERC acknowledged the clinical experts' response and agreed that it may be reasonable to consider dd schedules as per physician discretion. The clinical experts mentioned that they suspect most clinicians will attempt to use dd schedule administration when possible, given

Implementation issues	Response
chemotherapy appropriate? • Will dd schedules be considered in combination with pembrolizumab, and in which clinical circumstances?	the evidence of better outcomes in TNBC with dd as opposed to treatment occurring every 3 weeks. It is worth acknowledging that G-CSF was permitted as per KEYNOTE-522 trial protocol to treat neutropenia at the investigator's discretion. It is not known how many patients were treated with G-CSF and whether any of those patients developed pneumonitis. One patient in the pembrolizumab group died of pneumonitis.
KEYNOTE-522 allowed for carboplatin dosing schedules either weekly or every 3 weeks. The pathologic complete response rate was higher in the patient group receiving weekly carboplatin dosing. Which dosing schedule of carboplatin is most appropriate for this combination (every 3 weeks vs. weekly)?	pERC agreed with the clinical experts that both dosing schedules are appropriate. The clinical experts noted that, in practice, a weekly schedule will be easier to implement as they can use dd AC and then switch to weekly paclitaxel with weekly carboplatin. The experts also noted that the sequence is better tolerated by patients, and it is easier to identify neuropathy earlier to adjust therapy. According to the clinical experts, both dosing schedules are appropriate; however, the preference should be for weekly administration given the higher pCR rate, with the option of administration every 3 weeks for medical reasons if weekly administration is not possible.
Patients in KEYNOTE-522 were not permitted to have capecitabine maintenance following surgery. • Is there clinical evidence to inform the relative efficacy and safety of adjuvant capecitabine vs. adjuvant pembrolizumab after neoadjuvant chemotherapy in this patient population? • Is there clinical evidence to inform the combination of capecitabine with pembrolizumab in the adjuvant setting for this patient population?	pERC acknowledged that standard of care now incorporates adjuvant capecitabine; however, there are no available data to inform the relative efficacy and safety of adjuvant capecitabine vs. adjuvant pembrolizumab after neoadjuvant chemotherapy, nor for the combination of capecitabine with pembrolizumab in the adjuvant setting for this patient population. The clinical experts noted that, unfortunately, the major gap is data availability. The clinical experts noted that it is unclear what should be done (i.e., no capecitabine at all, even if there is no pCR; or attempt it with pembrolizumab; or stop pembrolizumab and switch to capecitabine). The clinical experts highlight that similar issues exist with adjuvant olaparib.
Considerations for initiation of therapy	
KEYNOTE-522 enrolled patients with untreated, non-metastatic TNBC (cT1c, N1-2 or T2-4, N0-2 per American Joint Committee on Cancer [AJCC]) independent of PD-L1 status. • Is the staging included in KEYNOTE-522 appropriate for use of pembrolizumab in the neoadjuvant setting for TNBC in clinical practice? • Is PD-L1 status required to be eligible for pembrolizumab in combination with neoadjuvant chemotherapy for early-stage TNBC?	pERC agreed with the clinical experts that the staging in KEYNOTE-522 is appropriate. The clinical experts also noted that PD-L1 status is not required for neoadjuvant therapy with pembrolizumab and chemotherapy.
KEYNOTE-522 did not include patients with stage I disease and triple-negative phenotype. • Is there potential for indication creep to earlier clinical stages of TNBC? • With regard to treatment selection in this patient	pERC agreed that indication creep is possible. pERC also noted that pT1cN0 patients are not included in the Health Canada indication. According to the experts, the clinical stage of the disease is the biggest driver of treatment selection. The clinical experts also noted

Implementation issues	Response
population, what is the biggest driver: is it the triple-negative phenotype or clinical stage?	that T1a/b node-negative tumours are usually resected upfront, even if triple-negative.
Considerations for continuation or renewal of therapy	
Total duration of pembrolizumab-based therapy in KEYNOTE-522 was one year (combined 17 doses including 8 cycles in neoadjuvant setting and 9 cycles in adjuvant setting). Pembrolizumab was permitted to be administered concurrently with any adjuvant radiation therapy or could be delayed until completion of radiation therapy. • For patients who may have a delay between completion of chemotherapy and access to surgery, should pembrolizumab be continued every 3 weeks until surgery (to complete a total of 17 doses combined from either the neoadjuvant or adjuvant phase)? • For patients who may require delays in pembrolizumab doses (e.g., in post-operative recovery, holding pembrolizumab therapy during radiation), is it reasonable to complete the total of 17 doses beyond a duration of 12 sequential calendar months? Is there an appropriate time frame within which all 17 doses should be completed?	pERC agreed with the clinical experts that if there is a delay for surgery, it is reasonable to continue single-agent pembrolizumab until surgery. As noted by the clinical experts, it will likely be applicable on a case-by-case basis, although most of the time, it will be reasonable to resume therapy for a total of 17 doses. According to the clinical experts, if there are extenuating delays, they would consider stopping therapy early. The clinical experts noted that there are no data to guide the decision-making; rather, looking at the clinical situation of the patient will guide the decision. For example, it might be worthwhile to review guidelines and efficacy in other solid tumours that use adjuvant pembrolizumab for their practice recommendations. pERC agreed with the clinical experts that it would be reasonable to resume therapy for a total of 17 doses.
Considerations for prescribing of therapy	
Pembrolizumab dosing in KEYNOTE-522 was 200 mg intravenously every 21 days for 17 doses. • If funded, in line with other indications for pembrolizumab, jurisdictions would implement a weight-based dose of 2 mg/kg (up to a cap of 200 mg). Other indications for pembrolizumab use extended dosing intervals of every 6 weeks (4 mg/kg up to a 400 mg cap). • Is a dosing interval of every 6 weeks for pembrolizumab appropriate for early-stage TNBC?	pERC agreed with the clinical experts that this approach seemed reasonable, given the clear interchangeable use in dosing for other tumour sites.
Generalizability	
Should patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 2 or greater be eligible for pembrolizumab in this indication?	pERC acknowledged the clinical experts' response and agreed that patients with good performance status should be eligible for pembrolizumab. The clinical experts noted that they would not offer pembrolizumab to patients with an ECOG PS of 3 or greater. An ECOG PS of 2 might be reasonable; however, other comorbidities would also have to be taken into consideration.
Patients on active treatment with a time-limited opportunity to add to pembrolizumab: Should patients currently receiving neoadjuvant chemotherapy in early-stage TNBC be eligible to have pembrolizumab added?	pERC agreed that a time-limited opportunity to add pembrolizumab should be available. The clinical experts generally agreed with this approach. However, the experts noted that if patients have completed neoadjuvant therapy, they would not offer pembrolizumab as a single agent in the adjuvant setting.

AC = anthracycline cyclophosphamide; ACT = anthracycline plus cyclophosphamide plus taxane; AJCC = American Joint Committee on Cancer; dd = dose dense; ECOG PS = Eastern Cooperative Oncology Group performance status; G-CSF = granulocyte colony-stimulating factor; pCR = pathologic complete response; PD-L1 = Programmed Death Ligand 1; t = taxane; TNBC = triple-negative breast cancer.

Clinical Evidence

Pivotal Study

Description of Study

KEYNOTE-522 is an ongoing, phase III, randomized, multi-centre, double-blind, placebo-controlled trial. The primary objective of KEYNOTE-522 was to evaluate pembrolizumab plus chemotherapy as neoadjuvant therapy followed by continued pembrolizumab monotherapy as adjuvant therapy, compared with placebo plus chemotherapy as neoadjuvant therapy followed by continued placebo as adjuvant therapy for patients with high-risk, early-stage TNBC. The study was initiated in March 2017 and has 194 participating centres across 21 countries in North America (7 centres in Canada), South America, Europe, Asia, and Australia.

Enrolled patients were male or female; 18 years of age and older; newly diagnosed; had a locally advanced, centrally confirmed TNBC (as defined by the most recent American Society of Clinical Oncology [ASCO]/College of American Pathologists [CAP] guidelines); were previously untreated; and had a locally advanced non-metastatic (M0) TNBC as per the current American Joint Committee on Cancer (AJCC) staging criteria for breast cancer, assessed by an investigator based on radiological and/or clinical assessment (T1c, N1-N2; T2-T4d, N0-N2).

Pathologic complete response using the ypT0/Tis ypN0 definition (assessed by a local pathologist) and EFS (assessed by an investigator) were co-primary outcomes investigated in the KEYNOTE-522 trial. OS, safety and tolerability, and HRQoL (using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 items [EORTC QLQ-C30], European Organization for Research and Treatment of Cancer Breast Cancer Specific Quality of Life Questionnaire 23 items [EORTC QLQ-BR23], and EQ-5D-5L questionnaires) were other secondary and exploratory outcomes investigated.

Patients were randomized in a 2:1 ratio based on 3 stratification factors: nodal status (positive versus negative), tumour size (T1/T2 versus T3/T4), and choice of carboplatin regimen (every 3 weeks or weekly).

By the fourth interim analysis (IA4) data cut-off (March 23, 2021), 1,608 patients had been screened and 1,174 randomized to either of the 2 trial arms. In total, 784 patients received pembrolizumab plus chemotherapy treatment and 390 patients received placebo plus chemotherapy. The majority of the patients enrolled were female (1 male enrolled), younger than 65 years of age, White, premenopausal, and had an ECOG PS of 0. More than 80% of patients were PD-L1 positive. In the neoadjuvant phase, more patients in the pembrolizumab plus chemotherapy arm (24.2%) had discontinued the study intervention compared to the placebo plus chemotherapy arm (14.9%). In the adjuvant phase, the most common reason for discontinuation was AEs (5.4%) in the pembrolizumab group and relapse or recurrence (4.6%) and withdrawal by participant (4.4%) in the placebo group.

Efficacy

Overall Survival

By the IA4 data cut-off (March 23, 2021), 135 out of 297 prespecified events had occurred, representing approximately 45% of the information fraction for OS for the final analyses. The median OS was not estimable, and the HR obtained between pembrolizumab plus

chemotherapy and pembrolizumab versus placebo plus chemotherapy and placebo was 0.72 (95% CI, 0.51 to 1.02; P value [1-sided] = 0.0321377).

Pathologic Complete Response Rate (Using ypT0/Tis ypN0)

At the IA1 data cut-off (September 24, 2018), the pCR rate was 64.8% (95% CI, 59.9% to 69.5%) in patients receiving pembrolizumab plus chemotherapy in the neoadjuvant phase and 51.2% (95% CI, 44.1% to 58.3%) for patients receiving placebo plus chemotherapy. At IA2 (April 24, 2019), the treatment difference in pCR rate (pembrolizumab plus chemotherapy versus placebo plus chemotherapy) was 9.2% (95% CI, 2.8% to 15.6%) with a P value of 0.00221. The pCR rate for pembrolizumab plus chemotherapy was 64.0% (95% CI, 60.2% to 67.6%) compared to 54.7% (95% CI, 49.1% to 60.1%) for placebo plus chemotherapy at the neoadjuvant phase. At IA4 (March 23, 2021), the pCR rate in the patients receiving pembrolizumab plus chemotherapy was 63% (95% CI, 59.5% to 66.4%) in the neoadjuvant phase and in patients receiving placebo plus chemotherapy in the neoadjuvant phase, the pCR rate was 55% (95% CI, 50.6% to 60.6%). Of note, pCR was not formally tested at IA4.

Event-Free Survival

At the IA4 data cut-off (March 23, 2021), the median EFS was not estimable in both study arms. The EFS HR between the 2 arms was 0.63 (95% CI, 0.48 to 0.82; P value [1-sided] = 0.0003093). The findings were consistent with data observed across interim analyses (at IA2, EFS HR values were 0.63 [95% CI, 0.43 to 0.93]; at IA3, EFS HR was 0.65 [95% CI, 0.48 to 0.88]). Five prespecified sensitivity analyses were conducted for EFS in the intention-to-treat (ITT) population. The results of the sensitivity analyses were consistent with the primary analysis (sensitivity analysis 1: EFS HR was 0.64 [95% CI, 0.48 to 0.84]; sensitivity analysis 2: EFS HR was 0.63 [95% CI, 0.48 to 0.82]; sensitivity analysis 3: EFS HR was 0.65 [95% CI, 0.50 to 0.85]; sensitivity analysis 4: EFS HR was 0.63 [95% CI, 0.48 to 0.84]; sensitivity analysis 5: EFS HR was 0.63 [95% CI, 0.48 to 0.82]).

Health-Related Quality of Life

Of note, multiplicity adjustments for type I error rate were not conducted for HRQoL outcomes, and P values were nominal. The findings were considered exploratory.

EORTC QLQ-C30 Questionnaire

Neoadjuvant Phase

Compliance rates in the neoadjuvant phase were similar at baseline for EORTC QLQ-C30 in both the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms among all patients (92.0% versus 95.8%). After 21 weeks of follow-up in the neoadjuvant phase, the completion rate among all patients was 80.7% versus 80.7% in the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms, respectively. The mean change from baseline in global health status/QoL score was −11.24 (95% CI, −12.82 to −9.66) versus −10.20 (95% CI, −12.30 to −8.10) in the pembrolizumab plus chemotherapy and pembrolizumab versus placebo plus chemotherapy and placebo arms, respectively, at the IA4 data cut-off (March 23, 2021). Physical functioning scale difference in least squares (LS) mean scores in patients receiving pembrolizumab plus chemotherapy treatment compared to placebo plus chemotherapy treatment was −2.85 (95% CI, −5.11 to −0.60). The LS mean difference in change from baseline between groups for global health status/QoL score and functional scores was −1.04 (95% CI, −3.46 to 1.38) and −2.85 (95% CI, −5.11 to −0.60), respectively. The LS mean difference between groups for emotional functioning was −0.69 (95% CI, −3.13 to 1.75).

Adjuvant Phase

Compliance rates in the adjuvant phase were similar at baseline for EORTC QLQ-C30 in both the pembrolizumab and placebo arms among all participants (90.7% versus 91.9%) at the March 23, 2021 data cut-off. After 24 weeks of follow-up in the adjuvant phase, the compliance rate among patients was 82.4% versus 80.8% in the pembrolizumab and placebo arms. Scores obtained in the different subscales were as follows: global health status/ QoL (mean change from baseline: 2.47 [95% CI, 1.05 to 3.88] versus 2.88 [95% CI, 1.05 to 4.71]); physical functioning (mean change from baseline: 1.60 [95% CI, 0.46 to 2.75] versus 3.18 [95% CI, 1.70 to 4.66]); and emotional functioning scales (mean change from baseline: −1.53 [95% CI, −3.03 to −0.03] versus −0.92 [95% CI, −2.88 to 1.04] in the pembrolizumab plus chemotherapy and pembrolizumab arm and placebo plus chemotherapy and placebo arm, respectively, at the IA4 data cut-off (March 23, 2021). The LS mean difference between groups for global health status/QoL score, physical functioning, and emotional functioning was −0.41 (95% CI, −2.60 to 1.77), −1.57 (95% CI, −3.36 to 0.21), and −0.60 (95% CI, −2.99 to 1.79), respectively.

EORTC QLQ-BR23 Questionnaire

Neoadjuvant Phase

Compliance rates in the neoadjuvant phase were similar at baseline for EORTC QLQ-BR23 in both the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms among all participants (91.6% versus 94.8%) at the March 23, 2021 data cut-off. After 21 weeks of follow-up in the neoadjuvant phase, the compliance rate for all patients was 80.5% versus 80.4% in the pembrolizumab plus chemotherapy arm and placebo plus chemotherapy arm, respectively. Mean change from baseline scores obtained in the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms were: −9.92 (95% CI, −11.34 to −8.49) versus −9.78 (95% CI, −11.53 to −8.03), respectively. The LS mean difference between groups for the EORTC QLQ-BR23 Breast Symptoms score was −0.13 (95% CI, −1.92 to 1.65).

Adjuvant Phase

Compliance rates in the adjuvant phase were similar at baseline for EORTC QLQ-BR23 in both the pembrolizumab and placebo arms among all participants (90.5% versus 92.2%, respectively) at the March 23, 2021 data cut-off. After 24 weeks of follow-up, the compliance rate was 82.2% versus 80.7% in the pembrolizumab and placebo arms, respectively. Mean change from baseline scores obtained in the pembrolizumab plus chemotherapy and pembrolizumab treatment arm when compared to the placebo plus chemotherapy and placebo treatment arm was −5.73 (95% CI, −7.32 to −4.15) versus −6.02 (95% CI, −8.04 to −4.01), respectively. The LS mean difference between groups for the EORTC QLQ-BR23 Breast Symptoms score was 0.29 (95% CI, −2.05 to 2.63).

EQ-5D Visual Analogue Scale

Neoadjuvant Phase

Compliance rates in the neoadjuvant phase were similar at baseline for the EQ-5D Visual Analogue Scale (EQ-5D VAS) in both the pembrolizumab plus chemotherapy and placebo plus chemotherapy arms among all participants (92.8% versus 96.3%, respectively) at the March 23, 2021 data cut-off. After 21 weeks of follow-up in the neoadjuvant phase, the compliance rate was 80.8% versus 81.0% in the pembrolizumab plus chemotherapy arm and placebo plus chemotherapy arm, respectively. Mean change from baseline in EQ-5D VAS scores in the pembrolizumab plus chemotherapy arm when compared to the placebo plus chemotherapy arm was −8.98 (95% CI, −10.48 to −7.47) versus −7.36 (95% CI, − 9.34 to −5.38), respectively.

The LS mean difference between groups for the EQ-5D VAS score was −1.61 (95% CI, −3.87 to 0.64).

Adjuvant Phase

Compliance rates in the adjuvant phase were similar at baseline for EQ-5D VAS in both the pembrolizumab and placebo arms among all participants (91.7% versus 91.9%). After 24 weeks of follow-up in the adjuvant phase, the compliance rate was 82.2% versus 80.3% in the pembrolizumab and placebo arms, respectively. Mean change from baseline in EQ-5D VAS scores in the pembrolizumab plus chemotherapy and pembrolizumab arm was 1.83 (95% CI, 0.66 to 3.00) compared to 2.42 (95% CI, 0.91 to 3.93) in the placebo plus chemotherapy and placebo treatment arm. The LS mean difference between groups for the EQ-5D VAS was −0.59 (95% CI, −2.40 to 1.23).

Harms

Overall, almost all patients in the pembrolizumab plus chemotherapy and pembrolizumab arm (99.2%) and in the placebo plus chemotherapy and placebo arm (100%) reported at least 1 AE by the March 23, 2021 data cut-off. AEs of grade 3 or higher were slightly more common (82.4%) in the pembrolizumab plus chemotherapy and pembrolizumab arm compared to the placebo plus chemotherapy and placebo arm (78.7%). The most common AEs in both treatment arms were nausea, alopecia, anemia, and neutropenia.

AEs of grade 3 to 5 reported in at least 5% of patients were also generally similar in both treatment arms, and included neutropenia (35.23% versus 34.4%), neutrophil count decreased (19% versus 23.7%), anemia (19.5% versus 15.7%), febrile neutropenia (18.4% versus 16.2%), and white blood cell count decreased (6.4% versus 2.8%) in the pembrolizumab plus chemotherapy and pembrolizumab arm and placebo plus chemotherapy and placebo arm, respectively. Overall, AEs resulting in death in the pembrolizumab plus chemotherapy and pembrolizumab arm (0.9%) were consistent with the placebo plus chemotherapy and placebo arm (0.3%). AEs leading to discontinuation of any study intervention in the combined neoadjuvant and adjuvant phases were higher in the pembrolizumab plus chemotherapy and pembrolizumab arm (29.9%) than in the placebo plus chemotherapy and placebo arm (15.4%). Overall, the incidence of AEs leading to the dose reduction of chemotherapy were generally similar between the pembrolizumab plus chemotherapy and pembrolizumab arm (12.8%) and the placebo plus chemotherapy and placebo arm (11.3%).

Notable harms were more common in the pembrolizumab plus chemotherapy and pembrolizumab arm (43.6%) compared to the placebo plus chemotherapy and placebo arm (21.9%). The most common notable harms reported in the 2 study arms were colitis (1.7% versus 0.8%), hyperthyroidism (5.2% versus 1.8%), hypophysitis (1.9% versus 0.3%), hypothyroidism (15.1% versus 5.7%), infusion reactions (18.0% versus 11.6%), nephritis (0.9% versus 0%), pneumonitis (2.2% versus 1.5%), severe skin reactions (5.7% versus 1.0%), and type 1 diabetes mellitus (0.5% versus 0.3%) in the pembrolizumab plus chemotherapy and pembrolizumab arm and the placebo plus chemotherapy and placebo arm, respectively.

Critical Appraisal

KEYNOTE-522 is a randomized, double-blind, multi-centre, phase III trial. A 2:1 randomization scheme was implemented, which allowed more patients in the pembrolizumab plus chemotherapy and pembrolizumab arm compared to the placebo plus chemotherapy and placebo arm. The baseline and demographic characteristics of patients were considered well balanced in both study arms, and the risk of selection bias was considered low. The

double-blind trial design lowered the risk of performance bias from the assessment of pCR, EFS, and OS outcomes. Subjective outcomes like HRQoL and safety also had a low risk of bias due to the double-blind nature of the trial. OS, EFS, pCR, and HRQoL were considered clinically meaningful outcomes investigated in the trial by the clinical experts, clinician groups, and patient groups consulted during the review. All interim and subgroup analyses were prespecified in the statistical plan. Multiplicity adjustments for type I errors were conducted for pCR, EFS, and OS according to a prespecified statistical hierarchy plan. Subgroup and HRQoL analyses were not adjusted for type I errors; therefore, the findings were considered exploratory. The magnitude of benefit of pembrolizumab plus chemotherapy followed by pembrolizumab in the adjuvant phase in improving HRQoL is uncertain, due to the lack of multiplicity adjustments to account for type I errors in the analyses conducted.

The reimbursement request was submitted for CADTH review as a pre-NOC, and the request aligned with the proposed Health Canada indication (indicated for the treatment of adult patients with early-stage TNBC in combination with chemotherapy as neoadjuvant treatment, and then continued as monotherapy as adjuvant treatment after surgery). The inclusion and exclusion criteria of the KEYNOTE-522 study were considered appropriate and the baseline and demographic characteristics were considered generalizable to Canadian practice by the clinical experts consulted. Most patients enrolled had an ECOG PS of 0 or 1. The clinical experts agreed that they might consider administering pembrolizumab to patients with an ECOG PS of 2, but would not offer treatment to patients with an ECOG PS of 3 or greater. Therefore, the magnitude of benefit of pembrolizumab in patients that did not meet the inclusion criteria outlined in the KEYNOTE-522 study is uncertain. The dosage of pembrolizumab aligns with the Health Canada NOC indication and the clinical experts anticipate dose modifications in practice to manage treatment-related toxicity. The choice of comparator for both neoadjuvant and adjuvant phases in the KEYNOTE-522 study was considered appropriate by the experts, given that the study was initiated before capecitabine or olaparib were available for public funding. pCR, EFS, and OS are validated outcomes recommended by the FDA for trials that include patients with TNBC. The clinical experts considered the outcomes important for patients with TNBC in Canadian practice. Some patients enrolled in the KEYNOTE-522 study were possibly exposed to more frequent assessments compared to patients in real-world practice. This may impact the generalizability of the findings to patients in real-world clinical practice. The experts noted that patients are assessed before every cycle in real-world clinical practice and may not necessarily undergo routine breast MRIs.

Indirect Treatment Comparison

Direct head-to-head clinical trials assessing pembrolizumab plus chemotherapy as neoadjuvant therapy followed by continued pembrolizumab monotherapy as adjuvant therapy compared to other treatments for adult patients with early-stage TNBC are limited. The sponsor did not provide any indirect evidence for this review. Published indirect evidence was considered and summarized for this review to address the lack of direct evidence for relevant comparators.

Description and Methods of Published Network Meta-Analysis

One published network meta-analysis (NMA) by Miyashita et al. (2020) was summarized for this review to supplement the assessment of pembrolizumab plus chemotherapy as neoadjuvant therapy followed by continued pembrolizumab monotherapy as adjuvant therapy compared to other treatments for adult patients with early-stage TNBC. The published NMA

did not assess adjuvant treatment of TNBC. The published NMA included 13 RCTs and 3,008 patients with TNBC.

Eligible studies included patients with TNBC who received treatment that included anthracycline, bevacizumab, pembrolizumab, platinum salts, or other therapies (i.e., chemotherapies aside from the previously noted therapies of interest). The dosing of these interventions was not specified. Outcomes of interest included the rate of pCR (defined as ypT0/is and ypN0) or toxicities, specifically febrile neutropenia; grade 3 or higher thrombocytopenia; nausea or vomiting; and diarrhea. The systematic review only included RCTs and did not report any additional criteria regarding the study design.

Information about the statistical model selected for the NMA was limited. The authors reported that a random effects (RE) model was used for the NMA. Heterogeneity within the network was estimated using the I^2 statistic, where an I^2 value greater than 50% was considered an indicator of substantial heterogeneity. Inconsistency was evaluated using Q statistics.

Efficacy Results

The analysis of the rate of pCR suggested a higher rate of pCR for treatments that include anthracyclines plus pembrolizumab plus platinum salts (A plus PD plus PI) relative to anthracyclines (risk ratio [RR] = 0.58; 95% CI, 0.43 to 0.77) and anthracyclines plus platinum salts (RR = 0.79; 95% CI, 0.63 to 0.99). Conclusions could not be drawn for comparisons with anthracyclines plus pembrolizumab, or platinum salts, due to serious imprecision in the effect estimates.

Harms Results

The analysis of tolerability outcomes in the published NMA that are reported here is specific to the neoadjuvant setting. The analysis of the rate of febrile neutropenia suggested a higher rate of febrile neutropenia when compared to anthracyclines (RR = 0.53; 95% CI, 0.33 to 0.86). Conclusions could not be drawn for comparisons with anthracyclines plus pembrolizumab, anthracyclines plus platinum salts, platinum salts, or other therapies ("C" node) due to serious imprecision in the effect estimates.

Regarding the analysis of the rate of grade 3 or higher nausea or vomiting, conclusions could not be drawn for comparisons with anthracyclines alone or in combination with platinum salts, or platinum salts, due to serious imprecision in the effect estimates. No conclusions could be drawn for comparisons within the analysis of the rate of grade 3 or higher diarrhea due to serious imprecision in the effect estimates.

Critical Appraisal

The results of the published NMA by Miyashita et al. (2020) were associated with a number of limitations due to the lack of important details about the included trials and methodology used to perform the NMA. As such, the appropriateness of conducting the NMA is uncertain. Most of the trials contributing to the network were at high risk of bias and are only applicable to the neoadjuvant phase of treatment. There was uncertainty regarding the plausibility of the transitivity assumption as sufficient assessment of potential effect modifiers was not reported. Results that were reported were associated with serious imprecision that limited the ability to draw conclusions for most of the comparisons in the network. Additionally, construction of treatment nodes used in the NMA preclude the ability to draw conclusions regarding comparisons of pembrolizumab plus chemotherapy as neoadjuvant therapy

followed by continued pembrolizumab monotherapy as adjuvant therapy to other specific treatment options for TNBC. Overall, the findings of the NMA are uncertain.

Conclusions

One pivotal study (KEYNOTE-522) and 1 published NMA provided evidence for this CADTH review. No additional evidence directly comparing pembrolizumab plus chemotherapy in the neoadjuvant setting and pembrolizumab in the adjuvant setting with other standard therapies for early-stage TNBC was identified. The pCR rate and EFS were co-primary end points assessed in the KEYNOTE-522 study. pCR, EFS, OS, and HRQoL including safety outcomes investigated in the KEYNOTE-522 trial were considered clinically meaningful by the clinical experts, and they align with outcomes highlighted as important by the patient groups. The median OS and median EFS was not estimable at IA4; thus, there is uncertainty in the effect of the intervention for OS and EFS. The clinical experts considered the pCR rate and percent change, and EFS between the 2 arms, clinically meaningful to clinicians and patients in clinical practice. The HRQoL assessments were considered exploratory due to the lack of multiplicity adjustments in the analyses. Both clinical experts and clinician groups stated that neoadjuvant therapy is the current standard for TNBC, and pembrolizumab would be the preferred treatment option if it were to receive public funding. The clinical experts considered the safety profile of pembrolizumab plus chemotherapy and pembrolizumab manageable in practice. The experts stated that most oncologists have experience using pembrolizumab for other indications and are familiar with AEs due to pembrolizumab. Immune-related AEs are anticipated following the use of pembrolizumab. Both clinical experts and clinician groups considered toxicity and disease progression as important factors when deciding treatment discontinuation in patients. The KEYNOTE-522 study is a randomized, phase III, double-blinded design, and adjustments of multiplicity for type I error were conducted in the analyses of key outcomes OS, PFS, and pCR. The OS findings are interim with other analyses planned after a prespecified number of events have occurred. The clinical experts considered the baseline and demographic characteristics of the KEYNOTE-522 study generalizable to Canadian practice.

One published NMA by Miyashita et al. (2020) was summarized for this review to supplement the assessment of pembrolizumab plus chemotherapy as neoadjuvant therapy followed by continued pembrolizumab monotherapy as adjuvant therapy compared to other treatments for adult patients with early-stage TNBC. The NMA presented findings of pCR and grade 3 AEs specific to the neoadjuvant setting, which was a key limitation identified. Other methodological limitations, such as the lack of important details reported in the NMA methodology, high risk of bias in the studies included, lack of information about the characteristics of trials included in the network, and imprecision of the estimates reported, precluded definitive conclusions of the findings observed for the different chemotherapy regimens and combinations assessed within the study.

Economic Evidence

Table 3: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis based on a Markov Model
Target population	Patients with high-risk, early-stage, triple-negative breast cancer (TNBC)
Treatments	Pembrolizumab regimen: in combination with chemotherapy as neoadjuvant therapy followed by pembrolizumab as a single agent as adjuvant therapy
Submitted price	Pembrolizumab, 100 mg, solution: $4,400.00 per 100 mg/4 mL vial for IV infusion
Treatment cost	At the sponsor-submitted price, the additional cost of pembrolizumab in the neoadjuvant and adjuvant setting is $11,733 per 28 days (fixed dose of 200 mg every 21 days)
Comparator	Chemotherapy as a neoadjuvant therapy followed by no additional adjuvant therapy
Perspective	Canadian publicly funded health care payer
Outcome	QALYs, LYs
Time horizon	Lifetime = 51 years
Key data source	The KEYNOTE-522 phase III, randomized, double-blind clinical trial of pembrolizumab plus chemotherapy vs. placebo plus chemotherapy as neoadjuvant therapy followed by pembrolizumab vs. placebo as adjuvant therapy for early-stage TNBC patients
Key limitations	• The sponsor assumed a continued and increasing effect of treatment on delaying locoregional recurrence (LRR) and distant metastases (DM) long after treatment curtailment. • Pessimistic assumptions were adopted relating to overall survival after LRR and DM, which contradicted evidence and clinical expert opinion elicited from CADTH. • The choice of survival function biased results in favour of pembrolizumab. • The sponsor assumed reduced dose intensity to estimate drug costs for pembrolizumab. • The analysis was restricted to conclusions drawn from the KEYNOTE-522 trial where the comparator was not reflective of current Canadian practice. This makes the results of the analysis contingent on the generalizability of the KEYNOTE-522 trial to Canadian practice. CADTH was unable to address this issue. • Assumptions regarding the fixed-dose regimen of pembrolizumab do not reflect its likely use in practice. • An error was identified in the model, where the mortality rate for the target population is lower than that of the general population.
CADTH reanalysis results	For CADTH reanalysis, the following changes were made: a treatment waning effect was implemented, more appropriate survival estimates were assumed for LRR and DM, relative dose intensity was set to 100% for all drugs, alternative survival function was adopted, and programming errors were fixed. The CADTH base case included a fixed-dose regimen for pembrolizumab. A scenario analysis adopted a weight-based dose for pembrolizumab. • CADTH base case: ICER for pembrolizumab regimen vs. chemotherapy: $81,408 per QALY (incremental costs: $106,930; incremental QALYs: 1.31) • CADTH scenario analysis (weight-based dosing): ICER for pembrolizumab regimen vs. chemotherapy: $67,657 per QALY (incremental costs: 89,402; incremental QALYs: 1.31) • Based on the CADTH base case, the price of pembrolizumab would need to be reduced by 36% to

Component	Description
	achieve cost-effectiveness at a $50,000 per QALY threshold. This decreases to 24% if a weight-based dosing regimen is used.

DM = distant metastases; ICER = incremental cost-effectiveness ratio; LRR = locoregional recurrence; QALY = quality-adjusted life-year; TNBC = triple-negative breast cancer.

Budget Impact

Based on CADTH's base case, the expected budget impact for funding pembrolizumab for the neoadjuvant and adjuvant treatment of TNBC in the drug plan perspective is expected to be $15,210,765 in year 1, $55,163,378 in year 2, and $67,716,386 in year 3, with a 3-year budget impact of $138,090,529. CADTH notes that this analysis does not account for a substantial increase in the budget impact that will occur in year 4. It was unclear whether this increase was due entirely to the timing of when individuals were diagnosed due to the complexity in the sponsor's model.

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: July 13, 2022

Regrets: One expert committee member did not attend.

Conflicts of interest: None