CADTH

CADTH Reimbursement Review

CADTH Reimbursement Recommendation

(Draft)

Nelarabine (Atriance)

Indication: Nelarabine for addition to front-line multi-agent therapy of pediatric, adolescent, and young adult patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL.

Sponsor: Pediatric Oncology Group of Ontario (POGO)

Recommendation: Reimburse with Conditions

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Recommendation

The CADTH pCODR Expert Review Committee (pERC) recommends that nelarabine be reimbursed for the treatment of pediatric, adolescent, and young adult patients with intermediate- or high-risk T-cell leukemia (T-ALL) in addition to front-line multi-agent chemotherapy only if the conditions listed in Table 1 are met.

Rationale for the Recommendation

Evidence from 1 phase III, randomized, open label study (COG AALL0434; N = 659) demonstrated that treatment with nelarabine when added to augmented Berlin-Frankfurt-Munster (aBFM) multi-agent chemotherapy resulted in added clinical benefit in patients aged 1 to 30 years with newly diagnosed intermediate- and high-risk T-ALL. The COG AALL0434 study showed that, compared with aBFM chemotherapy alone, the addition of nelarabine to aBFM chemotherapy led to a statistically significant and clinically meaningful improvement in disease-free survival (DFS). The 5–year DFS rate was 88.2% (standard error [SE] ± 2.4%) in patients who received nelarabine in addition to aBFM chemotherapy compared with 82.1% (SE ± 2.7%) in patients who received aBFM chemotherapy alone (p = 0.029). The COG AALL0434 study showed that the 5–year cumulative incidence rate of central nervous system (CNS) relapse was lower in patients who received nelarabine in addition to aBFM chemotherapy compared with those who received aBFM chemotherapy alone (1.3% [SE ± 0.6%] versus 6.9% [SE ± 1.4%], respectively), which was considered clinically meaningful by clinical experts. While notable adverse events, such as central neurotoxicity, peripheral motor and sensory neuropathies, were not insignificant, the safety profile of nelarabine was considered to be expected and manageable in patients with newly diagnosed T-ALL.

Patients identified a need for new treatments targeting the T-ALL population that improve quality of life and have long-term efficacy with fewer and less severe adverse effects. pERC concluded that nelarabine meets some of the needs identified by patients, as it improves disease progression and has manageable side effects. While health-related quality of life (HRQoL) has not been evaluated or reported in the COG AALL0434 study, the reduction in CNS relapse rates with treatment with nelarabine may reduce the need for cranial radiation and transplantation, and therefore has a potential to improve patients' long-term quality of life.

Using publicly listed prices for both nelarabine and all other drug costs, the incremental cost-effectiveness ratio (ICER) for nelarabine + standard of care (SOC; defined as aBMF chemotherapy) was $26,362 per quality-adjusted life-year (QALY) gained compared with SOC alone. At this ICER, nelarabine is cost-effective at a willingness to pay (WTP) threshold of $50,000 per QALY gained for pediatric, adolescent, and young adult (aged 1 to 30 years old) patients with intermediate- and high-risk T-ALL.

Table 1. Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation		
1. Treatment with nelarabine should be initiated as an addition to front-line multi-agent chemotherapy in patients aged 1 to 30 years with intermediate- and high-risk T-ALL.	Evidence from the COG AALL0434 study demonstrated that treatment with nelarabine in addition to aBFM chemotherapy resulted in added clinical benefit for patients aged 1 to 30 years with newly diagnosed intermediate- and high-risk T-ALL.	–
2. Patients are not eligible for treatment with nelarabine if they meet any of the following criteria: 2.1 have any prior cytotoxic chemotherapy, except for steroids and/or IT cytarabine 2.2 have pre-existing peripheral neurotoxicity of CTCAE Grade 2 or greater 2.3 pregnant or lactating females.	Patients who had any prior cytotoxic chemotherapy, except for steroids and/or IT cytarabine, pre-existing peripheral neurotoxicity of CTCAE Grade 2 or greater, and pregnant or lactating females were excluded from the COG AALL0434 study.	–
Discontinuation		
3. Treatment with nelarabine must be discontinued upon the occurrence of any of the following: 3.1. disease progression 3.2. neurological toxicity of CTCAE Grade 4 related to nelarabine 3.3. signs or symptoms suggestive of an ascending polyneuropathy, including a Guillain-Barré-like syndrome, even if these symptoms resolve.	These discontinuation criteria align with the study protocol, and/or clinical experts and clinician group input.	–
Prescribing		
4. Nelarabine should be prescribed by clinicians with expertise and experience in treating T-ALL.	This helps ensure that nelarabine is prescribed only for appropriate patients and adverse effects are managed in an optimized and timely manner.	–

aBFM = augmented Berlin-Frankfurt-Munster; COG = Children's Oncology Group; ICER = incremental cost effectiveness ratio; IT = intrathecal; QALY = quality-adjusted life-year; SOC = standard of care.

Discussion Points

- pERC acknowledged the input from clinical experts that the addition of nelarabine to front-line multi-agent chemotherapy is currently considered the standard of care for pediatric, adolescent, and young adult patients with newly diagnosed T-ALL and is reimbursed in some formularies (e.g., through a hospital budget in Ontario, Nova Scotia, and New Brunswick, or by the Children and Women's Health budget for pediatric patients in Newfoundland and Labrador).
- pERC discussed that T-ALL in pediatric, adolescent, and young adult patients is a rare disease with poor prognosis, where there is significant unmet need. pERC acknowledged the input from clinical experts on the importance of ensuring successful front-line treatment of patients with newly diagnosed T-ALL to minimize CNS relapse rates. pERC discussed that in the COG AALL0434 study, up-front treatment with nelarabine in addition to aBMF chemotherapy resulted in a reduction in CNS relapse rates and therefore, may translate to help reduce the need for cranial radiation in the real-world setting (which was emphasized by clinical experts and clinician group as a significant burden for patients and their families). pERC also discussed the input from clinical experts that reduction in the CNS relapse rates has a potential to reduce the need for transplantation that exposes patients to a significant risk of morbidity (e.g., infection, second malignant neoplasm, neurocognitive impairment).
- pERC noted that only patients with intermediate- and high-risk T-ALL were included in the COG AALL0434 study. While there was no clinical evidence reviewed for patients with low-risk T-ALL, pERC acknowledged the input from clinical experts that some centers across Canada are prescribing nelarabine to all patients with newly diagnosed T-ALL, including patients at low risk.
- pERC noted that in the COG AALL0434 study, patients with a prior seizure disorder requiring anti-convulsant therapy were not eligible to receive nelarabine. However, although these patients were excluded from the COG AALL00434 study and the results may not be generalizable to these patients, pERC acknowledged the input from the clinical experts that this exclusion criterion is not typical of clinical practice.
- pERC also noted that median DFS rate was not reported and HRQoL was not evaluated and acknowledged the uncertainty in long-term overall survival.
- pERC discussed the cost-effectiveness of nelarabine plus SOC (defined as aBMF chemotherapy) compared with SOC alone. pERC noted that due to the uncertainty regarding long-term extrapolations of OS, there is uncertainty in the magnitude of the clinical benefit associated with nelarabine plus SOC and thus the ICER. A price reduction may be required to ensure the cost-effectiveness of nelarabine at a WTP threshold of $50,000 per QALY gained.

Background

Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children, representing one quarter of cancer diagnosis in children under 15 years old. In Canada, the incidence of ALL is between 1.3 and 1.4 cases per 100,000 persons of all ages between 2015 and 2018. Worldwide, the estimated annual incidence is 1 to 5 cases per 100,000 population based on results of a systematic review searched up to 2019. The latest reported mortality rate from 2017 showed that 144 Canadians died from ALL. The mortality rate from ALL is lowest in individuals diagnosed at an age younger than 15 years, and 90% of children below 15 years of age are cured when treated appropriately. Mortality increases with age, especially in patients aged greater than 40 years. Patients with ALL had signs or symptoms of bone marrow failure (e.g., fatigue, dyspnea, bleeding, bruising or infection), organ infiltration (e.g., enlarged lymph nodes, mediastinum, liver, and spleen), and systemic complaints (e.g., fevers, fatigue, joint/bony pain and night sweats). In extramedullary ALL, symptoms of central nervous system and testicular disease can also present.

ALL is classified according to the immunophenotype (i.e., if malignant cells originate from B cells or T cells). In children, approximately 80% to 85% of ALL cases are B cell phenotypes, i.e., B-cell ALL, or B-lineage ALL (B-ALL), and 15% to 20% of ALL cases are T cell phenotypes, (i.e., T-cell ALL, or T-lineage ALL [T-ALL]); whereas in adults, nearly 75% of ALL cases are B-ALL, and approximately 25% of ALL cases are T-ALL. T-ALL is notably more difficult to treat (with lower overall survival and event-free survival rates) than B-ALL in pediatric and young adult patients. Although T-ALL is a high-risk subtype of ALL, studies have demonstrated improved outcomes when treated with appropriate intensive therapy, for example, the event-free survival patients with T-ALL increased from 15% to 20% almost 40 years ago to 75% or higher today. Diagnosis of ALL and identification of phenotypes are confirmed by bone marrow histology, immunophenotyping, cytogenetics and occasionally molecular biology specialized techniques. The adverse prognostic factors for T-ALL may include presence of minimal residual disease (MRD) after induction and/or consolidation therapies, early T-precursor (ETP) T-ALL, and specific chromosomal abnormalities detected by bone marrow cytogenetics or PCR evaluation.

Nelarabine is a water-soluble pro-drug of the cytotoxic deoxyguanosine analogue antimetabolite, 9-beta-D-arabinofuranosylguanine (ara-G). With administration of nelarabine, the converted ara-GTP accumulate in leukemic cells and lead to inhibition of deoxyribonucleic acid (DNA) synthesis which results in cell death. The approved Health Canada indication for nelarabine is for the treatment of patients with T-ALL and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. The recommended dose of nelarabine is 1,500 mg/m²/day IV over 2 hours on days 1, 3, and 5, repeated every 21 days in adults, and 650 mg/m²/day IV over 1 hour on days 1 to 5, repeated every 21 days in children aged 15 years and younger. Nelarabine is available as 5 mg/mL solution for intravenous infusion. In sponsor's submission to CADTH, nelarabine (for injection) is indicated for addition to front-line multi-agent therapy of pediatric, adolescent, and young adult patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL.

Nelarabine received approvals from the US FDA in October, 2005 for the treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed after treatment with at least 2 chemotherapy regimens, and in March, 2023 for the upfront treatment of patients with T-ALL.

Sources of Information Used by the Committee

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

- a review of 1 phase III, 2x2 pseudo-factorial randomized, open label trial in patients with intermediate- and high-risk T-ALL
- patients' perspectives gathered by 1 patient groups, the Leukemia & Lymphoma Society of Canada (LLSC)
- input from public drug plans and cancer agencies that participate in the CADTH review process
- 2 clinical specialists with expertise diagnosing and treating patients with T-ALL
- input from 3 clinician groups, including the Department of Hematology, Oncology, and Bone Marrow Transplant, British Columbia Children's Hospital, the Pediatric Hematology/Oncology program at the Janeway Children's Health and Rehabilitation Centre in St. John's, Newfoundland and Labrador, and Ontario Health-Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee

- a review of the pharmacoeconomic model and report submitted by the sponsor

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups who responded to CADTH's call for input and from clinical experts consulted by CADTH for the purpose of this review.

Patient Input

This section was prepared by CADTH staff based on the input provided by patient groups. The full original patient inputs received by CADTH have been included in the stakeholder section at the end of this report.

The patient input for this review was collected by the Leukemia & Lymphoma Society of Canada (LLSC). The LLSC is a national charitable organization dedicated to blood cancer with a focus of improving the quality of life of people affected by blood cancers and their families by funding life-enhancing research and providing educational resources, services, and support. The information for this review was obtained from 2 online surveys conducted in June 2019 (20 respondents, 80% were aged from 1 to 14 years, 20% were aged 15 years and older) and March 2023 (46 respondents, 38% were aged from 1 to 14 years, 12% were aged from 15 to 19 years, 50% were aged 20 years and older) among patients with ALL aged less than or equal to 30 years at diagnosis, or their caregivers. A total of 23 respondents from both surveys were diagnosed with T-ALL.The LLCS input included 9 patient respondents with experience with using nelarabine for the treatment of ALL. Out of 3 respondents in Survey 2019, 1 patient accessed the drug through compassionate use, and 2 patients through a clinical trial.

Patient and caregiver respondents' experience with the disease are jointly summarized in 4 themes, based on the results of both Survey 2019 and Survey 2023. First, the survey respondents indicated that pediatric ALL is a difficult experience that impacts all aspects of life including physical and mental health, financial well-being, social life, and relationships, etc. Caregivers of children with ALL indicated that the pathway to diagnosis was not a straight line, and in many cases took multiple visits to a physician before the diagnosis could be made. Second, survey respondents indicated that the ALL symptoms impeded patients' ability to participate in regular life activities. According to the results of both surveys, the most critical physical effects that individuals with ALL experienced prior to diagnosis were fatigue, pain, and nausea or vomiting. Caregivers highlighted that children with ALL were particularly distressed by the instability, disruptions, and changes to their home and family life that they experienced due to ALL. Third, the survey respondents indicated that ALL had a significant effect on patients' and their families' quality of life in several areas which included more than just physical impacts. According to the survey results, the most significant detrimental impacts on patients and their caregivers included daily routines (88%), physical functioning (85%), mental functioning (85%), work life (82%), social life (79%), lifestyle (74%), and family life (71%). In addition, survey respondents noted that the impact of the associated feelings the respondents had experienced throughout diagnosis and treatment of ALL included sadness (76%), fear (74%), nervous, anxious, depressed (74%), frustration (72%), stress/worry (72%), overwhelmed/feeling out of control (70%), loneliness/isolation (70%), post-traumatic stress (68%), and helplessness or hopelessness (66%). Last, survey respondents highlighted that there have been considerable consequences for patients with ALL and their families regarding their financial stability, and the ability to maintain employment/financial status due to ALL diagnosis and treatment schedules. According to the survey results, 38% of patient respondents and 29% of caregiver respondents noted that they have endured missed career development or advancement opportunities due to their experience with ALL. Approximately 79% of survey respondents reported that they experienced a decrease in income as a direct result of diagnosis and treatment of ALL.

The survey results showed that the types of ALL treatment that patients have received since their diagnosis included chemotherapy (94%), high dose chemotherapy (67%), maintenance therapy (51%), radiation (43%), stem cell or bone marrow transplant (22%), immunotherapy (12%), surgery (6%), and other (received steroids as part of their treatment, 4%). The survey respondents reflected that ALL treatment created difficulties and challenges in all areas of life for patients, caregivers, and their families. For example, a caregiver respondent shared the treatment experiences in Survey 2019, "Chemo was horrible and continues to get worse. My daughter was high risk and is now 1/3 way through maintenance. Continues to be sick, not go to school, starting to endure multiple fractures because her bones are so weak. It is horrible and there has to be a better way". For some ALL treatment, the need to travel to and from treatment where necessary was a significant barrier for patients and caregivers. The Survey 2023 data showed that among the patients who received the ALL treatment other than nelarabine, 37% of them had to travel long distances by car in their

province or state. Approximately 78% of those who did not have nelarabine treatment had to pay out of pocket for drugs not covered by provincial providers, and only 20% of nelarabine users incurred the same expense. The survey respondents who received treatment other than nelarabine expressed that the quality of life for patients, caregivers and their families was severely impacted by the ALL treatment and noted their adverse effects including nausea and vomiting, weakness or loss of strength, low white blood cell count, low platelet count, and pain.

The surveys found that the patients with ALL and their caregivers hope to return to the comfort of normalcy and quality of life prior to onset of disease. The survey results showed that the most important factors they consider when making decisions about currently available treatments were physician recommendation (82% of the respondents), side effects (79%), quality of life (79%), and possible impact on disease (76%). The survey participants commented that for any new treatments, they are concerned about the long-term effects and safety that the treatments may have on a child and his/her future health. It is hoped that the new treatment may have fewer and less severe adverse effects, and improved treatment logistics (e.g., fewer trips to the hospital, removing steroids from treatment, and shortening the maintenance period), and provision of the associated mental health supports.

Nine survey respondents with T-ALL reported experience with treatment with nelarabine. About 56% of the respondents reported that nelarabine eliminated the disease for some time before relapsing, 11% reported that nelarabine kept the disease stable, and 33% of respondents indicated that the results are unknown at this time. The 5 respondents rated the following adverse effects as having no impact on the patient during the treatment with nelarabine: seizures, fever, headaches, shortness of breath or persistent cough, infections, increased transaminase, increased bilirubin, and decreased albumin. About 40% of patient respondents rated the following adverse effects as having either a large or extremely large impact on the patient during nelarabine treatment: low platelet count, low red blood count, anemia, low white blood count, and extreme sleepiness. Although the distance from the treatment facility to home and the need to travel for treatment with nelarabine affected quality of life of patients and their caregivers, survey respondents were willing to endure because the treatment works. Two patient respondents felt that treatment with nelarabine was “neutral” in comparison to other treatments, 2 patients felt that nelarabine treatment was “less challenging” than their other treatments, and 1 patient felt that nelarabine was “more challenging” than other treatments. According to the patient input received, the responses of patients who have received nelarabine reflect that nelarabine gave back life, hope, and normalcy to patients and their families after treatment. The LLSC advocated for nelarabine to be approved for the indication under review and suggested that it will help alleviate the gaps in current T-ALL therapy among patients including pediatrics, and therefore relatively improve quality of life and psychosocial aspects for patients and their families.

Clinician input

Input from clinical experts consulted by CADTH

All CADTH review teams include at least one clinical specialist with expertise regarding the diagnosis and management of the condition for which the drug is indicated. Clinical experts are a critical part of the review team and are involved in all phases of the review process (e.g., providing guidance on the development of the review protocol; assisting in the critical appraisal of clinical evidence; interpreting the clinical relevance of the results; and providing guidance on the potential place in therapy). The following input was provided by 2 clinical specialists with expertise in the diagnosis and management of T-ALL.

The clinical experts consulted by CADTH for this review indicated that the main goals of T-ALL treatment are to reduce relapse rates, prolong life, improve health-related quality of life (HRQoL), and reduce treatment-related morbidity, including treatment with cranial radiation. The clinical experts highlighted the importance of ensuring successful first-line treatment in patients with newly diagnosed T-ALL in order to minimize the relapse rate, as patients with relapsed T-ALL require total body irradiation (TBI)-based stem cell transplantation. The clinical experts further noted that less than half of patients with relapsed or refractory T-ALL are cured by transplantation, and transplantation exposes patients to a significant risk of early (graft-versus-host disease, infection, and other treatment-related mortality), and late (second primary malignancy, end organ toxicity, neurocognitive impairment, and reduced quality of life) morbidity.

The clinical experts consulted for this review emphasized that nelarabine is currently being considered by many centers in Canada and the United States as the standard of care for patients with newly diagnosed T-ALL, and it is not recommended to prescribe nelarabine only to patients with relapsed T-ALL. The clinical experts mentioned that nelarabine may be used as a single agent

(largely in adults in the salvage setting), or in combination with multi-agent chemotherapy in patients with newly diagnosed T-ALL. The clinical experts consulted indicated that nelarabine should be used as part of front-line therapy for all patients with newly diagnosed T-ALL, regardless of CNS status at diagnosis. They further noted that while currently available evidence shows that nelarabine improves outcomes in patients with intermediate- and high-risk T-ALL, it is biologically reasonable that nelarabine would also be effective in treating patients with low-risk T-ALL. The clinical experts mentioned that patients with T-ALL are identified by the characteristic immunophenotypic proliferation of T-lymphoblasts in a bone marrow sample, and misdiagnosis of patients with T-ALL is uncommon. According to clinical experts, it is not possible to identify patients who are likely to demonstrate a response to treatment.

For assessing response to treatment of newly diagnosed T-ALL, the outcomes used to determine whether a patient is responding include improved overall and event-free survival, reduced relapse rates, improved HRQoL, and reduced treatment with cranial radiation. The clinical experts consulted indicated that children with newly diagnosed T-ALL are assessed at defined time points throughout the treatment plan, and responses are assessed through bone marrow biopsy, lumbar puncture, and frequent blood counts. The bone marrow aspirate or biopsy is repeated if the patient's condition does not improve as expected, or if the patient's condition deteriorates unexpectedly. The clinical experts pointed out that the most meaningful early outcome in children with T-ALL is the achievement of MRD-negative remission during treatment; failure to achieve such remission or disease relapse during treatment are considered indications for escalation of therapy. The clinical experts indicated that the use of nelarabine in patients with newly diagnosed T-ALL is expected to increase the proportion of patients who achieve MRD-negative complete response, and to decrease the proportion of patients who relapse (both extramedullary and marrow) during treatment. According to clinical experts, the potential reasons for discontinuing treatment with nelarabine include refractory disease, disease progression, significant toxicity (i.e., neurotoxicity Grade of 4). The clinical experts indicated that nelarabine should be prescribed under the direction of an oncologist in a hospital or outpatient setting.

The clinical experts noted that in Ontario, nelarabine added to front-line multi-agent therapy is offered to intermediate- or high- risk (as per indication under review) T-ALL patients, however, some centers across Canada are successfully prescribing nelarabine to all patients with T- ALL, including those at low risk. The clinical experts cautioned the impact of a reimbursement recommendation consistent with the reimbursement request and expressed the need for consideration to expand the reimbursement population to include low-risk T-ALL.

Clinician group input

The clinician group input was obtained from 3 clinician groups, including the Department of Hematology, Oncology, and Bone Marrow Transplant, British Columbia Children's Hospital (represented by 16 clinicians), the Pediatric Hematology/Oncology program at the Janeway Children's Health and Rehabilitation Centre in St. John's, Newfoundland and Labrador, and Ontario Health-Cancer Care Ontario (OH-CCO) Hematology Cancer Drug Advisory Committee. OH-CCO's Cancer Drug Advisory Committees provide guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs and the Systemic Treatment Program. The information in this review was gathered through review of literature, and discussion with T-cell acute lymphoblastic leukemia (T-ALL) experts, or counselling the clinicians via video conferencing and email.

The clinician groups indicated that not all patients with T-ALL respond to the currently available treatments. Clinicians from the British Columbia Children's Hospital noted that T-ALL represents 10-15% of newly diagnosed pediatric acute leukemia, and with standard of care therapy, cure can be achieved in the majority of children. However, nearly 20% of the pediatric patients with T-ALL experience relapsed or refractory disease, and salvage of relapsed or refractory disease is dismal, with less than 25% overall survival. Currently, the standard treatment for pediatric patients with newly diagnosed T-ALL includes multi-agent chemotherapy (pediatric-inspired intensive chemotherapy regimens) delivered over approximately 3 years, with additional cranio-spinal radiation therapy for patients with CNS disease. Clinicians from the British Columbia Children's Hospital highlighted that the unmet need would be to improve event-free survival, reduce the risk of relapse, including CNS relapse, as patients with CNS disease must include cranial radiation therapy as part of their treatment, either at diagnosis or during relapse, and the additional cranial radiation is associated with a significant risk of chronic neurocognitive sequelae, especially in young children.

According to the clinician groups, nelarabine can be used as per the Children's Oncology Group (COG) trial COG AALL0434 that investigated efficacy and safety of adding nelarabine to standard of care. According to the clinician groups, patients between the age

of 1 to 30 years with newly diagnosed T-ALL are most likely to respond to nelarabine and are the most in need of an intervention. The clinician groups noted that the diagnosis of this disease includes the confirmation of an abnormal clonal population of immature T-lymphoblasts in bone marrow, circulating blood, cerebral spinal fluid, or tissue, which is not dependent on any specific cytogenetic or molecular testing. All clinician groups agreed that the use of nelarabine for newly diagnosed T-ALL among patients aged between 1 and 30 years would be incorporated into a multi-agent chemotherapy backbone similar to that used in the COG AALL0434 study. The clinicians from the British Columbia Children's Hospital noted that nelarabine is not a symptomatic management therapy, and that it should be used in the context of newly diagnosed pediatric T-ALL, and not as a second-line therapy for those who have responded poorly to first-line therapy. The clinician groups mentioned that patients with non-T-ALL forms of hematological malignancies are least suitable for nelarabine treatment.

The clinicians from the British Columbia Children's Hospital indicated that pediatric patients undergoing standard treatment for T-ALL will undergo regular follow-up disease assessments after induction and consolidation cycles of chemotherapy, which may include bone marrow aspirate and biopsy, minimal residual disease testing, spinal fluid assessment, peripheral blood assessment, and as required, imaging, and physical examination of extramedullary sites of disease. The clinician groups identified that the following factors should be used to evaluate response to treatment in patients with T-ALL: the achievement of remission (i.e., no detectable leukemic disease), and the persistence of disease remission over time without relapse. The clinician groups pointed out several reasons which may lead to the discontinuation of nelarabine, including disease progression, or significant intolerance to the treatment, e.g., severe or progressive neurotoxicity including but not limited to myelopathy, sensory changes, central neurocognitive decompensation, Guillan-Barre-like syndrome, and paralysis. The clinician from the Janeway Children's Health and Rehabilitation Centre indicated that nelarabine has been considered standard of care at their site for several years, without specifying the indication of the drug. Two clinician groups highlighted that nelarabine should be administered by leukemia specialists at outpatient settings, or under the direction and supervision of a pediatric hematologist-oncologist who is familiar with the treatment of pediatric T-ALL and is equipped to anticipate and support the potential adverse effects of nelarabine.

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

Drug Program Implementation Questions	Response
Relevant Comparators	
Standard COG protocol (multi-drug regimen) for T-ALL.	*Comment from the drug programs to inform pERC deliberations.*
Considerations for Initiation of Therapy	
Can re-treatment with nelarabine be considered in a later line of therapy in cases of relapsed disease?	The clinical experts indicated that nelarabine could be considered as part of reinduction or reconsolidation treatment prior to alloHSCT in patients with relapsed T-ALL. pERC noted that this is out of scope for this review.
Considerations for Prescribing of Therapy	
The recommended dose is a total of six courses of 650 mg/m^2/day, administered intravenously over 1 hour on 5 consecutive days with a total of 6 cycles administered as part of a multi-drug regimen.	*Comment from the drug programs to inform pERC deliberations.*
Generalizability	
Should patients with Low-Risk T-ALL (excluded from trial) be eligible for front-line treatment with Nelarabine in combination with multiagent chemotherapy?	There is no clinical evidence available regarding the use of nelarabine in patients with low-risk T-ALL.

Drug Program Implementation Questions	Response
	The clinical experts highlighted that patients with low-risk T-ALL were excluded from nelarabine randomization in COG AALL0434 and therefore did not receive the drug due to concerns about neurotoxicity; however, neurotoxicity rates reported in the study were minimal. The clinical experts indicated that nelarabine is currently considered the standard of care for patients with newly diagnosed T-ALL, and some centers across Canada are prescribing nelarabine to all patients with T-ALL, including those at low risk. Thus, the clinical experts emphasized that nelarabine can be used in patients with low-risk T-ALL. The clinical experts cautioned the impact of a reimbursement recommendation consistent with the reimbursement request and expressed the need for consideration to expand the reimbursement population to include low-risk T-ALL. pERC acknowledged the input from the clinical experts and also noted that there is no clinical evidence available for patients with low-risk T-ALL.
Should adult patients (> age 30) be considered for treatment with nelarabine?	The clinical experts indicated that nelarabine can be prescribed to patients with T-ALL over 30 years of age, given that the older the patient, the higher the risk of the disease. The clinical experts noted that most patients with newly diagnosed T-ALL are young, and the number of newly diagnosed T-ALL in patients over 30 years of age is low. pERC acknowledged the input from the clinical experts and also noted that there is no clinical evidence available regarding the use of nelarabine in patients over 30 years of age.
Most pediatric centres are currently using nelarabine (hospital budget) in frontline T-ALL protocols	*Comment from the drug programs to inform pERC deliberations.*
Care Provision Issues	
Nelarabine is prepared as an undiluted solution in either an IV bag or syringe for delivery via infusion pump. Each dose usually requires multiple vials per patient. Vial sharing would not be likely due to the small patient population. However, with published extended stability data, more than one daily dose of nelarabine may be compounded at once which could reduce vial wastage.	*Comment from the drug programs to inform pERC deliberations.*
Requires monitoring for potential neurological side effects.	*Comment from the drug programs to inform pERC deliberations.*

alloHSCT = allogeneic hematopoietic stem cell transplant; COG = Children's Oncology Group; pERC = pan-Canadian Oncology Drug Review Expert Review Committee; T-ALL = T-cell acute lymphoblastic leukemia.

Clinical Evidence

Pivotal Studies and RCT Evidence

Description of studies

The COG AALL0434 trial was a phase III, 2x2 pseudo-factorial randomized, open label trial. The primary objective of the trial was to assess the relative efficacy and safety of nelarabine for addition to front-line augmented Berlin-Frankfurt-Munster (aBFM) multi-agent therapy of pediatric, adolescent, and young adult (AYA) patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL. This study was conducted by the Children's Oncology Group (COG) under an investigational new drug application held by the National Cancer Institute. A total of 1,596 patients with T-ALL were enrolled from January 2007 to July 2014 across 215 sites in the USA, Australia, Canada, New Zealand, and Switzerland.

The COG AALL0434 trial used a sequential design to evaluate nelarabine during the initial safety and efficacy phases. First, an initial safety phase[17] was conducted to assess the tolerability of adding nelarabine to the aBFM backbone containing either Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase (C-MTX), or high-dose methotrexate (HD-MTX) with leucovorin rescue. During the initial safety phase, only patients with high-risk T-ALL (N = 94) were randomized to receive the aBFM backbone with randomization to 1 of 4 treatment arms after completion of induction therapy as follows:

- Arm A: Augmented BFM with C-MTX without nelarabine, n = 24
- Arm B: Augmented BFM with C-MTX with nelarabine, n = 24
- Arm C: Augmented BFM with HD-MTX with leucovorin rescue and without nelarabine, n = 23
- Arm D: Augmented BFM with HD-MTX with leucovorin rescue and nelarabine, n = 23

The initial safety phase endpoints included sensory neuropathy, motor neuropathy, central neurotoxicity (encephalopathy, seizure, stroke, extrapyramidal tract symptoms, acute mental status changes and somnolence), and mortality. After the completion of the initial safety analysis for nelarabine in patients with high-risk T-ALL, the study was approved to move into the efficacy phase of the COG AALL0434 trial[15]. During the efficacy phase of COG AALL0434, patients with intermediate- and high-risk T-ALL (N = 659) were randomized to 1 of 4 treatment arms after completion of induction therapy as follows:

- Arm A: Augmented BFM with C-MTX without nelarabine, n = 151
- Arm B: Augmented BFM with C-MTX with nelarabine, n = 147
- Arm C: Augmented BFM with HD-MTX with leucovorin rescue and without nelarabine, n = 185
- Arm D: Augmented BFM with HD-MTX with leucovorin rescue and nelarabine, n = 176

The primary efficacy endpoint in the efficacy phase of COG AALL0434 was disease-free survival (DFS), and the secondary efficacy endpoints were overall survival (OS), and central nervous system (CNS) relapse. The safety outcomes of the efficacy phase of COG AALL0434 included central neurotoxicity, peripheral motor neuropathy, and peripheral sensory neuropathy. Patients with low-risk T-ALL did not participate in the nelarabine randomization in either the safety or efficacy phases of the COG AALL0434 trial. Treatment duration with nelarabine was 2 years from the start of the interim maintenance phase for females, and 3 years for males.

Baseline characteristics were well balanced between the treatment groups. Half of the patients (49.9%) were under the age of 10 years, and 33.4% of patients were between 10 and 15 years of age, and 16.7% were 16 years of age or older. A total of 74.8% of patients were male, and 25.2% were female. A total of 70.6% of patients had CNS1, 20.8% had CNS2, and 8.6% had CNS3 at diagnosis. Bone marrow M1 at the end of induction was determined in 95.3% of patients, and M2 marrow in 4.7% of patients. A total of 83.3% of patients did not have allogeneic hematopoietic stem cell transplant (alloHSCT), while 3.2% underwent alloHSCT.

Efficacy Results

Table 3 presents a summary of key results from the efficacy phase of the COG AALL0434 trial.

Overall survival

The 5–year OS rate was 90.3% (standard error [SE] ± 2.2%) in patients who were randomly assigned to receive nelarabine compared with 87.9% (SE ± 2.3%) in those who did not receive nelarabine (P = 0.168). In patients with intermediate-risk T-ALL who were randomly assigned to receive versus not receive nelarabine, the 5–year OS rates were 91.3% (SE ± 2.7%) versus 92.4% (SE ± 2.4%), respectively (P = 0.617). In patients with high-risk T-ALL who were randomly assigned to receive versus not receive nelarabine, the 5-year OS rates were 88.5% (SE ± 3.8%) versus 79.2% (SE ± 4.6%), respectively (P = 0.051).

Disease-free survival

A total of 97 (14.7%) patients experienced any DFS events, including 39 patients who received nelarabine compared with 58 patients who did not receive nelarabine. Out of 97 patients, 70 (10.6%) patients had relapse, 12 (1.8%) patients had secondary malignant neoplasm, and 15 (2.3%) patients died during remission. The 5–year DFS rate was 88.2% (SE ± 2.4%) in patients who were randomly assigned to receive nelarabine compared with 82.1% (SE ± 2.7%) in patients who did not receive nelarabine (P = 0.029). The analysis by treatment arms showed that 5–year DFS rates were 91.4% (SE ± 3.1%) in patients who received C-MTX regimen with nelarabine (n = 147), 87.2% (SE ± 3.5%) in those who received C-MTX regimen without nelarabine (n = 151), 85.5% (SE ± 3.6%) in those who received HD-MTX regimen with nelarabine (n = 176), and 78.1% (SE ± 4.0%) in those who received HD-MTX regimen without nelarabine (n = 185) (P = 0.01).

In patients with intermediate-risk T-ALL who were randomly assigned to receive versus not receive nelarabine, the 5-year DFS rates were 90.8% (SE ± 2.8%) versus 86.3% (SE ± 3.1%), respectively (P = 0.077). In patients with high-risk T-ALL who were randomly assigned to receive versus not receive nelarabine, the 5–year DFS rates were 83.5% (SE ± 4.4%) versus 74.1% (SE ± 4.8%), respectively (P = 0.106). The 5–year DFS rates in patients with CNS3 disease who were assigned to receive HD-MTX with nelarabine versus HD-MTX without nelarabine were 93.1% (SE ± 6.5%) and 67.9% (SE ± 12.2%), respectively (P = 0.014).

CNS relapse

The 5–year cumulative incidence rate of CNS relapse (isolated and combined) was 1.3% (SE ± 0.6%) in patients who received nelarabine compared with 6.9% (SE ± 1.4%) in patients who did not receive nelarabine (P = 0.0001). Among patients with CNS3 disease, CNS relapse occurred in 1 (3.4%) patient who was assigned to receive HD-MTX regimen with nelarabine compared with 6 (21.4%) patients who were assigned to receive HD-MTX regimen without nelarabine.

Health-related quality of life

Health-related quality of life was not measured or reported in the COG AALL0434 trial.

Harms Results

In the efficacy phase safety analysis of the COG AALL0434 trial, the rates of non-targeted toxicity of CTCAE Grade of 3 or higher were 41.2% in patients who received nelarabine compared with 46.1% in patients who did not receive nelarabine. The targeted neurotoxicity and overall toxicity rates were a little higher among patients who received nelarabine compared to those who did not. Out of 323 patients who received nelarabine, 11 (3.4%) patients experienced central neurotoxicity of CTCAE Grade of 3 or higher, 26 (8.0%) experienced peripheral motor neuropathy of CTCAE Grade of 3 or 4, and 29 (9.0%) experienced peripheral sensory neuropathy of CTCAE Grade of 3 or 4. Out of 336 patients who did not receive nelarabine, 7 (2.1%) patients experienced central neurotoxicity of CTCAE Grade of 3 or higher, 19 (5.7%) experienced peripheral motor neuropathy of CTCAE Grade of 3 or 4, and 27 (8.0%) experienced peripheral sensory neuropathy of CTCAE Grade of 3 or 4.

Table 3. Summary of Key Results of the Efficacy Phase of COG AALL0434, ITT

Detail	COG AALL0434					
	Nelarabine N = 323	No nelarabine N = 336	Arm A C-MTX without nelarabine N = 151	Arm B C-MTX with nelarabine N = 147	Arm C HD-MTX without nelarabine N = 185	Arm D HD-MTX with nelarabine N = 176
Efficacy						
Overall survival						
5-year OS rate[a] (SE), %	90.3 ± 2.2	87.9 ± 2.3	NR	NR	NR	NR
P value[b]	0.168		NR			
Disease-free survival						
5-year DFS rate[c] (SE), %	88.2 ± 2.4	82.1 ± 2.7	87.2 ± 3.5	91.4 ± 3.1	78.1 ± 4.0	85.5 ± 3.6
P value	0.029		0.01			
Relapse, n (%)	27 (8.4)	43 (12.8)	11 (7.3)	10 (6.8)	32 (20.2)	17 (9.7)
CNS relapse, n (%)	1 (0.3)	14 (4.2)	1 (0.7)	0 (0)	13 (7.0)	1 (0.6)
BM relapse, n (%)	12 (3.7)	14 (4.2)	5 (3.3)	2 (1.4)	9 (4.9)	10 (5.7)
CNS and BM relapse, n (%)	2 (0.6)	8 (2.4)	1 (0.7)	1 (0.7)	7 (3.8)	1 (0.6)
CNS relapse						
5-year CNS relapse rate[d] (SE), %	1.3 ± 0.63	6.9 ± 1.4	NR	NR	NR	NR
P value[b]	0.0001		NR	NR	NR	NR
Second malignancy[e], n (%)	4 (1.2)	7 (2.1)	3 (2.0)	5 (3.4)	2 (1.1)	2 (1.1)
Remission death, n (%)	5 (1.5)	10 (3.0)	4 (2.6)	0 (0)	6 (3.2)	5 (2.8)
Harms[f]						
Central neurotoxicity[g], n (%)	11 (3.4)	7 (2.1)	NR	NR	NR	NR
Peripheral motor neuropathy[h], n (%)	26 (8.0)	19 (5.7)	NR	NR	NR	NR
Peripheral sensory neuropathy[h], n (%)	29 (9.0)	27 (8.0)	NR	NR	NR	NR

BM = bone marrow; CNS = central nervous system; C-MTX = escalating-dose methotrexate without leucovorin rescue plus pegaspargase; DFS = disease-free survival; HD-MTX = high-dose methotrexate with leucovorin rescue; ITT = intention to treat; SE = standard error; NR = not reported; OS = overall survival.

[a] Percentage (SE) of patients alive from the KM estimates

[b] P-value has not been adjusted for multiple testing.

[c] Percentage (SE) of disease-free events from the KM estimates.

[d] Cumulative incidence rate.

[e] Included Ewing sarcoma, acute myeloid leukemia, mucoepidermoid carcinoma, malignant melanoma, Langerhans cell histiocytosis, myelodysplastic syndrome, malignant histiocytosis histiocytic medullary reticulosis, lymphoproliferative disease, and malignant lymphoma.

[f] Safety analyses of the efficacy phase of COG AALL0434.

[g] CTCAE Grade of 3, 4, or 5.

[h] CTCAE Grade of 3 or 4.

Source: Dunsmore et al. (2020)

Critical Appraisal

The COG AALL0434 trial was an open-label, phase 3, 2x2 pseudo-factorial randomized trial comparing nelarabine and aBFM backbone in pediatric, adolescent, and young adult patients with newly diagnosed intermediate- and high-risk T-ALL. Detailed information on randomization and treatment allocation is not available. The open-label design of the trial was most likely due to the nature of treatment administration, which made blinding infeasible. Knowledge of the assigned treatment could have led to bias in the reporting of subjective AEs; however, the extent and direction of bias due to treatment knowledge is uncertain. There is no information available regarding the treatment discontinuation rates and the proportion of protocol deviations. The study utilized 2x2 pseudo-factorial randomization to compare 2 separate treatments, including C-MTX versus HD-MTX, and nelarabine versus no nelarabine. Since there was no interaction between the 2 randomized treatments, the trial was powered to examine the main effects of the 2 randomized comparisons separately. However, it is unclear whether the study was powered to provide a statistically rigorous evaluation of the two-stage procedure, including methotrexate and nelarabine randomizations. In addition, no adjustments for multiple comparisons were made in the trial. The primary (DFS) and secondary outcomes (OS and CNS relapse) were considered appropriate for the disease setting, and were conducted using the ITT population, which maintains randomization and minimizes the risk of bias by comparing groups with similar prognostic factors. The median DFS was not reported in either treatment group; thus, the longer-term efficacy of nelarabine for DFS is unknown for upfront therapy of newly diagnosed T-ALL. The clinical experts consulted noted that the results of the DFS analysis were clinically meaningful based on the absolute event rate reduction within the selected study population; however, there is no known or accepted minimally important difference (MID) for DFS rates in this population. There is no information available regarding the dropout rates and how missing values in the trial were handled in the trial. Although HRQoL has been identified as an important outcome by both clinicians and patients, it has not been evaluated or reported in the COG AALL0434 trial.

In general, the clinical experts consulted for this review confirmed that the population of the COG AALL0434 trial was similar to patients seen in clinics, and there is no concern generalizing the findings from the trial to the Canadian clinical setting. A total of 373 patients were not eligible for post-induction therapy, including 353 patients who discontinued protocol therapy at the end of induction therapy mainly due to refusal of further protocol therapy by patient, parent or guardian (61.7%), which further reduces the generalizability of the trial results. The clinical experts indicated that the failure to continue protocol therapy after induction may be related to the fact that some patients may already have neurotoxicity events and are reluctant to take more medication that could cause more neurotoxicity events. Another reason mentioned by the clinical experts is that all patients in the trial received prophylactic cranial radiation, which may cause more harm to the patient, especially in children younger than 5 years of age.

The COG AALL0434 trial included patients aged 1 to 30 years, and most patients were aged under 15 years of age. The clinical experts consulted indicated that this is reflective of Canadian clinical practice. The clinical experts further noted that nelarabine can be prescribed to patients with T-ALL over 30 years of age, given that the older the patient, the higher the risk of the disease. The clinical experts consulted emphasized that nelarabine is currently considered the standard of care in addition to aBFM backbone therapy for patients with newly diagnosed T-ALL, and is reimbursed in some formularies (i.e., nelarabine may be funded through a hospital budget). The clinical experts consulted mentioned that patients with low-risk T-ALL did not receive nelarabine in the trial due to concerns about neurotoxicity; however, neurotoxicity rates reported in the study were minimal. They also highlighted that some centers across Canada are successfully prescribing nelarabine to all patients with T-ALL, including those at low risk. All patients in the COG AALL0434 trial received prophylactic cranial radiation therapy at a dose of 12 Gy, and patients with CNS3 disease received cranial radiation therapy at a dose of 18 Gy. However, the clinical experts consulted for this review stated that attempts should be made to prevent radiation exposure in young children and adolescents, given the late cognitive effects that can be associated with radiation therapy.

Long-Term Extension Studies

No long-term extension studies were identified for this review.

Indirect Comparisons

No studies with indirect evidence were identified for this review.

Studies Addressing Gaps in the Pivotal and RCT Evidence

No studies addressing gaps in the pivotal and RCT evidence were identified for this review.

Economic Evidence

Table 4: Cost and Cost-Effectiveness

Component	Description
Type of economic evaluation	Cost-utility analysis Microsimulation model
Target population	Children, adolescents, and young adults (aged 1 to 30.99 years) with newly diagnosed, intermediate- or high-risk T-ALL
Treatment	Nelarabine in addition to SOC
Dose Regimen	Nelarabine as an add-on therapy to aBFM where dosing is expected to be aligned with the COG AALL0434 trial (i.e., 650 mg/m^2 on days 1 to 5 and 43 to 47 of the consolidation phase, days 29 to 33 of the delayed intensification phase, and days 29 to 33 for the first 3 cycles of the maintenance phase)
Submitted Price	$545.42[a] per 50 mL vial
Treatment Cost	Course cost as an add on to aBMF[b]: • Consolidation: 17,386 • Delayed Intensification: 8,693 • Maintenance: 8,693
Comparator	SOC, defined as aBFM multi-drug chemotherapy protocol
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, LYs
Time horizon	Lifetime (90 years)
Key data source	COG AALL0434
Key limitations	• Long-term efficacy of nelarabine + SOC for the first-line treatment of children, adolescents, and young adults with newly diagnosed intermediate- or high-risk T-ALL is unknown. While data in the COG AALL0434 trial suggest nelarabine is associated with a modest but clinically meaningful benefit in 5-year OS rates compared to SOC, clinical expert feedback received by CADTH noted that the duration of treatment and follow-up period were likely too short to observe the beneficial effect of nelarabine on OS. Similarly, nelarabine was associated with a 5-year DFS benefit in the trial (between-group difference of 6.1%), however as median DFS was not reported the long-term DFS benefit remains unknown. • The reimbursement requested population excludes low-risk patients and adult (30 years and older) patients. Clinical expert feedback received by CADTH noted that nelarabine, as an add-on to first-line therapy, is already prescribed to low-risk pediatric patients in some centers across Canada and that a patient's age should not exclude a patient from being eligible for nelarabine. The cost-effectiveness of nelarabine + SOC in low-risk T-ALL and in adult patients ages 30 years or older is unknown. • Drug costs may be underestimated due to incorrect drug pricing and BSA assumptions, as the dosing of nelarabine is based on patient's BSA which was assumed to be aligned with a 9-year-olds over the entire treatment duration (i.e., ranging from 2 to 3 years, based on gender). • Clinical efficacy data comparing nelarabine + aBFM SOC to Hyper CVAD, in newly diagnosed adult patients with intermediate- or high-risk T-ALL, is not available; therefore, the comparative cost-effectiveness of nelarabine + aBFM SOC to Hyper CVAD is unknown.
CADTH reanalysis results	• CADTH revised the unit price for several drugs, including nelarabine, to address one of the identified key limitations as part of its reanalysis. • In the CADTH reanalysis, the ICER for nelarabine + SOC was $26,362 per QALY gained compared to SOC alone. Therefore, no price reduction is required for nelarabine + SOC to be

Component	Description
	considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained at current list prices. • CADTH was unable to address the limitation pertaining to uncertainties in the long-term efficacy of nelarabine + SOC. Should a smaller OS difference be observed for nelarabine + SOC versus SOC as a first-line treatment for children, adolescents, and young adults with newly diagnosed intermediate- or high-risk T-ALL then a smaller QALY benefit would be expected – leading to a higher ICER for nelarabine + SOC versus SOC alone. In the absence of available data, the magnitude of long-term OS efficacy remains unknown.

aBFM = augmented Berlin-Frankfurt-Münster, BSA = body surface area, COG = Children's Oncology Group, DFS = disease free survival, Hyper CVAD = cyclophosphamide-vincristine, doxorubicin-dexamethasone-methotrexate-leucovorin-cytarabine, ICER = incremental cost-effectiveness ratio; LY = life-year; OS = overall survival, QALY= quality-adjusted life-year; SOC = standard of care; T-ALL = T-cell acute lymphoblastic leukemia.

[a] model uses the price of $582.49 based on applying an inflation adjustment to derive 2022 values.

[b] Costs calculated using a $579.54 per 50 mL vial of nelarabine wholesale price from IQVIA Delta PA (accessed April 2023).

Budget Impact

CADTH identified the following key limitations with the sponsor's BIA: the market share for nelarabine was likely underestimated, drug costs may be underestimated due to utilization of incorrect drug unit costs and patient BIA dependent assumptions. The CADTH base case updated unit drug costs. In the CADTH base case, the estimated incremental budget impact of reimbursement nelarabine as an add-on therapy to the first-line treatment of patients (aged 1 to 30) for intermediate- or high-risk T-ALL is $1,888,641 in year 1, $2,340,039 in year 2, and $2,358,411 year 3. Therefore, the three-year budget impact was $6,587,091.

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. Catherine Moltzan, Ms. Amy Peasgood, Dr. Anca Prica, Dr. Adam Raymakers, Dr. Patricia Tang, Dr. Marianne Taylor, and Dr. W. Dominika Wranik.

Meeting date: August 9, 2023

Regrets:

3 expert committee members did not attend.

Conflicts of interest:

None