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CADTH Reimbursement Review

Nelarabine (Atriance)

Sponsor: Pediatric Oncology Group of Ontario

Therapeutic area: T-cell acute lymphoblastic leukemia

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Abbreviations

aBFM	augmented Berlin-Frankfurt-Münster
AE	adverse event
ALL	acute lymphoblastic leukemia
alloHSCT	allogeneic hematopoietic stem-cell transplant
ara-GTP	9-beta-D-arabinofuranosylguanine triphosphate
AYA	adolescent and young adult
B-ALL	B-cell acute lymphoblastic leukemia
C-MTX	Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase
CNS	central nervous system
CNS1	central nervous system disease with no blasts
CNS2	central nervous system disease with a white blood cell count of 5 or lower with blasts
CNS3	central nervous system disease with a white blood cell count greater than 5 with blasts
COG	Children's Oncology Group
CTCAE	Common Terminology Criteria for Adverse Events
DFS	disease-free survival
HD-MTX	high-dose methotrexate with leucovorin rescue
HRQoL	health-related quality of life
ITT	intention to treat
LLSC	Leukemia & Lymphoma Society of Canada
M1	less than 5% blasts
M2	5% to 25% blasts
M3	greater than 25% blasts
MRD	minimal residual disease
NCI	National Cancer Institute
OH-CCO	Ontario Health (Cancer Care Ontario)
OS	overall survival
SE	standard error
T-ALL	T-cell acute lymphoblastic leukemia
T-LBL	T-cell lymphoblastic lymphoma
WBC	white blood cell

Executive Summary

An overview of the submission details for the drug under review is provided in Table 1.

Table 1: Background Information of Application Submitted for Review

Item	Description
Information on drug submitted for review	
Drug product	Nelarabine (Atriance), 5 mg/mL solution for IV infusion
Sponsor	Pediatric Oncology Group of Ontario
Approved Health Canada indication	Nelarabine (Atriance) is indicated for the treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens
Reimbursement request	For addition to front-line multidrug therapy of pediatric and adolescent and young adult patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL
Health Canada approval status	Unlabelled indication
Health Canada review pathway	NA
NOC date	NA
Recommended dose	Six 5-day courses of nelarabine 650 mg/m^2 daily, IV infusion[a]

NA = not applicable; NOC = Notice of Compliance; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma.

[a]Recommended dosage for the treatment of patients with newly diagnosed T-ALL according to the Children's Oncology Group AALL0434 trial.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children, representing one-quarter of cancer diagnoses in children under the age of 15 years.[1,2] In Canada, the incidence of ALL between 2015 and 2018 was between 1.3 and 1.4 cases per 100,000 persons of all ages.[3] Worldwide, the estimated annual incidence is 1 to 5 cases per 100,000 persons based on results of a systematic review of the literature up to 2019.[2] The latest reported mortality data from 2017 showed that 144 Canadians died from ALL.[4] The mortality rate from ALL is lowest in individuals diagnosed before the age of 15 years, and 90% of children younger than 15 are cured when treated appropriately. Mortality increases with age, particularly in patients older than 40 years.[1] 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 and bony pain, and night sweats). Symptoms of central nervous system (CNS) and testicular disease can also present in extramedullary ALL.[5,6]

ALL is classified according to immunophenotype (i.e., if malignant cells originate from B-cells or T-cells).[1,7] In children, approximately 80% to 85% of ALL cases are B-cell phenotypes (i.e., B-lineage or B-cell acute lymphoblastic leukemia [B-ALL]), and 15% to 20% of ALL cases are T-cell phenotypes, (i.e., T-lineage or T-cell acute lymphoblastic leukemia [T-ALL]); whereas in adults, nearly 75% of ALL cases are B-ALL and approximately 25% of ALL cases are T-ALL.[8-11] T-ALL is notably more difficult to treat, with lower overall survival (OS) and event-free survival rates than B-ALL in pediatric and young adult patients.[12-14] Although T-ALL is a high-risk subtype of ALL, studies have demonstrated improved outcomes when treated with

appropriate intensive therapy. For example, event-free survival with T-ALL has increased from 15% to 20% almost 40 years ago to 75% or higher today.[15-17] Diagnosis of ALL and identification of phenotypes are confirmed by bone marrow histology, immunophenotyping, cytogenetics, and, occasionally, specialized molecular-biology techniques.[8,18] The adverse prognostic factors for T-ALL may include the presence of minimal residual disease (MRD) after induction and/or consolidation therapies, early T-cell precursor T-ALL, and specific chromosomal abnormalities detected by bone marrow cytogenetics or polymerase chain reaction evaluation.[1,2,8,19-23]

The objective of this report is to review and critically appraise the evidence submitted by the Pediatric Oncology Group of Ontario on the beneficial and harmful effects of nelarabine (Atriance) as an addition to front-line multidrug therapy in the treatment of intermediate- or high-risk T-ALL in pediatric and adolescent and young adult (AYA) patients.

Stakeholder Perspectives

The information in this section is a summary of input provided by the patient and clinician groups that 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 are included in the stakeholder section at the end of this report.

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 on 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% aged from 1 to 14 years and 20% aged 15 years and older) and March 2023 (46 respondents; 38% aged from 1 to 14 years, 12% aged from 15 to 19 years, and 50% aged 20 years and older) among patients with ALL who were aged no more than 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 using nelarabine for the treatment of ALL. Out of 3 respondents in the 2019 survey, 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 the 2019 and 2023 surveys. First, the survey respondents indicated that pediatric ALL affects all aspects of life, including physical and mental health, financial well-being, social life, and relationships. Caregivers of children with ALL indicated that the pathway to diagnosis is not a straight line, and in many cases it takes multiple visits to a physician before a diagnosis can be made. Second, survey respondents indicated that the symptoms of ALL impede patients' abilities to participate in regular life activities. According to the results of both surveys, the most critical physical effects that individuals with ALL experienced before 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 that 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 impacts of the associated feelings the respondents had experienced throughout diagnosis and treatment of ALL included sadness (76%), fear (74%), nervousness, anxiety, depression (74%), frustration (72%), stress and worry (72%), feeling overwhelmed and/or out of control (70%), loneliness and isolation (70%), posttraumatic stress (68%), and helplessness or hopelessness (66%). Last, survey respondents emphasized that there have been considerable consequences for patients with ALL and their families regarding their financial stability and the ability to maintain employment or financial status due to their ALL diagnosis and treatment schedules. According to the survey results, 38% of patient respondents and 29% of caregiver respondents noted that they have missed career 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 a 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 treatments (e.g., 4% received steroids as part of their treatment). The survey respondents noted that treatment of ALL created difficulties and challenges in all areas of life for patients, caregivers, and their families. For example, a caregiver respondent in the 2019 survey reported that, "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 treatments, the need to travel to and from treatment where necessary was a significant barrier for patients and caregivers. The 2023 survey data showed that, among the patients who received a treatment for ALL other than nelarabine, 37% 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 affected by the ALL treatment, and they listed nausea and vomiting, weakness or loss of strength, low white blood cell (WBC) and platelet counts, and pain as adverse effects.

The surveys found that the patients with ALL and their caregivers hope to return to the comfort of normalcy and quality of life they enjoyed before the onset of disease. The survey results showed that the most important factors they considered 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 were concerned about the long-term effects and safety that the treatments may have on a child and his or her

future health. It is hoped that the new treatment may have fewer and less-severe adverse effects, improve treatment logistics (e.g., fewer trips to the hospital, removing steroids from treatment, and shortening the maintenance period), and provide associated mental health supports.

Nine survey respondents with T-ALL reported experience 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 who reported temporary disease elimination 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 during nelarabine treatment: low platelet count, low red blood cell count, anemia, low WBC count, and extreme sleepiness. Although the distance from the treatment facility to home and the need to travel for treatment with nelarabine affected the quality of life of patients and their caregivers, survey respondents were willing to endure the inconvenience because the treatment worked. Two patient respondents described treatment with nelarabine as "neutral" compared to other treatments, 2 patients reported that nelarabine treatment was "less challenging" than their other treatments, and 1 patient described nelarabine as "more challenging" than other treatments. According to the patient input received, patients who have received nelarabine report that nelarabine gave back life, hope, and normalcy to them 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 pediatric patients, and therefore improve the quality and psychosocial aspects of life for patients and their families.

Clinician Input

Input From Clinical Experts Consulted by CADTH

All CADTH review teams include at least 1 clinical specialist with expertise in 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 (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 reduced relapse rates, prolong life, improved health-related quality of life (HRQoL), and reduced treatment-related morbidity, including morbidity associated with cranial radiation treatment. The clinical experts highlighted the importance of ensuring successful first-line treatment in patients with newly diagnosed T-ALL to minimize relapse rates, as patients with relapsed T-ALL require a total body irradiation (TBI)-based stem-cell transplant. The clinical experts further noted that less than half of patients with relapsed or refractory T-ALL are cured by transplant, and transplants expose patients to a significant risk of early morbidity in the form of graft-versus-host disease, infection, and other treatment-related mortality, and late morbidity through second primary malignancy, end organ toxicity, neurocognitive impairment, and reduced quality of life.

The clinical experts consulted for this review emphasized that nelarabine is currently being considered by many centres in Canada and the US as the standard of care for patients with newly diagnosed T-ALL, and recommended not prescribing nelarabine alone to patients with relapsed T-ALL. The clinical experts mentioned that nelarabine may be used as a single drug (largely in adults in the salvage setting), or in combination with multidrug chemotherapy in patients with newly diagnosed T-ALL. The clinical experts indicated that nelarabine should be used as part of front-line therapy for all patients with newly diagnosed T-ALL, regardless of CNS disease status at diagnosis. They added that, while currently available evidence shows that nelarabine improves outcomes in patients with intermediate- and high-risk T-ALL, it is reasonable to assume that nelarabine would also be effective in patients with low-risk T-ALL. The clinical experts noted 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 OS and event-free survival, reduced relapse rates, improved HRQoL, and reduced treatment with cranial radiation. The clinical experts indicated that children with newly diagnosed T-ALL are assessed at defined time points throughout a 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 deteriorates unexpectedly. The clinical experts pointed out that the most meaningful early outcome in children with T-ALL is MRD-negative remission during treatment; failure to achieve such remission or disease relapse during treatment is considered an indication of the need for escalation of therapy. The clinical experts expected the use of nelarabine in patients with newly diagnosed T-ALL would increase the proportion of patients who achieve an MRD-negative complete response and decrease the proportion of patients who experience a relapse (extramedullary or marrow) during treatment. According to the clinical experts, the potential reasons for discontinuing treatment with nelarabine include refractory disease, disease progression, and significant toxicity (i.e., neurotoxicity grade of 4). They added that nelarabine should be prescribed under the direction of an oncologist in a hospital or outpatient setting.

The clinical experts noted that, according to the indication under review, in Ontario, nelarabine can be added to front-line multidrug therapy for patients with intermediate- or high-risk T-ALL; however, some centres across Canada are successfully prescribing nelarabine to all patients with T- ALL, including those at low risk. The clinical experts cautioned that the impact of a reimbursement recommendation be consistent with the reimbursement request and recommended considering expanding the reimbursement population to include patients with low-risk T-ALL.

Clinician Group Input

Clinician group input was obtained from 3 groups, including the Department of Hematology, Oncology, and Bone Marrow Transplant at the 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 the 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 OH-CCO's mandate, Provincial Drug Reimbursement Programs, and the Systemic Treatment Program. The information in this review was gathered through a literature review, discussions with T-ALL experts, and consultations with clinicians via videoconferencing and email.

The clinician groups indicated that not all patients with T-ALL respond to currently available treatments. Clinicians from the British Columbia Children's Hospital noted that T-ALL represents 10% to 15% of newly diagnosed cases of pediatric acute leukemia, and that, with standard-of-care therapy, the majority of children can be cured. However, nearly 20% of pediatric patients with T-ALL experience relapsed or refractory disease, and salvage rates of relapsed or refractory disease are dismal, with an OS rate of less than 25%. Currently, the standard treatment for pediatric patients with newly diagnosed T-ALL includes multidrug chemotherapy (pediatric-inspired intensive chemotherapy regimens) delivered over approximately 3 years, with additional craniospinal radiation therapy for patients with CNS disease. Clinicians from the British Columbia Children's Hospital highlighted the unmet need to improve event-free survival and 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 additional cranial radiation is associated with a significant risk of chronic neurocognitive sequelae, particularly in young children.

According to the clinician groups, nelarabine can be used following the protocol of Children's Oncology Group (COG) trial AALL0434, which investigated the efficacy and safety of adding nelarabine to standard of care.[15,17] 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 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 multidrug 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 hematological malignancies other than T-ALL 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, MRD 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: achievement of remission (i.e., no detectable leukemic disease) and persistence of disease remission over time without relapse. The clinician groups identified several factors that may lead to the discontinuation of nelarabine, including disease progression and significant intolerance to treatment (e.g., severe or progressive neurotoxicity including but not limited to myelopathy, sensory changes, central neurocognitive decompensation, Guillain-Barré–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 advised that nelarabine should be administered by leukemia specialists at outpatient settings, or under the direction and supervision of a pediatric hematologist-oncologist familiar with the treatment of pediatric T-ALL and equipped to anticipate and support the potential adverse effects of nelarabine.

Drug Program Input

The Provincial Advisory Group identified the following jurisdictional implementation issues: relevant comparators, considerations for initiation of therapy, and prescribing of therapy, generalizability, and care provision issues. The clinical experts consulted by CADTH weighed evidence from the COG AALL0434 trial and other clinical considerations to provide responses to the Provincial Advisory Group's drug program implementation questions (Table 4).

Nelarabine received approvals from the FDA in October 2005 for the treatment of patients with T-ALL and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed after treatment with at least 2 chemotherapy regimens,[24] and in March 2023 for the upfront treatment of patients with T-ALL.[25]

Clinical Evidence

Pivotal Studies and Randomized Controlled Trial Evidence

Description of Studies

The COG AALL0434 trial was a phase III, 2 × 2 pseudofactorial 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-Münster (aBFM) multidrug therapy of pediatric and AYA patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL. This study was conducted by the COG under an investigational new-drug application held by the National Cancer Institute (NCI). A total of 1,596 patients with T-ALL were enrolled from January 2007 to July 2014 across 215 sites in the US, 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 an aBFM backbone containing either Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase (C-MTX), or high-dose methotrexate with leucovorin rescue (HD-MTX). 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:

- arm A: aBFM with C-MTX without nelarabine, n = 24
- arm B: aBFM with C-MTX with nelarabine, n = 24
- arm C: aBFM with HD-MTX with leucovorin rescue and without nelarabine, n = 23
- arm D: aBFM with HD-MTX with leucovorin rescue and nelarabine, n = 23.

The initial safety phase end points 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, patients with intermediate- and high-risk T-ALL (N = 659) were randomized to 1 of 4 treatment arms after completion of induction therapy:

- arm A: aBFM with C-MTX without nelarabine, n = 151
- arm B: aBFM with C-MTX with nelarabine, n = 147
- arm C: aBFM with HD-MTX with leucovorin rescue and without nelarabine, n = 185
- arm D: aBFM with HD-MTX with leucovorin rescue and nelarabine, n = 176.

The primary efficacy end point in the efficacy phase of COG AALL0434 was disease-free survival (DFS), and the secondary efficacy end points were OS and 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, 33.4% 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 CNS disease with no blasts (CNS1), 20.8% had CNS disease with a WBC count of 5 or lower with blasts (CNS2) and 8.6% had CNS disease with a WBC count of greater than 5 with blasts (CNS3) at diagnosis. Bone marrow with less than 5% blasts (M1) at the end of induction was found in 95.3% of patients, and marrow with between 5% and 25% blasts (M2) was found in 4.7% of patients. A total of 83.3% of patients had not received an allogeneic hematopoietic stem-cell transplant (alloHSCT), while 3.2% had undergone an alloHSCT.

Efficacy Results

Table 2 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 nelarabine versus those who did 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 nelarabine or 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 patients (14.7%) experienced DFS events, including 39 patients who received nelarabine compared with 58 patients who did not receive nelarabine. Out of 97 patients, 70 (10.6%) had a relapse, 12 (1.8%) had a secondary malignant neoplasm, and 15 (2.3%) 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 arm showed that the 5-year DFS rates were 91.4% (SE ± 3.1%) in patients who received the C-MTX regimen with nelarabine (n = 147), 87.2% (SE ± 3.5%) in those who received the C-MTX regimen without nelarabine (n = 151), 85.5% (SE ± 3.6%) in those who received the HD-MTX regimen with nelarabine (n = 176), and 78.1% (SE ± 4.0%) in those who received the HD-MTX regimen without nelarabine (n = 185) (P = 0.01).

In patients with intermediate-risk T-ALL who were randomly assigned to receive nelarabine versus not who did 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 nelarabine versus those who did 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).

Central Nervous System 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 patient (3.4%) who was assigned to receive the HD-MTX regimen with nelarabine compared with 6 patients (21.4%) who were assigned to receive the HD-MTX regimen without nelarabine.

Health-Related Quality of Life

HRQoL 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 a nontargeted toxicity with a Common Terminology Criteria for Adverse Events (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 marginally higher among patients who received nelarabine compared to those who did not. Out of 323 patients who received nelarabine, 11 (3.4%) experienced a central neurotoxicity with a CTCAE grade of 3 or higher, 26 (8.0%) experienced a peripheral motor neuropathy with a CTCAE grade of 3 or 4, and 29 (9.0%) experienced a peripheral sensory neuropathy with a CTCAE grade of 3 or 4. Out of 336 patients who did not receive nelarabine, 7 patients (2.1%) experienced a central neurotoxicity with a CTCAE grade of 3 or higher, 19 (5.7%) experienced a peripheral motor neuropathy with a CTCAE grade of 3 or 4, and 27 (8.0%) experienced a peripheral sensory neuropathy with a CTCAE grade of 3 or 4.

Table 2: Summary of Key Results of the Efficacy Phase of COG AALL0434, ITT Population

Detail	COG AALL0434[15]					
	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 overall survival 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 disease-free survival 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 = Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase; DFS = disease-free survival; HD-MTX = high-dose methotrexate with leucovorin rescue; ITT = intention-to-treat; NR = not reported; SE = standard error.

[a]Percentage (SE) of patients alive from the Kaplan-Meier estimates.

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

[c]Percentage (SE) of disease-free events from the Kaplan-Meier 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 the COG AALL0434 trial.

[g]Common Terminology Criteria for Adverse Events grade of 3, 4, or 5.

[h]Common Terminology Criteria for Adverse Events grade of 3 or 4.

Source: Dunsmore et al. (2020).[15]

Critical Appraisal

The COG AALL0434 trial was an open-label, phase III, 2 × 2 pseudofactorial randomized trial comparing nelarabine and an aBFM backbone in pediatric and AYA 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 adverse events (AEs); however, the extent and direction of bias due to treatment knowledge is uncertain. No information is available regarding the treatment-discontinuation rates and the proportion of protocol deviations. The study utilized 2 × 2 pseudofactorial randomization to compare 2 separate treatments: C-MTX versus HD-MTX and nelarabine versus no nelarabine. Because 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 2-stage procedure, including methotrexate and nelarabine randomizations. In addition, no adjustments for multiple comparisons were made in the trial. The primary outcome (DFS) and secondary outcomes (OS and CNS relapse) were considered appropriate for the disease setting and were conducted using the intention-to-treat (ITT) population, which maintained randomization and minimized the risk of bias by comparing groups with similar prognostic factors. The clinical experts consulted for this review 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. No information is available regarding the dropout rates and how missing values in the trial were handled in the trial. Although HRQoL was identified as an important outcome by both clinicians and patients, it was not 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 patient populations seen in clinics, and no concerns were raised about generalizing the findings from the trial to the Canadian clinical setting. However, of the 373 patients who were not eligible for postinduction therapy, 353 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 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 experienced neurotoxicity events and were reluctant to take more medication that could cause more such events. The clinical experts also noted that all patients in the trial received prophylactic cranial radiation, which may cause more harm to the patient, particularly in children aged younger than 5 years.

The COG AALL0434 trial included patients aged 1 to 30 years, and most patients were aged under 15 years. The clinical experts indicated that this is reflective of Canadian clinical practice. The clinical experts also pointed out that nelarabine can be prescribed to patients with T-ALL over 30 years of age, given that the older the patient, the greater the risk of the disease. The clinical experts 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 by some formularies (e.g., nelarabine may be funded through a hospital budget). The clinical experts 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 pointed out that some centres 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, according to the clinical experts consulted for this review, 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 Randomized Controlled Trial Evidence

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

Conclusions

Based on data from the COG AALL0434 trial, nelarabine in combination with an aBFM backbone demonstrated a clinically meaningful and statistically significant benefit compared to an aBFM backbone alone in improving DFS in patients with newly diagnosed intermediate- and high-risk T-ALL. As the median DFS was not reported in either treatment group, the longer-term efficacy of nelarabine for DFS is unknown for upfront therapy of newly diagnosed T-ALL. Compared with placebo, treatment with nelarabine (when added to an aBFM backbone) was associated with a reduction in CNS relapse rates. According to clinical experts consulted for this review, nelarabine could help optimize upfront treatment of T-ALL and improve outcomes in terms of disease recurrence and CNS relapse. In the COG AALL0434 trial, the improvement in OS was modest; however, the duration of treatment exposure and follow-up period were likely too short to observe any beneficial effect of nelarabine on mortality. While notable AEs (central neurotoxicity and peripheral motor and sensory neuropathies) were not insignificant in the COG AALL0434 trial, the clinical experts consulted for this review considered the safety profile of nelarabine to be expected and manageable in patients with newly diagnosed T-ALL. Although HRQoL was identified as an important outcome by both clinicians and patients, it was not evaluated or reported in the COG AALL0434 trial. The clinical experts consulted by CADTH for this review indicated that nelarabine is currently considered the standard of care in addition to aBFM backbone therapy for patients with newly diagnosed T-ALL.

Introduction

The objective of this report is to review and critically appraise the evidence submitted by the Pediatric Oncology Group of Ontario on the beneficial and harmful effects of nelarabine, 650 mg/m^2 daily for IV infusion, in the treatment of pediatric and AYA patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL.

Disease Background

ALL is the most common type of cancer in children, representing one-quarter of cancer diagnoses in children under the age of 15 years.[1,2] In Canada, the incidence of ALL between 2015 and 2018 was between 1.3 and 1.4 cases per 100,000 persons of all ages.[3] Worldwide, the estimated annual incidence is 1 to 5 cases per 100,000 persons based on results of a systematic review of the literature up to 2019.[2] The latest reported mortality rate from 2017 showed that 144 Canadians died from ALL.[4] The mortality rate from ALL is lowest in individuals diagnosed before the age of 15 years, and 90% of children younger than 15 are cured when treated appropriately. Mortality increases with age, particularly in patients older than 40 years.[1] 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, or spleen), and systemic complaints (e.g., fevers, fatigue, joint and/or bone pain, and night sweats). Symptoms of CNS and testicular disease can also present in extramedullary ALL.[5,6]

ALL is classified according to immunophenotype (i.e., if malignant cells originate from B-cells or T-cells).[1,7] In children, approximately 80% to 85% of ALL cases are B-cell phenotypes (i.e., B-ALL), and 15% to 20% of ALL cases are T-cell phenotypes, (i.e., T-ALL); whereas in adults, nearly 75% of ALL cases are B-ALL, and approximately 25% of ALL cases are T-ALL.[8-11] T-ALL is notably more difficult to treat (with lower OS and event-free survival rates) compared with B-ALL in pediatric and young adult patients.[12-14] Although T-ALL is a high-risk subtype of ALL, studies have found that outcomes improve when patients are treated with appropriate intensive therapy; for example, event-free survival in patients with T-ALL has increased from 15% to 20% almost 40 years ago to 75% or higher today.[15-17]

Diagnosis of ALL and identification of phenotypes are confirmed by bone marrow histology, immunophenotyping, cytogenetics, and, occasionally, specialized molecular-biology techniques.[8,18] The adverse prognostic factors for T-ALL may include the presence of MRD after induction and/or consolidation therapies, early T-cell precursor T-ALL, and specific chromosomal abnormalities detected by bone marrow cytogenetics or a polymerase chain reaction evaluation.[1,2,8,19-23]

Standards of Therapy

The contents of this section were informed by clinical expert input. The following summary was validated by the CADTH review team.

Patients with newly diagnosed T-ALL are usually treated with risk-based multidrug chemotherapy regimens for 2 to 3 years, with or without cranial radiation therapy.[26] Treatment of children and young adults with T-ALL demands a complicated risk assessment, assignment of therapies, and the need for supportive care (e.g., management of neurologic side effects).[27] Risk stratification for T-ALL in the COG approach is primarily dependent on the assessment of extramedullary disease at diagnosis, the status of MRD and extramedullary disease at the end of induction therapy (day 29), and at the end of consolidation therapy for patients who do not experience remission at the end of induction.[27,28] The clinical experts consulted for this review indicated that the main goals of T-ALL therapy are to reduce relapse rates, prolong life, improve HRQoL, and reduce treatment with cranial radiation. The clinical experts highlighted the importance of ensuring successful first-

line treatment in patients with newly diagnosed T-ALL to minimize the relapse rate, as patients with relapsed T-ALL require TBI-based stem-cell transplant. The clinical experts added that less than half of patients with relapsed or refractory T-ALL are cured by transplant, and transplants expose patients to significant risks of early morbidity in the form of graft-versus-host disease, infection, and treatment-related mortality, and late morbidity through second primary malignancy, neurocognitive impairment, and reduced quality of life.

The clinical experts consulted for this review indicated that the standard-of-care therapy for T-ALL includes an aBFM multidrug regimen that is consistent with the backbone used in the COG AALL0434 trial.[15,17] The aBFM regimen involves the following drugs divided into several phases of therapy for T-ALL (i.e., induction, consolidation, intensification, and maintenance), including therapy targeting the CNS: cytarabine at a dose of 75 mg/m^2, pegaspargase at a dose of 2,500 units/m^2, age-adjusted intrathecal cytarabine, vincristine at a dose of 1.5 mg/m^2, age-adjusted intrathecal methotrexate, prednisone at a dosage of 30 mg/m^2 twice daily, dexamethasone at a dosage of 5 mg/m^2 twice daily, daunorubicin at a dose of 25 mg/m^2, cyclophosphamide at a dose of 1,000 mg/m^2, cytarabine at a dose of 75 mg/m^2, mercaptopurine at a dose of 60 mg/m^2, IV methotrexate at a dose of 100 mg/m^2, doxorubicin at a dose of 25 mg/m^2, thioguanine at a dose of 60 mg/m^2, leucovorin at a dose of 15 mg/m^2, and cranial or testicular radiation therapy (Table 8). The clinical experts indicated that nelarabine is currently being used as part of the standard of care in Canadian pediatric oncology programs for patients with newly diagnosed T-ALL in addition to an aBFM backbone, and is reimbursed in some formularies (i.e., 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).

Another regimen used for the treatment of T-ALL in adult patients is the chemotherapy combination of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone,[27,29] which includes 2 courses. Course A consists of cyclophosphamide at a dose of 300 mg/m^2, dexamethasone at a dose of 40 mg, doxorubicin at a dose of 300 mg /m^2, and vincristine at a dose of 1.4 mg/m^2; and course B consists of a CNS prophylaxis with intrathecal methotrexate and cytarabine. In hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone, the total daily dose is divided into smaller doses and given more than once a day. Another regimen for the treatment of T-ALL mentioned by the clinical experts is the Dana-Farber regimen[30] for patients under the age of 60 who test negative for the Philadelphia chromosome. This combination treatment consists of doxorubicin at a dose of 30 mg/m^2, vincristine at 2 mg, dexamethasone at 9 mg/m^2, mercaptopurine at 50 mg/m^2, pegaspargase at 1,000 to 2,000 units/m^2, methotrexate at 30 mg/m^2, intrathecal cytarabine at 40 mg, intrathecal methotrexate at 12 mg, and intrathecal hydrocortisone at 15 mg.

Drug Under Review

Key characteristics of nelarabine (for injection) are summarized in Table 3, along with other front-line treatments available for the treatment of patients with T-ALL.

Nelarabine is a water-soluble prodrug of the cytotoxic deoxyguanosine analogue antimetabolite 9-beta-D-arabinofuranosylguanine. Nelarabine is not active itself, and after being demethoxylated by adenosine deaminase to 9-beta-D-arabinofuranosylguanine, phosphorylated by deoxyguanosine kinase and deoxycytidine kinase to a 5′-monophosphate, is subsequently converted intracellularly to its active

5′-triphosphate form, 9-beta-D-arabinofuranosylguanine triphosphate (ara-GTP).[31] With administration of nelarabine, the converted ara-GTP accumulates in leukemic cells, where it inhibits DNA synthesis, resulting in cell death. It has been reported that ara-GTP accumulates in T-cells in a dose-dependent manner.[32,33] In vitro, T-cells are more sensitive to the cytotoxic effects of nelarabine compared to B-cells.[31] Nelarabine is associated with a preferential cytotoxicity in treatment of T-ALL.[32,34]

The recommended dosage of nelarabine is 1,500 mg/m^2 per day IV over 2 hours on days 1, 3, and 5, repeated every 21 days, for adults, and 650 mg/m^2 per day IV over 1 hour on days 1 to 5, repeated every 21 days, for children aged 15 years and younger.[31] The optimal dosing regimen and duration of treatment for patients between the ages of 16 and 21 years have not been determined.[31] A treatment duration for nelarabine has not been clearly established.[31] In clinical trials, treatment with nelarabine was continued until a clinical benefit was observed, disease progressed, the patient became a candidate for bone marrow transplant, or unacceptable toxicity. Nelarabine should be discontinued at the first sign of grade 2 neurologic events as defined by NCI common toxicity criteria.[31] Treatment withholding or discontinuation may be required based on individual safety and tolerability.[31] Nelarabine should be administered under the supervision of health care practitioners experienced in the use of anticancer drugs.[31]

The dossiers for nelarabine were submitted to CADTH with a status of unlabelled indication. The approved Health Canada indication for nelarabine is for the treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens.[31] The sponsor's requested reimbursement criteria are not aligned with the Health Canada–approved indication. In the sponsor's submission to CADTH, nelarabine (for injection) is indicated for addition to front-line multidrug therapy of pediatric and AYA patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL.[35]

Nelarabine received approvals from the 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,[24] and in March 2023 for the upfront treatment of patients with T-ALL.[25]

Table 3: Key Characteristics of Front-Line Treatments for T-ALL

Drug name	Mechanism of action	Indication[a]
Drug under review		
Nelarabine (Atriance)[31]	Nelarabine is demethoxylated by adenosine deaminase to ara-G (a deoxyguanosine analogue antimetabolite) and subsequently converted intracellularly to its active form, 5′-triphosphate (ara-GTP), which exerts cytotoxic effects through inhibition of DNA synthesis resulting in cell death.	For the treatment of patients with T-ALL and T-LBL whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens.[a]
aBFM regimens		
Cytarabine[36]	Cytarabine is a cytotoxin that inhibits DNA polymerase. In culture, cytarabine exhibits cell-phase specificity, primarily killing cells undergoing DNA synthesis (S phase) and under certain	For induction and maintenance of remission in acute leukemia in both adults and children.

Drug name	Mechanism of action	Indication[a]
	conditions blocking the progression of cells from the G1 phase to S phase.	
Daunorubicin (Cerubidine)[37]	Daunorubicin inhibits the synthesis of nucleic acids, both by binding DNA and by inhibiting the reproduction of DNA and the synthesis of RNA in the cell nucleus. As a result, there is an interruption of cell division.	Cerubidine is indicated for the initial treatment of myeloblastic and acute lymphoblastic leukemias. It can also induce remission in patients with chronic myeloid leukemia, a reticulosarcoma, Ewing or Wilms' tumours, and lymphosarcoma.
Pegaspargase (Oncaspar)[38] or erwinia asparaginase (Erwinase)[b39]	Pegaspargase hydrolyzes the nonessential amino acid L-asparagine into aspartic acid and ammonia, depleting the circulating pool of serum L-asparagine and inhibiting protein synthesis, DNA synthesis, and RNA synthesis, particularly in leukemic blasts that are not able to synthesize L-asparagine, and therefore undergo apoptosis. The mechanism of erwinia asparaginase is based on a metabolic defect in asparagine synthesis of the malignant cells. Asparaginase hydrolyzes circulating asparagine, resulting in the starvation and death of the malignant cells.	Pegaspargase: a component of a multidrug chemotherapeutic regimen for the treatment of patients with ALL. Erwinia asparaginase is used primarily in combination with other antineoplastic drugs to induce remission in children and adults with ALL. It may also be used to treat patients who have developed hypersensitivity (but not anaphylaxis) to L-asparaginase derived from *Escherichia coli*.
Vincristine[40]	Vincristine arrests cells in metaphase as a spindle inhibitor. The inhibition links to a reversible binding of the drug to microtubule and spindle proteins in S phase. Vincristine is also associated with an interference of RNA synthesis.	For treatment of acute leukemia.
Methotrexate[41,42]	The cytotoxicity of methotrexate, a folate antagonist, results from 3 actions: inhibition of dihydrofolate reductase (the enzyme that reduces folic acid to tetrahydrofolic acid), inhibition of thymidylate synthase, and alteration of the transport of reduced folates, resulting in a deficiency in the cellular pools of thymidylate and purines and therefore in a decrease in nucleic acid synthesis. Methotrexate interferes with DNA synthesis, repair, and cellular replication. Methotrexate also has immunosuppressive activity that may be a result of inhibition of lymphocyte multiplication.	Methotrexate tablets USP is indicated for neoplastic diseases: • choriocarcinoma: as a single chemotherapy or in combination with other drugs • acute lymphoblastic leukemia, as maintenance therapy • head and neck cancer, in combination with other chemotherapies • metastasis of unknown primary, as palliative combination chemotherapy • Burkitt's lymphoma • advanced stages of childhood lymphoma (III and IV, St. Jude's Children's Research Hospital Staging System) • advanced cases of mycosis fungoides (cutaneous T-cell lymphoma). • Methotrexate injection USP is also indicated for: • breast cancer, as part of cyclophosphamide-methotrexate-fluorouracil therapy

Drug name	Mechanism of action	Indication[a]
		• gastric cancer, palliative combination chemotherapy • osteogenic sarcoma (adjuvant), palliative combination chemotherapy • bladder cancer (advanced) • leptomeningeal spread of malignancies (carcinomatosis, leukemia, and lymphoma) as a single chemotherapy or alternating with cytarabine. Methotrexate is indicated as a disease-modifying antirheumatic drug in the following diseases in which standard therapeutic interventions fail: severe disabling psoriasis and psoriatic arthritis, severe disabling rheumatoid arthritis, and severe disabling seronegative arthritides.
Prednisone (TEVA-Prednisone)[43] or dexamethasone (Apo-Dexamethasone,[44] dexamethasone sodium phosphate injection[45])	Prednisone has an anti-inflammatory effect through the inhibition of leukocyte migration to sites of tissue injury, as well as the impairment of phagocytosis and reduced capillary permeability. Prednisone also has an immunosuppressant effect mainly due to a transient lymphopenia of T lymphocytes, and inhibition of immunoglobulin production of monocytes. Dexamethasone has anti-inflammatory, antiallergic, antipyretic, and immunosuppressive properties. Being a highly potent and long-acting glucocorticoid with negligible sodium-retaining properties, dexamethasone is suitable for use in patients with hypertension and cardiac failure. With a biological half-life of 36 to 54 hours, dexamethasone is suitable in conditions where continuous glucocorticoid action is required.	Both prednisone and dexamethasone are indicated for various diseases, including neoplastic diseases (adjunct treatment) for palliative management of leukemias and lymphomas in adults and acute leukemia of childhood.
Mercaptopurine (Purinethol)[41]	Mercaptopurine is a purine analogue that forms metabolites, including thioguanine nucleotides, which incorporate into DNA or RNA, resulting in cell-cycle arrest and cell death.	Used as maintenance therapy for acute lymphatic (lymphocytic, lymphoblastic) leukemia as part of a combination regimen.
Doxorubicin[45]	Doxorubicin can bind to DNA and inhibit nucleic acid synthesis.	Used as a single drug or in combination with other approved cancer chemotherapeutic drugs to produce regression in neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms tumours, neuroblastomas, soft-tissue sarcomas, bone sarcomas, breast carcinomas, gynecologic carcinomas, testicular carcinomas, bronchogenic carcinoma, Hodgkin disease, non-Hodgkin lymphoma, thyroid carcinoma, bladder carcinomas,

Drug name	Mechanism of action	Indication[a]
		squamous-cell carcinomas of the head and neck, and gastric carcinomas. Used by instillation into the bladder for the topical treatment of superficial bladder tumours.
Cyclophosphamide[46]	Cyclophosphamide, a nitrogen mustard derivative, is a polyfunctional alkylating drug. Its active metabolite, phosphoramide mustard, exhibits the alkylating action. The cytotoxic action of the active metabolite is due to crosslinking of DNA and RNA strands and inhibition of DNA synthesis. Cyclophosphamide is a potent immunosuppressive drug that also inhibits cholinesterase activity.	Used alone or as a component of combination therapy to treat: • frequently responsive myeloproliferative and lymphoproliferative disorders, including malignant lymphomas (Hodgkin disease, non-Hodgkin lymphomas, follicular lymphomas, lymphocytic lymphomas, diffuse histiocytic lymphomas, lymphoblastic lymphomas, Burkitt lymphomas), multiple myelomas, leukemia (chronic lymphocytic leukemia, chronic myelogenous leukemia, acute myelogenous leukemia, acute myelomonocytic leukemia, and ALL in children), and frequently responsive solid malignancies (neuroblastomas, carcinomas of the breast, and retinoblastomas) • frequently responsive solid malignancies, including neuroblastomas, carcinomas of the breast, and retinoblastomas. • malignant neoplasms of the lung. For acute lymphoblastic (stem cell) leukemia (ALL) in children, cyclophosphamide given during remission is effective in prolonging remission duration.
Thioguanine (Lanvis)[47]	The drug's tumour-inhibitory properties may be due to 1 or more of its effects on (a) feedback inhibition of de novo purine synthesis; (b) inhibition of purine nucleotide interconversions; or (c) incorporation into DNA and RNA, resulting in a sequential blockade of the synthesis and utilization of purine nucleotides	For treatment of acute leukemia.
aBFM plus cranial radiation therapy		
aBFM regimens	See above for details	See above for details
Folic acid derivative		
Leucovorin[48]	Leucovorin enhances the cytotoxicity of fluoropyrimidines such as fluorouracil by their metabolites, methylene tetrahydrofolate and fluorodeoxyuridine monophosphate, forming a stable ternary complex with thymidylate synthase and thereby decreasing intracellular levels of that	Leucovorin calcium is indicated: • to diminish the toxicity and counteract the effects of overdosage of folic acid antagonists • to diminish the systemic toxicity of

Drug name	Mechanism of action	Indication[a]
	enzyme and the product thymidylate. The cell then dies as a result of thymine starvation.	methotrexate after administration of methotrexate as a chemotherapeutic drug, as part of chemotherapeutic treatment programs in the management of several forms of cancer • to treat megaloblastic anemias due to folate deficiency, as in sprue and other nutritional deficiencies, and megaloblastic anemias of pregnancy and infancy • for pretreatment followed by fluorouracil to prolong survival in the palliative treatment of patients with advanced colorectal cancer.
Hyper-CVAD Part A		
Cyclophosphamide	See above for details	See above for details
Doxorubicin	See above for details	See above for details
Vincristine	See above for details	See above for details
Asparaginase (Erwinase)[b,39]	Mechanism is based on a metabolic defect in asparagine synthesis of the malignant cells. Asparaginase hydrolyzes circulating asparagine, resulting in the starvation and death of the malignant cells.	Primarily in combination with other antineoplastic drugs to induce remission in children and adults with ALL. It may also be used to treat patients who have developed hypersensitivity (but not anaphylaxis) to L-asparaginase derived from *Escherichia coli*.
Dexamethasone	See above for details	See above for details
Hyper-CVAD Part B		
Methotrexate	See above for details	See above for details
Cytarabine	See above for details	See above for details

Table 4: Key Characteristics of Front-Line Treatments for T-ALL (Continued)

Drug name	Route of administration	Recommended dose	Serious adverse effects or safety issues
Drug under review			
Nelarabine (Atriance)[31]	IV	Adults: 1,500 mg/m^2/day IV over 2 hours on days 1, 3, and 5, repeated every 21 days Children 15 years and younger: 650 mg/m^2/day IV over 1 hour on days 1 to 5, repeated every 21 days The optimal dosing regimen and duration of treatment for patients between the ages of 16 and 21 years have not been determined	CNS effects (i.e., severe somnolence, convulsions, spinal cord necrosis) Peripheral neuropathy (i.e., numbness, paresthesia, motor weakness, paralysis, craniospinal demyelination, and ascending peripheral neuropathies similar to Guillain-Barré syndrome).

Drug name	Route of administration	Recommended dose	Serious adverse effects or safety issues
aBFM regimens			
Cytarabine[36]	IV infusion, SC injection, intrathecal injection	Adults: induction remission: 200 mg/m^2 daily by continuous infusion for 5 days (120 hours); total dose = 1,000 mg/m^2 Repeated approximately every 2 weeks. Maintenance: similar schedules as during induction, with a greater time spacing between courses in most maintenance programs Children: induction and maintenance in children, similar regimens as adults; dosage may be also calculated based on body weight or surface area; when specified amounts of a drug are indicated for the adult dosage, these should be adjusted for children using such factors as age, body weight or body surface area	Cardiomyopathy with subsequent death Gastrointestinal toxicity, at times fatal Acute pancreatitis CNS toxicity, severe neurologic adverse reactions, paraplegia, necrotizing leukoencephalopathy, and spinal cord toxicity Infection Pulmonary toxicity, adult respiratory distress syndrome and pulmonary edema. Myelosuppression Serious drug interactions: IV cytarabine given concomitantly with intrathecal methotrexate may increase the risk of severe neurologic adverse reactions such as headache, paralysis, coma, and stroke-like episodes
Daunorubicin (Cerubidine)[37]	IV	Initial treatment for ALL: 1 mg/kg (30 mg/m^2) daily for 3 to 6 days. Total dose should not exceed 30 mg/kg Maintenance therapy: If the marrow is not completely ablastic after 4 weeks, a weekly injection of 1 mg/kg daunorubicin may be given; the total cumulative dose should not exceed 25 mg/kg, e.g., approximately 500 mg/m^2 for a child of 10 kg; 600 mg/m^2 for a child of 20 kg; 750 mg/m^2 for a child of 30 kg and 900 mg/m^2 for an adult of 60 kg	Thrombocytopenia, anemia, localized infection, cardiopathy, secondary leukemias, severe aplasia, tumour lysis syndrome, colitis, neutropenic enterocolitis (typhlitis), and enterocolitis have been reported. Serious infection (sepsis, septic shock and pneumonia), at times fatal Cerubidine must not be administered to patients who exhibit myocardial lesions or to those above 75 years of age
Pegaspargase (Oncaspar)[38] or erwinia asparaginase (Erwinase)[b39]	Pegaspargase: IM, IV Erwinia asparaginase: IM, SC, or bolus IV	Pegaspargase is employed as part of combination chemotherapy protocols. In adults > 21 years of age: 2,000 U (equivalent to 2.67 mL/m^2 body surface area) every 14 days; in pediatric patients with body surface area > 0.6 m^2 and < 21 years of age: 2,500 U (equivalent to 3.3 mL/m^2 body surface area) every 14 days. In children with a body surface area < 0.6 m^2: 82.5 U (equivalent to 0.1 mL/kg	Pegaspargase: anaphylaxis and serious allergic reactions, CNS toxicity (convulsion, confusional state and somnolence), glucose intolerance, infections, pancreatitis, thrombosis Erwinia asparaginase: pancreatitis, septicemia, bleeding, contact irritant, adverse reactions (hypersensitivity reactions),

Drug name	Route of administration	Recommended dose	Serious adverse effects or safety issues
		body weight) every 14 days Erwinia asparaginase dosing depends on the regimen; from 6,000 U/m^2 of body surface IM 3 times weekly for 9 doses, to 10,000 U/m^2 SC on days 1, 3, 5 of week 4 and day 1 of week 5; the lowest age range of children studied overall in trials was 2 to 6 months	liver function abnormalities; immunosuppressive activity reported
Vincristine[40]	IV	Administered at weekly intervals: • adults: 1.4 mg/m^2 • children: 2 mg/m^2 For children weighing ≤ 10 kg, the initial dosage is recommended to be 0.05 mg/kg once a week (rather than dosing to body surface area), with cautious escalation thereafter, based on effects	Hair loss, leukopenia, neuritic pain, constipation, neuromuscular side effects (sensory impairment, paresthesia, neuritic pain, motor difficulties), convulsions, serious bone marrow depression, anemia, leukopenia, and thrombocytopenia have been reported Neurotoxicity appears to be dose-related; patients with the demyelinating form of Charcot-Marie-Tooth syndrome, patients receiving radiation therapy through ports that include the liver, or pregnant women should not be given vincristine sulphate injection For IV only; fatal if given by other routes
Methotrexate[41,42]	IM, IV, intra-arterial, intrathecal, intracerebroventricular, oral	Oral dosage depends on the regimen.[49] Injection dosage for ALL:[42] • Induction: daily 3.3 mg/m^2 of methotrexate in combination with 60 mg/m^2 of prednisone for 4 to 6 weeks • Maintenance: IV of methotrexate twice weekly in total weekly doses of 30 mg/m^2, or IV in doses of 2.5 mg/kg every 14 days • Methotrexate SC not indicated for treatment of neoplastic diseases[50]	Ulcerative stomatitis, leucopenia, nausea, abdominal distress, malaise, undue fatigue, chills and fever, dizziness, decreased resistance to infection Methotrexate injection USP formulations that contain benzyl alcohol are contraindicated in neonates and for intrathecal, intracerebroventricular, or high-dose therapy Fetal deaths and/or congenital anomalies have been reported; contraindicated for women of childbearing potential until pregnancy is excluded and pregnant patients with psoriasis or rheumatoid arthritis Nitrous oxide anesthesia with methotrexate is contraindicated

Drug name	Route of administration	Recommended dose	Serious adverse effects or safety issues
Prednisone (TEVA-Prednisone)[43] or dexamethasone (Apo-Dexamethasone,[44] dexamethasone sodium phosphate injection[45])	Prednisone: oral Dexamethasone: IV, IM, intra-articular, intralesional, oral	Prednisone: dosages are variable and must be individualized based on the disease under treatment and the response of the patient; initial dosage of 5 mg to 60 mg per day depending on the regimen Dexamethasone: dosages are variable and must be individualized based on severity of the disease and the response of the patient; initial dosage of 0.5 mg to 15 mg per day for oral[44] and 0.5 mg to 20 mg per day for injection[51] depending on the regimen	Prednisone and dexamethasone: same as the typical adverse effects of all systemic corticosteroids, including masking of infections, opportunistic infections, infections, fluid and electrolyte disturbances, pathologic fractures, and suppression of growth in children
Mercaptopurine (Purinethol)[41]	Oral	Maintenance: 1.5 mg/kg to 2.5 mg/kg orally once daily as part of combination chemotherapy maintenance regimen	Bone marrow suppression, macrophage activation syndrome, hepatotoxicity, immunosuppression, carcinogenic and mutagenic, teratogenic
Doxorubicin[45]	IV, intravesical	IV administration: depends on the regimen; dosing schedule can be 60 to 75 mg/m^2 as a single IV injection administered at 21-day intervals; weekly doses of 20 mg/m^2; or 30 mg/m^2 on each of 3 successive days repeated every 4 weeks	Cardiomyopathy (decrease in left ventricular ejection fraction, signs and symptoms of congestive heart failure), secondary malignancies (secondary acute myelogenous leukemia, myelodysplastic syndrome), extravasation and tissue necrosis, myelosuppression and sequelae (fever, infections, septic shock, hemorrhage, tissue hypoxia, or death), hepatic impairment
Cyclophosphamide[46]	IV, oral	Initial: • Adults: IV 40 to 50 mg/kg (1.5 to 1.8 g/m^2) as 10 to 20 mg/kg/day for 2 to 5 days • Children: IV 2 to 8 mg/kg (60 to 250 mg/m^2) in divided doses for 6 or more days Maintenance: • Adults: options of IV 10 to 15 mg/kg (350 to 550 mg/m^2) every 7 to 10 days, 3 to 5 mg/kg (110 to 185 mg/m^2) twice weekly, or orally taken 1 to 5 mg/kg/day • Children: options of IV 10 to15 mg/kg every 7 to 10 days, or 30 mg/kg at 3- to 4-week intervals or when	Secondary malignancy, acute cardiac toxicity, severe QT prolongation associated with ventricular tachyarrhythmia, hepatotoxicity, severe myelosuppression (cyclophosphamide should not be administered to patients with a leukocyte count below 2,500 cells/mm^3 and/or a platelet count below 50,000 cells/mm^3), urotoxicity, acute pulmonary toxicity, and fulminating anaphylaxis (with fatal outcome) Drug-drug interaction with depolarizing muscle relaxants causes inhibition of

Drug name	Route of administration	Recommended dose	Serious adverse effects or safety issues
		bone marrow recovery occurs, or orally taken 2 to 5 mg/kg (50 to 150 mg/m^2) twice weekly	cholinesterase activity Live vaccines may lead to vaccine-induced infection in patients on cyclophosphamide
Thioguanine (Lanvis)[47]	Oral	Initial dosage of approximately 2 mg/kg body weight/day, followed by cautiously increasing to 3 mg/kg/day, if after 4 weeks on the initial dosage there is no clinical improvement and no leukocyte depression For pediatric patients (≤ 18 years of age), similar dosages can be administered, with appropriate correction for body surface area	Myelosuppression including life-threatening infections and bleeding, especially in patients with thiopurine S-methyltransferase deficiency Liver toxicity Potential severe infection after immunization using a live organism vaccine Not recommended for maintenance therapy or similar long-term continuous treatments due to the high risk of liver toxicity
aBFM plus cranial radiation therapy			
aBFM regimens	See above for details	See above for details	See above for details
Folic acid derivative			
Leucovorin[48]	IV, IM	Use after chemotherapy with methotrexate: leucovorin is given about 6 to 24 hours following methotrexate administration, in amounts equal to the weight of methotrexate give; if the 24-hour serum creatinine has increased by 50% over baseline or if the 24-hour methotrexate level is greater than 5×10^{-6} M or the 48-hour level is greater than 9×10^{-7} M, the dosage of leucovorin should be increased to 100 mg/m^2 IV every 3 hours until the methotrexate level is less than 10^{-8} M. Due to the calcium content of leucovorin solution, no more than 160 mg of leucovorin should be injected, per minute, IV	Leucovorin should only be given by IM or IV injection and must not be administered intrathecally Leucovorin should only be used with 5-fluorouracil or methotrexate under the direct supervision of a clinician experienced in the use of cancer chemotherapeutic drugs Patients receiving any combination therapy regimen involving leucovorin and fluorouracil should be carefully monitored for diarrhea and/or stomatitis or mucositis as these are the first indications that severe and potentially life-threatening toxicity could develop Fatalities have occurred as a result of gastrointestinal toxicity (predominantly mucositis and diarrhea), or myelosuppression Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis, some fatal, have been

Drug name	Route of administration	Recommended dose	Serious adverse effects or safety issues
			reported in patients receiving leucovorin in combination therapy
Hyper-CVAD Part A			
Cyclophosphamide	See above for details	See above for details	See above for details
Doxorubicin	See above for details	See above for details	See above for details
Vincristine	See above for details	See above for details	See above for details
Asparaginase (Erwinase)[b39]	IM, SC, or bolus IV	Depends on the regimen: from 6,000 U/m^2 of body surface IM 3 times weekly for 9 doses, to 10,000 U/m^2 SC on days 1, 3, 5 of week 4 and day 1 of week 5 The lowest age range of children studied overall in trials was 2 to 6 months	Pancreatitis, septicemia, bleeding, contact irritant, adverse reactions (hypersensitivity reactions), liver function abnormalities. Immunosuppressive activity reported
Dexamethasone	See above for details	See above for details	See above for details
Hyper-CVAD Part B			
Methotrexate	See above for details	See above for details	See above for details
Cytarabine	See above for details	See above for details	See above for details

aBFM = augmented Berlin-Frankfurt-Münster; ALL = acute lymphoblastic leukemia; ara-G = 9-beta-D-arabinofuranosylguanine; ara-GTP = 9-beta-D-arabinofuranosylguanine triphosphate; CNS = central nervous system; hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IM = intramuscular; SC = subcutaneous; T-ALL = T-cell acute lymphoblastic leukemia; T-LBL = T-cell lymphoblastic lymphoma; USP = United States Pharmacopeia.

[a]Health Canada–approved indication.

[b]Erwinase (Erwinia L-asparaginase) is labelled as "Cancelled Post Market" according to the Health Canada Drug Product Database.

Source: Product monographs.[31,36-51]

Stakeholder Perspectives

Patient Group Input

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

The patient input for this review was collected by the LLSC. The LLSC is a national charitable organization dedicated to blood cancer with a focus on 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% aged from 1 to 14 years and 20% aged 15 years and older) and March 2023 (46 respondents; 38% aged from 1 to 14 years, 12% aged from 15 to 19 years, and 50% aged 20 years and older) among patients with ALL aged less than or equal to 30 years at diagnosis, or their caregivers. It was unclear whether the patients with T-ALL were included in the surveys. The LLCS input included 9 patient respondents

with experience with nelarabine for the treatment of ALL. In particular, of 3 respondents in the 2019 survey, 1 accessed the drug through compassionate use, and 2 through a clinical trial.

Patient and caregiver respondents' experience with the disease are jointly summarized in 4 themes, based on the results of both the 2019 and 2023 surveys. First, the survey respondents indicated that pediatric ALL is a difficult experience that affects all aspects of life, including physical and mental health, financial well-being, social life, and relationships. Caregivers of children with ALL indicated that the pathway to diagnosis is not a straight line, and in many cases it takes multiple visits to a physician before a diagnosis can be made. Second, survey respondents indicated that the ALL symptoms impede patients' abilities to participate in regular life activities. According to the results of both surveys, the most critical physical effects that individuals with ALL experienced before diagnosis were fatigue, pain, and nausea or vomiting. Caregivers emphasized 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 in addition to physical impacts. According to the survey results, the most significant detrimental impacts on patients and their caregivers were on 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 associated feelings the respondents had experienced throughout diagnosis and treatment of ALL included sadness (76%), fear (74%), nervous, anxious, depressed (74%), frustration (72%), stress and/or worry (72%), a sense of being overwhelmed and/or out of control (70%), loneliness and isolation (70%), posttraumatic stress (68%), and helplessness or hopelessness (66%). Last, survey respondents reported considerable consequences for patients with ALL and their families regarding their financial well-being and the ability to maintain employment and/or financial stability due to an ALL diagnosis and treatment schedules. According to the survey results, 38% of patient respondents and 29% of caregiver respondents described missing 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 reported that ALL treatment created difficulties and challenges in all areas of life for patients, caregivers, and their families. For example, in the 2019 survey a caregiver respondent stated, "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 treatments, the need to travel to and from treatment where necessary was a significant barrier for patients and caregivers. Data from the 2023 survey showed that, among the patients who received an ALL treatment other than nelarabine, 37% had to travel long distances by car in their province or state. Approximately 78% of those who did not receive 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 a treatment other than nelarabine reported that the quality of life for patients, caregivers and their families was severely affected by the ALL treatment and described adverse effects of nausea and vomiting, weakness or loss of strength, low WBC and platelet counts, and pain.

The surveys found that the patients with ALL and their caregivers hope to restore the comfort of normalcy and quality of life they enjoyed before the onset of disease. The survey results showed that the most important factors to 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 they are concerned about the long-term effects and safety that any new treatments may have on a child and their 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 reported experience 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 who reported temporary disease elimination 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 during nelarabine treatment: low platelet count, low red blood cell count, anemia, low WBC count, and extreme sleepiness. Although the distance from the treatment facility to home and the need to travel for nelarabine treatment affected the quality of life of patients and their caregivers, survey respondents were willing to endure this inconvenience because the treatment worked. Two patient respondents described treatment with nelarabine as “neutral” in comparison to other treatments, 2 patients indicated that nelarabine treatment was “less challenging” than their other treatments, and 1 patient reported that nelarabine was “more challenging” than other treatments. According to the patient input received, the responses of patients who have received nelarabine indicate that nelarabine restored life quality, hope, and normalcy to patients and their families after treatment. The LLSC recommended that nelarabine be approved for the indication under review and suggested that it will help alleviate the gaps in current ALL therapy among patients, including pediatrics patients, and therefore 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 1 clinical specialist with expertise in 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 (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.

Unmet Needs

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

Place in Therapy

The clinical experts indicated that nelarabine is currently being considered by many centres in Canada and the US as the standard of care for patients with newly diagnosed T-ALL, and recommended not prescribing nelarabine alone to patients with relapse. The clinical experts noted that nelarabine may be used as a single drug (largely in adults in a salvage setting), or in combination with multidrug chemotherapy in patients with newly diagnosed T-ALL, such as the aBFM backbone used in the COG AALL0434 trial.[15,17]

Patient Population

The clinical experts 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 highlighted that, while currently available evidence shows that nelarabine improves outcomes in patients with intermediate- and high-risk T-ALL, it is reasonable to assume that nelarabine would also be effective in the treatment of patients with low-risk T-ALL. According to the clinical experts, it is not possible to identify patients whose disease is likely to respond to treatment. The clinical experts noted 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.

Assessing the Response to Treatment

To assess a response to treatment of newly diagnosed T-ALL, the outcomes used to determine whether a patient is responding include improved OS 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 biopsy is repeated if the patient's condition does not improve as expected or deteriorates unexpectedly. According to the clinical experts, the most meaningful early outcome in children with T-ALL is achievement of MRD-negative remission during treatment; failure to achieve such remission or disease relapse during treatment are considered indications

that support escalation of therapy. The clinical experts expected that the use of nelarabine in patients with newly diagnosed T-ALL would increase the proportion of patients who achieve an MRD-negative complete response, and decrease the proportion of patients who relapse during treatment.

Discontinuing Treatment

According to the clinical experts, the potential reasons for discontinuing treatment with nelarabine include refractory disease, disease progression, and significant toxicity (i.e., grade 4 neurotoxicity according to the CTCAE).

Prescribing Considerations

According to the clinical experts, nelarabine should be prescribed under the direction of an oncologist in a hospital or outpatient setting.

Low-Risk T-Cell Acute Lymphoblastic Leukemia

The clinical experts noted that, in Ontario, nelarabine added to front-line multidrug therapy is offered to patients with intermediate- or high-risk T-ALL (according to the indication under review); however, some centres across Canada are successfully prescribing nelarabine to all patients with T-ALL, including those at low risk. The clinical experts cautioned that the impact of a reimbursement recommendation should be consistent with the reimbursement request and recommended considering expanding the reimbursement population to include low-risk T-ALL.

Clinician Group Input

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

The clinician group input was obtained from 3 clinician groups, including the Department of Hematology, Oncology, and Bone Marrow Transplant at the 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 the 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 a review of the literature, and discussions with T-ALL experts or consulting 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% to 15% of newly diagnosed pediatric acute leukemia, and with standard-of-care therapy, the majority of children can be cured. However, nearly 20% of pediatric patients with T-ALL experience relapsed or refractory disease, and the salvage rate of relapsed or refractory disease is poor, with an OS of less than 25%. Currently, the standard treatment for pediatric patients with newly diagnosed T-ALL includes multidrug chemotherapy (pediatric-inspired intensive chemotherapy regimens) delivered over approximately 3 years, with additional craniospinal radiation therapy for patients with CNS disease. Clinicians from the British Columbia Children's Hospital emphasized the unmet need to improve event-free survival and 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. The clinician groups further noted that 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 following the protocol used by the COG AALL0434 trial that investigated efficacy and safety of adding nelarabine to standard of care.[15,17] According to the clinician groups, patients between the ages of 1 and 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 diagnosis of this disease includes 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 between the ages of 1 and 30 years would be incorporated into a multidrug 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 forms of hematological malignancies other than T-All 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 receive regular follow-up disease assessments after induction and consolidation cycles of chemotherapy, which may include bone marrow aspirate and biopsy, MRD testing, spinal fluid assessment, peripheral blood assessment, and imaging and physical examination of extramedullary sites of disease, as required. The clinician groups reported that achievement of remission (i.e., no detectable leukemic disease) and the persistence of disease remission over time without relapse should be used to evaluate response to treatment in patients with T-ALL. The clinician groups identified several events that may warrant discontinuation of nelarabine, including disease progression and significant intolerance to treatment (e.g., severe or progressive neurotoxicity including but not limited to myelopathy, sensory changes, central neurocognitive decompensation, Guillain-Barré–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 familiar with the treatment of pediatric T-ALL and equipped to anticipate and respond to the potential adverse effects of nelarabine.

Drug Program Input

The drug programs provide input on each drug being reviewed through CADTH's reimbursement review processes by identifying issues that may affect their ability to implement a recommendation. The implementation questions and corresponding responses from the clinical experts consulted by CADTH are summarized in Table 4.

Table 5: Summary of Drug Plan Input and Clinical Expert Response

Drug program implementation questions	Clinical expert response
Relevant comparators	
Issues with the choice of comparator in the submitted trial: Standard COG protocol (multidrug regimen) for T-ALL.	Comment from the drug programs to inform pERC deliberations.
Considerations for initiation of therapy	
Eligibility to re-treatment: Can re-treatment with nelarabine be considered in a later line of therapy in cases of relapsed disease?	Nelarabine could be considered as part of reinduction or reconsolidation treatment before alloHSCT in patients with relapsed T-ALL.
Considerations for prescribing of therapy	
Dosing, schedule and frequency, dose intensity: The recommended dose is a total of 6 courses of 650 mg/m^2/day, administered IV over 1 hour on 5 consecutive days with a total of 6 cycles administered as part of a multidrug regimen.	Comment from the drug programs to inform pERC deliberations.
Generalizability	
Populations of interest matching the indication but with insufficient data: Should patients with low-risk T-ALL (excluded from trial) be eligible for front-line treatment with nelarabine in combination with multidrug chemotherapy?	There is no clinical evidence available regarding the use of nelarabine in patients with low-risk T-ALL. Patients with low-risk T-ALL were excluded from nelarabine randomization in the COG AALL0434 trial 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 centres across Canada are successfully prescribing nelarabine to all patients with T- ALL, including those at low risk. Nelarabine can therefore be used in patients with low-risk T-ALL. The impact of a reimbursement recommendation should be consistent with the reimbursement request and expanding the reimbursement population to include patients with low-risk T-ALL should be considered.
Populations outside the indication or reimbursement request but of interest to jurisdictions: Should adult patients (> 30 years of age) be considered for treatment with nelarabine?	There is no clinical evidence available regarding the use of nelarabine in patients older than 30 years. Nelarabine can be prescribed to patients older than 30 years with T-ALL, given that the older the patient, the higher the risk of the disease. Most patients with newly diagnosed T-ALL are young, and the number of newly diagnosed T-ALL in patients older than 30 years is low.
Patients on active treatment with a time-limited opportunity to switch to the drug(s) under review: Most pediatric centres are currently using nelarabine (hospital budget) in front-line T-ALL protocols	Comment from the drug programs to inform pERC deliberations.
Care provision issues	
Drug preparation, storage, administration or dispensing: 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	Comment from the drug programs to inform pERC deliberations.

Drug program implementation questions	Clinical expert response
be unlikely due to the small patient population. However, with published extended stability data, more than 1 daily dose of nelarabine may be compounded at once, which could reduce vial wastage.	
Other care provision issues: Requires monitoring for potential neurologic side effects.	Comment from the drug programs to inform pERC deliberations.

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

Clinical Evidence

The objective of CADTH's Clinical Review is to review and critically appraise the clinical evidence submitted by the Pediatric Oncology Group of Ontario on the beneficial and harmful effects of nelarabine for addition to front-line multidrug therapy of pediatric and AYA patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-cell acute lymphoblastic leukemia (T-ALL). The focus will be placed on comparing nelarabine to relevant comparators and identifying gaps in the current evidence.

Systematic Review (Pivotal and Protocol-Selected Studies)

Objectives

To perform a systematic review of the beneficial and harmful effects of nelarabine for addition to front-line multidrug therapy of pediatric and AYA patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL.

Methods

Studies selected for inclusion in the systematic review include those meeting the selection criteria presented in Table 6. Outcomes included in the CADTH review protocol reflect those considered to be important to patients, clinicians, and drug plans.

An information specialist performed the literature search for clinical studies, using a peer-reviewed search strategy according to CADTH's *PRESS Peer Review of Electronic Search Strategies* checklist.[52]

Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid and Embase via Ovid. All Ovid searches were run simultaneously as a multifile search. Duplicates were removed using Ovid deduplication for multifile searches, followed by manual deduplication in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the population, intervention, comparison, outcomes and study (PICOS) framework and research questions. The main search concept was nelarabine (Atriance). The following clinical trials registries were searched: the US National Institutes of Health's clinicaltrials.gov, WHO's International Clinical Trials Registry Platform search portal, Health Canada's Clinical Trials Database, the European Union Clinical Trials Register, and the European Union Clinical Trials Information System.

Table 6: Inclusion Criteria for the Systematic Review

Criteria	Description
Patient populations	Populations: Pediatric, adolescent, and young adult patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-cell acute lymphoblastic leukemia. Subgroups: • MRD response (M1, M2, or M3) at the end of consolidation • CNS status at diagnosis
Intervention	Nelarabine in addition to front-line multidrug therapy

Comparators	• Augmented Berlin-Frankfurt-Münster chemotherapy:
	  ◦ Cytarabine
	  ◦ Daunorubicin
	  ◦ Pegaspargase or erwinia asparaginase
	  ◦ Vincristine
	  ◦ Methotrexate
	  ◦ Prednisone or dexamethasone
	  ◦ Mercaptopurine
	  ◦ Doxorubicin
	  ◦ Cyclophosphamide
	  ◦ Thioguanine
	  ◦ Mercaptopurine
	  ◦ Leucovorin
	• Augmented Berlin-Frankfurt-Münster chemotherapy plus cranial radiation therapy[a]
	• Hyper-CVAD[b]:
	  ◦ Course A:
	  ▪ Cyclophosphamide
	  ▪ Doxorubicin
	  ▪ Vincristine
	  ▪ Asparaginase
	  ▪ Dexamethasone
	  ◦ Course B:
	  ▪ Methotrexate
	  ▪ Cytarabine

Outcomes	Efficacy outcomes: • Overall survival • Progression-free survival • Disease-free survival • CNS relapse • Bone marrow relapse • Response rate • Relapse-free survival[c]

Criteria	Description
	• Duration of response[d] • Health-related quality of life[d] Harms outcomes: • Adverse events • Serious adverse events • Withdrawal due to adverse events • Mortality • Notable harms/harms of special interest: neurotoxicity (including peripheral motor neuropathy) and peripheral sensory neuropathy central neurotoxicity (including convulsions, central neurocognitive decompensation, and spinal cord necrosis)
Study design	Published and unpublished phase III and IV randomized controlled trials Published real-world evidence

CNS = central nervous system; hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; M1 = less than 5% blast; M2 = 5% to 25% blasts; M3 = greater than 25% blasts; MRD = minimal residual disease.

[a]Used in patients with CNS disease with a white blood cell count greater than 5 with blasts.

[b]Used in adult patients with T-cell acute lymphoblastic leukemia.

[c]Including time to relapse.

[d]These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

No filters were applied to limit the retrieval by study type. Retrieval was not limited by publication date or by language. Conference abstracts were excluded from the search results. Appendix 1 provides detailed search strategies. The initial search was completed on March 31, 2023. Regular alerts updated the search until the meeting of the CADTH pan-Canadian Oncology Drug Review Expert Committee on August 9, 2023.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from CADTH's Grey Matters: A Practical Tool For Searching Health-Related Grey Literature. Included in this search were the websites of regulatory agencies (FDA and European Medicines Agency). Google was used to search for additional internet-based materials. Appendix 1 provides more information on the grey literature search strategy.

These searches were supplemented by a review of bibliographies of key papers and by contacting appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Findings From the Literature

A total of 296 studies were identified from the literature search and 2 reports[15,17] of a single study were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 7. A list of excluded studies is presented in Appendix 2.

Pivotal Studies and Randomized Controlled Trial Evidence

The following summary was validated by the CADTH review team.

Description of Studies

Characteristics of the included study are summarized in Table 7.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

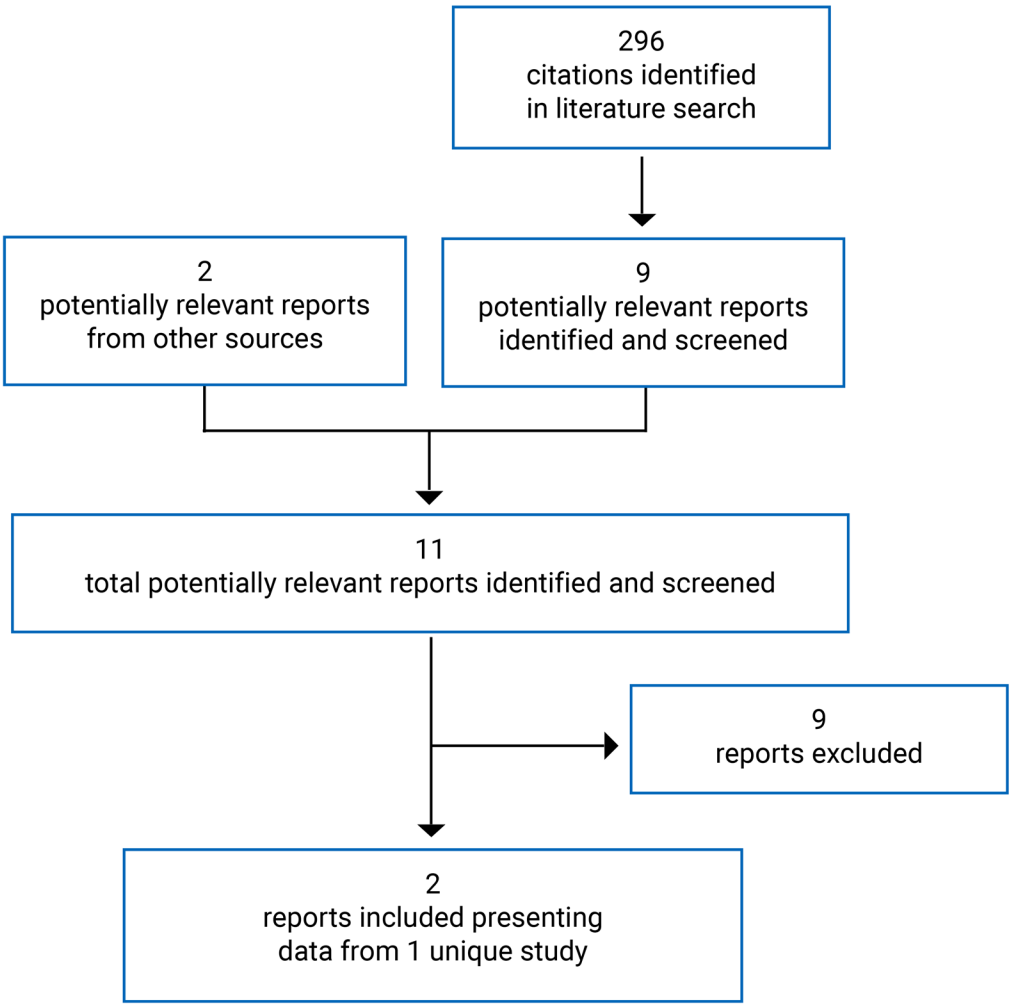


Table 7: Details of the Pivotal Study

Detail	COG AALL0434
Designs and populations	
Study design	Phase III, 2 × 2 pseudofactorial randomized, open-label trial
Locations	215 sites in the US, Australia, Canada, New Zealand, and Switzerland
Patient enrolment dates	Start date: January 2007 End date: July 2014
Randomized (N), initial safety phase	94 patients[a] • Arm A: aBFM with C-MTX without nelarabine — 24 patients • Arm B: aBFM with C-MTX with nelarabine — 24 patients

Detail	COG AALL0434
	• Arm C: aBFM with HD-MTX without nelarabine — 23 patients • Arm D: aBFM with HD-MTX with nelarabine — 23 patients

Randomized (N), efficacy phase	659 patients[b]
	• Arm A: aBFM with C-MTX without nelarabine — 151 patients
	  ◦ 97 patients with intermediate-risk T-ALL
	  ▪ 1 patient with alloHSCT
	  ◦ 54 patients with high-risk T-ALL
	  ▪ 4 patients with alloHSCT
	• Arm B: aBFM with C-MTX with nelarabine — 147 patients
	  ◦ 95 patients with intermediate-risk T-ALL
	  ◦ 52 patients with high-risk T-ALL
	  ▪ 2 patients with alloHSCT
	• Arm C: aBFM with HD-MTX without nelarabine — 185 patients
	  ◦ 123 patients with intermediate-risk T-ALL
	  ▪ 27[c] patients with CNS3 or testicular disease
	  ◦ 62 patients with high-risk T-ALL
	  ▪ 11[c] patients with CNS3 or testicular disease
	  ▪ 8 patients with alloHSCT
	• Arm D: aBFM with HD-MTX with nelarabine — 176 patients
	  ◦ 118 patients with intermediate-risk T-ALL
	  ▪ 25[c] patients with CNS3 or testicular disease
	  ◦ 58 patients with high-risk T-ALL
	  ▪ 8[c] patients with CNS-3 or testicular disease
	  ▪ 6 patients with alloHSCT

Nonrandomly assigned during efficacy phase (not included in this review)	487 patients[d] • Arm A: aBFM with C-MTX — 221 patients • Arm C: aBFM with HD-MTX — 266 patients • Arm De: aBFM with HD-MTX with nelarabine — 43 patients
Inclusion criteria	• Patients must be greater than 1 and less than 31 years of age • Patients with T-ALL should be enrolled in the AALL08B1 trial[f] before treatment and enrolled in the COG AALL0434 trial • Newly diagnosed T-ALL[g] ◦ Patients with pre-existing peripheral neurotoxicity of CTCAE grade of 2 or higher, as determined before induction treatment phase, were not eligible to receive nelarabine
Exclusion criteria	• Pregnant or lactating females • Down syndrome • Prior cytotoxic chemotherapy (except for corticosteroids and/or intrathecal cytarabine) • Patients with a pre-existing, medication-dependent seizure disorder were not eligible for nelarabine randomization.
Intervention	Six 5-day courses of nelarabine 650 mg/m^2/dose, IV infusion

Detail	COG AALL0434
Comparator(s)	aBFM regimen: • Cytarabine, age-adjusted, intrathecally • Vincristine, 1.5 mg/m^2 (max dose 2 mg), IV • Prednisone, 30 mg/m^2, twice a day, orally • Daunorubicin, 25 mg/m^2, IV • Pegaspargase, 2,500 units/m^2 • Methotrexate, age-adjusted, intrathecally or orally • Cyclophosphamide, 1,000 mg/m^2, IV • Mercaptopurine, 25 to 75 mg/m^2/day, orally[h] • Doxorubicin, 25 mg/m^2 • Thioguanine, 60 mg/m^2/d • Dexamethasone, 5 mg/m^2 twice a day, orally • Leucovorin, 15 mg/m^2, orally • Cranial radiation therapy[i] • Testicular radiation therapy[j]
Study duration	
Induction	28 days
Consolidation[k]	Arms A and C: 56 days Arms B and D: 77 days
Interim maintenance[l]	56 days
Delayed intensification[m]	63 days
Maintenance[n]	From week 30 until end of therapy (2 to 3 years)
Outcomes	
Primary end point	Disease-free survival[o]
Secondary and exploratory end points	Secondary: • Overall survival[p] • CNS relapse[q] • Testicular relapse[r] • Bone marrow relapse[s] • Event-free survival[t] Safety: Adverse events with CTCAE grade 3 or higher, sensory neuropathy, motor neuropathy, central neuropathies, non-neurologic toxicities, and mortality.
Publication status	
Publications	Dunsmore et al. (2020)[15] Winter et al. (2015)[17]

aBFM = augmented Berlin-Frankfurt-Münster chemotherapy; ALL = acute lymphoblastic leukemia; alloHSCT = allogeneic hematopoietic stem-cell transplant; ANC = absolute neutrophil count; C- MTX = Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase; COG = Children's Oncology Group; CNS = central nervous system; CNS1 = central nervous system disease with no blasts; CNS2 = central nervous system disease with a white blood cell count of 5 or lower with blasts; CNS3 = central nervous system disease with a white blood cell count greater than 5 with blasts; CSF = cerebral spinal fluid; CTCAE = Common Terminology Criteria for Adverse Events; HD-MTX = high-dose methotrexate with leucovorin rescue; M1 = less than 5% blast; M2 = 5% to 25% blasts; M3 = greater than 25% blasts; T-ALL = T-cell acute lymphoblastic leukemia: WBC = white blood cell.

[a]Patients with high-risk T-ALL.

[b]Patients with intermediate- or high-risk T-ALL.

[c]Patients with CNS3 or testicular disease were assigned to receive HD-MTX regimen with or without nelarabine.

[d]Patients with low- or intermediate-risk T-ALL during the safety phase, or patients with seizure disorder or pre-existing peripheral neuropathy during the efficacy phase.

[e]Patients with induction failure, including those who had allogeneic hematopoietic stem-cell transplant, were nonrandomly assigned to arm D and could remain on study if an M1 or M2 marrow was achieved by the end of consolidation.[15]

[f]AALL08B1 aimed to provide a risk-classification scheme for all patients with newly diagnosed ALL, which will be used to assign treatment on COG front-line ALL treatment studies, and to capture classification data for correlative studies accompanying current COG ALL treatment protocols.

[g]A diagnosis of T-ALL is established when leukemic blasts lack myeloperoxidase or evidence of B-lineage derivation (CD19/CD22/CD20), and express either surface or cytoplasmic CD3 or 2 or more of the antigens CD8, CD7, CD5, CD4, CD2 or CD1a. If surface CD3 is expressed on all leukemic cells, additional markers of immaturity, including TdT, CD34 or CD99 will be assessed for expression. Cases with uncertain expression will receive additional review within the appropriate COG reference laboratory.

[h]A dose of 60 mg/m^2 in patients in any of 4 treatment arms during consolidation therapy, 25 mg/m^2 in patients in arms C and D during interim maintenance therapy, and 75 mg/m^2 per day in patients in any of 4 treatment arms during maintenance therapy.

[i]Cranial radiation therapy: CNS1 or CNS2: 1.5 Gy/day over 8 fractions; CNS3: 1.8 Gy/day in 10 fractions for intermediate-risk and high-risk participants only. Intrathecal therapy is not held during the concomitant administration of cranial radiation therapy.

[j]Testicular radiation therapy: for biopsy-proven, persistent disease only: 2 Gy/day in 12 fractions.

[k]Starts on day 36 (7 days following end of induction) or when peripheral counts recover with an ANC of 750/μL or greater and a platelet count of 75,000/μL or greater (whichever occurs later).

[l]Begin interim maintenance when peripheral counts recover with an ANC of 750/μL or greater and a platelet count of 75,000/μL or greater. All therapy should be interrupted for patients with presumed or proven severe infections and resumed when the signs of infection have abated. Obtain blood counts 10 days after initial dose of methotrexate.

[m]Patients should have an ANC of 750/μL or greater and a platelet count of 75,000/μL or greater before starting therapy on days 1 and 29. Once delayed intensification has begun, it may be interrupted for myelosuppression on day 29 only. Once the day 1 therapy or day 29 cyclophosphamide has been given, the remainder of the therapy should not be held solely for myelosuppression, which is expected to occur. Therapy must be interrupted for patients with serious proven or presumed infection and resumed when the signs of infection have abated.

[n]Maintenance begins when peripheral counts recover with an ANC of 750/μL or greater and a platelet count of 75,000/μL of greater. Only mercaptopurine and oral methotrexate will be interrupted for myelosuppression. For females with T-ALL, continue to repeat 12-week cycles of maintenance therapy until the total duration of therapy is 2 years from the start of interim maintenance (approximately week 121). For males with T-ALL, continue to repeat 12-week cycles of maintenance therapy until the total duration of therapy is 3 years from the start of interim maintenance (approximately week 173).

[o]Disease-free survival was defined as the time from postinduction randomization to first event (relapse, second malignant neoplasm, or remission death) or date of last contact.

[p]Overall survival was defined as the time from study enrolment or, for the randomized cohorts, from postinduction randomization to death or date of last contact.

[q]Positive cytomorphology and a WBC/μL of 5 or higher or positive cytomorphology with CSF WBC of 0 to 4/μL on 2 successive months. If any CSF evaluation shows positive cytomorphology and a WBC/μL of less than 5, a second CSF evaluation is required in 4 weeks. Identification of leukemic clone in CSF by flow cytometry (CD2, CD3, CD34, or the same T-cell immunophenotypic markers that were identified at diagnosis) or fluorescence in situ hybridization for diagnostic karyotypic abnormality is encouraged.

[r]Testicular relapse should be documented by testicular biopsy if the testicular relapse was isolated.

[s]Bone marrow relapse was defined as M3 marrow at any point after day 29.

[t]Event-free survival was defined as time from study enrolment to first event (induction failure, induction death, relapse, second malignant neoplasm, or remission death) or date of last contact.

Sources: Dunsmore et al. (2020),[15] Winter et al. (2015),[17] and study protocol and statistical analysis plan.[53]

Description of the COG AALL0434 Trial

The COG AALL0434 trial was a phase III, 2 × 2 pseudofactorial 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 aBFM multidrug therapy of pediatric and AYA patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL. This study was conducted by the COG under an investigational new-drug application held by the NCI. A total of 1,596 patients with T-ALL were enrolled from January 2007 to July 2014 across 215 sites in the US, Australia, Canada, New Zealand, and Switzerland. In 2010, the COG AALL0434 trial was amended to include patients with T-LBL using a separate analysis and reporting plan for these patients.

The COG AALL0434 trial used a sequential design to evaluate nelarabine during the initial safety[17] and efficacy[15] phases. The initial safety phase end points included sensory neuropathy, motor neuropathy, central neurotoxicity (encephalopathy, seizure, stroke, extrapyramidal tract symptoms, acute mental status changes,

and somnolence), and mortality. The primary efficacy end point in the efficacy phase of the trial was DFS, and the secondary efficacy end points were OS, and CNS relapse. The efficacy phase safety outcomes included central neurotoxicity, peripheral motor neuropathy, and peripheral sensory neuropathy. Treatment duration with nelarabine was 2 years from the start of the interim maintenance phase for females, and 3 years for males.

Randomization and Treatment Allocation

First, patients with T-ALL must have been enrolled in the AALL08B1[53] study before enrolment in the COG AALL0434 trial and initiation of treatment. The AALL08B1 trial was an observational, case-only study that aimed to provide a risk-classification scheme for all patients with newly diagnosed ALL that was used to assign treatment to patients on a COG front-line ALL study. Patients underwent blood-sample collection and bone marrow biopsies were conducted at baseline and during and after induction therapy for immunophenotyping for ALL confirmation and classification, DNA ploidy, genomic variation, and cytogenetic analysis by flow cytometry. A diagnosis of T-ALL was established when leukemic blasts lacked myeloperoxidase or evidence of B-lineage derivation (CD19/CD22/CD20), and expression of either surface or cytoplasmic CD3 or 2 or more of the antigens CD8, CD7, CD5, CD4, CD2 or CD1a.

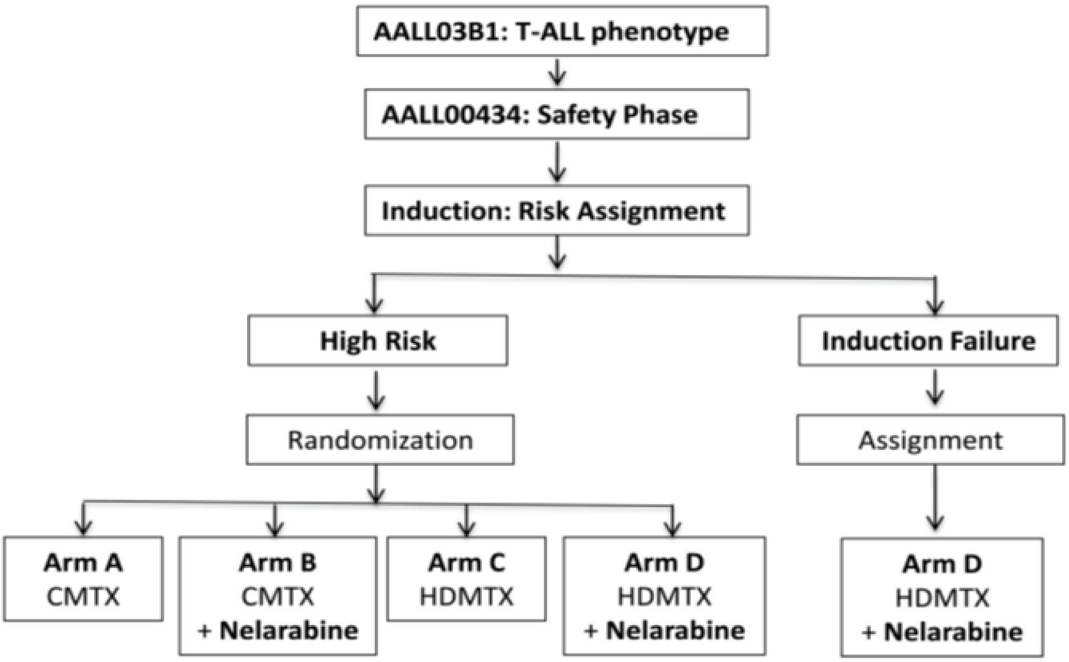
At the end of induction therapy, each patient with T-ALL was randomly assigned to a treatment arm through an electronic remote data entry system after a risk assessment (low, intermediate, or high) was made. Details on the randomization process and treatment allocation are not available.

Patients with T-ALL (n = 94) were randomly assigned to 1 of 4 treatment arms:

- arm A: aBFM with C-MTX without nelarabine, n = 24
- arm B: aBFM with C-MTX with nelarabine, n = 24
- arm C: aBFM with HD-MTX with leucovorin rescue without nelarabine, n = 23
- arm D: aBFM with HD-MTX with leucovorin rescue and nelarabine, n = 23.

First, an initial safety phase[17] was conducted to assess the tolerability of adding nelarabine to an aBFM backbone containing either the C-MTX or HD-MTX regimen. During the initial safety phase, only patients with high-risk T-ALL were randomized to 1 of the 4 treatment arms to receive the aBFM backbone after completion of induction therapy. Patients with high-risk T-ALL and CNS3 or testicular involvement were nonrandomly assigned to receive the HD-MTX regimen and randomized to receive or not receive nelarabine (arms C or D) (Figure 2). A total of 600 patients were enrolled in the COG AALL0434 trial from January 2007 to February 2010, when an initial safety analysis was performed. Only patients with high-risk T-ALL without CNS3 disease were included in the initial safety phase analysis.

Figure 2: Study Schema for Initial Safety Phase of the COG AALL0434 Trial



CMTX = Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase; HDMTX = high-dose methotrexate with leucovorin rescue; T-ALL = T-cell acute lymphoblastic leukemia.

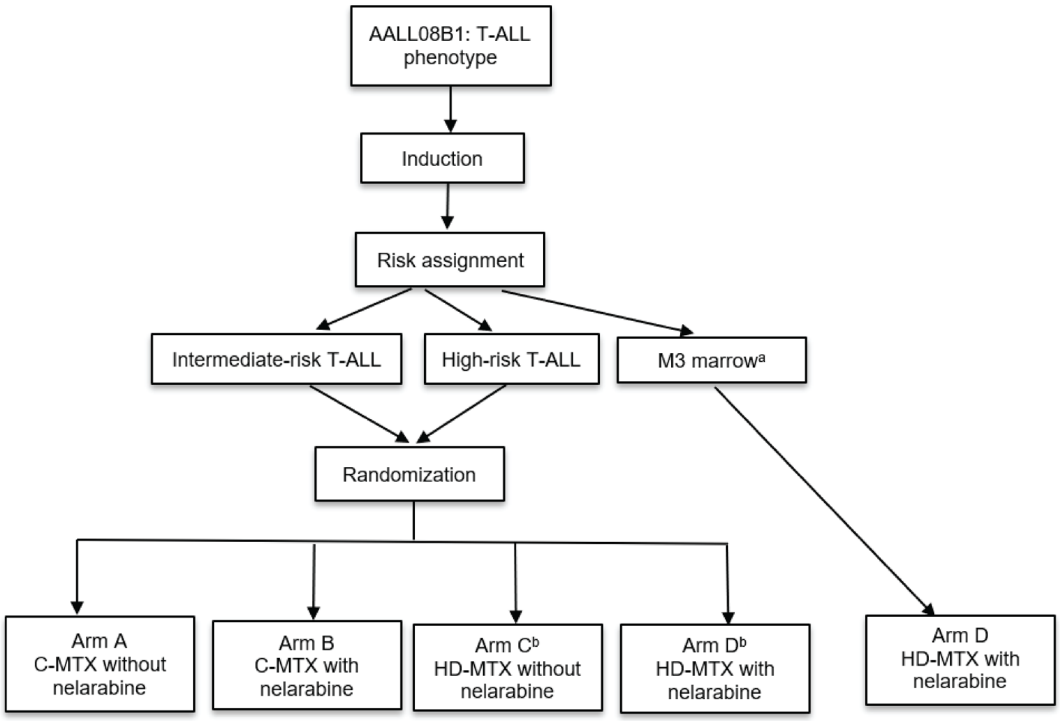
Source: Reprinted from Winter et al. (2015).[17] Reprinted from Winter SS, Dunsmore KP, Devidas M, et al., Safe integration of nelarabine into intensive chemotherapy in newly diagnosed T-cell acute lymphoblastic leukemia: Children's Oncology Group Study AALL0434, Pediatr Blood Cancer, 2015 Jul;62(7):1176 to 83, © 2015 Wiley Periodicals, Inc.

After 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] (Figure 3). 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:

- arm A: aBFM with C-MTX without nelarabine, n = 151
- arm B: aBFM with C-MTX with nelarabine, n = 147
- arm C: aBFM with HD-MTX with leucovorin rescue without nelarabine, n = 185
- arm D: aBFM with HD-MTX with leucovorin rescue and nelarabine, n = 176.

Patients with low-risk T-ALL did not participate in the nelarabine randomization in either the safety or efficacy phases. Patients with intermediate-risk T-ALL were eligible for the nelarabine randomization during the efficacy phase but did not participate in the nelarabine randomization during the initial safety phase. Patients with high-risk T-ALL were eligible to receive nelarabine during both the safety and efficacy phases of the COG AALL0434 trial. Patients with CNS3 or testicular disease were assigned to receive HD-MTX with or without nelarabine.[15] Patients with induction failure were nonrandomly assigned to receive the HD-MTX regimen with nelarabine and could remain on study if an M1 or M2 marrow was achieved by the end of consolidation. Patients may also have been taken off study for alternative therapy, including blood or marrow transplant.

Figure 3: Study Schema for the Efficacy Phase of the COG AALL0434 Trial



C- MTX = Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase; CNS3 = central nervous system disease with a white blood cell count greater than 5 with blasts; HD-MTX = high-dose methotrexate with leucovorin rescue; M3 = greater than 25% blasts; T-ALL = T-cell acute lymphoblastic leukemia.

[a] Patients with M3 marrow at the end of induction therapy were nonrandomly assigned to receive HD-MTX with nelarabine.

[b] Patients with CNS3 and/or testicular disease at diagnosis were assigned to HD-MTX treatment (arms C and D).

Source: Dunsmore et al. (2020).[15]

Risk Assignment at the End of Induction Therapy

During induction therapy, bone marrow assessment was performed on day 8, and again on day 15 if no M1 marrow was found. Evaluation of bone marrow assessment and MRD was performed on day 29.

Low-risk T-ALL was defined as the NCI standard risk: age from 1 to 10 years, a WBC of less than 50,000 cells/μL, a CNS1 status (total nucleated cells, 5 per high-powered field with no blasts) with M1 marrow (on day 8 or 15, and M1 marrow with an MRD of less than 0.1% on day 29.

Patients with intermediate-risk T-ALL were those with any NCI high-risk features (age ≥ 10 years and/or an initial WBC of 50,000/μL or greater), with any CNS or testicular disease, any marrow response by day 15 and day 29 with an MRD of less than 1%.

Patients with high-risk T-ALL were defined as those having either M2 marrow, or an MRD of 1% or greater on day 29 of induction therapy. Patients with high-risk T-ALL must have attained M1 marrow by morphology at the end of consolidation therapy to continue on the study.

Patients with T-ALL induction failures were those having M3 marrow on day 29 and who were nonrandomly assigned to receive HD-MTX with nelarabine. No participants were assigned a risk based on cytogenetics, immunophenotype, or genomic alterations.

CNS1 was defined as the absence of blasts on the cytospin-positive preparation in cerebral spinal fluid, regardless of the number of WBCs. CNS2 was defined as having a WBC count of less than 5 and cytospin-positive for blasts equal to or greater than 5 µL of WBCs with a negative Steinherz-Bleyer algorithm. CNS3 disease was defined as the presence in the cerebral spinal fluid of at least 5/µL WBCs and cytospin-positive for blasts and/or clinical signs of CNS leukemia, including:

- red blood cell count of less than 10/µL, WBC count equal to or greater than 5/µL and cytospin-positive for blasts (CNS3a)
- red blood cell count equal to or greater than 10/µL, WBC count equal to or greater than 5/µL and positive by Steinherz-Bleyer algorithm (CNS3b)
- clinical signs of CNS leukemia, such as facial nerve palsy, brain or eye involvement, or hypothalamic syndrome (CNS3c).

In the COG AALL0434 trial, pre-treatment with steroids may alter the risk assessment as follows:

- Patients who received steroids within 1 week of a T-ALL diagnosis:
  - Patients receiving IV or oral steroids for less than 48 hours per week immediately before diagnosis were stratified according to the predetermined schema, if complete blood count (CBC) results obtained before the initiation of steroid therapy are available; presteroid CBC results and age were used to determine risk assignment.
  - If patients received IV or oral steroids for more than 48 hours, they were categorized as slow early responders and assigned to the intermediate-risk category, with M1 and/or their MRD less than 1% on the day 29 assessment.
  - In the absence of pre-steroid CBC results, patients with M2 and/or an MRD of more than 1% on the day 29 assessment were assigned to the high-risk category.
- Patients who received steroids within 1 month of a T-ALL diagnosis:
  - Patients who received steroids for less than 48 hours within 1 month of diagnosis did not have their risk assignment changed.
  - Patients who received steroids for more than 48 hours within 1 month of diagnosis were assigned to the intermediate- or high-risk category depending on the day 29 bone marrow status.

Populations

Inclusion and Exclusion Criteria

Patients eligible for enrolment in both the safety and efficacy phases of the COG AALL0434 trial included those newly diagnosed with T-ALL (as measured by marrow blasts greater than 25% or a WBC count equal to or greater 25,000/µL with blasts equal or greater than 50%). Patients must have been older than 1 year of age and under 31 years of age. A diagnosis of T-ALL was established when leukemic blasts lacked

myeloperoxidase or evidence of B-lineage derivation (CD19/CD22/CD20, and expression of either surface or cytoplasmic CD3 or 2 or more of the antigens CD8, CD7, CD5, CD4, CD2 or CD1a). If surface CD3 was expressed on all leukemic cells, additional markers of immaturity, including TdT, CD34, or CD99, were assessed for expression. All patients with T-ALL must have been enrolled in the AALL08B1 trial before treatment and enrolment in the COG AALL0434 trial. Patients should not have had any prior cytotoxic chemotherapy, except for steroids and/or intrathecal cytarabine. Patients with a prior seizure disorder requiring anticonvulsant therapy or pre-existing CTCAE grade 2 (or higher) peripheral neurotoxicity, as determined before induction treatment phase, were not eligible to receive nelarabine. Pregnant or lactating females and patients with Down syndrome were excluded from the COG AALL0434 trial. Patients who entered the COG AALL0434 trial and later tested positive for the Philadelphia chromosome were excluded from protocol therapy before day 15 of the induction phase of treatment to participate in the AALL0622 trial.

Interventions

Table 8 summarizes the treatment details for patients enrolled in the COG AALL0434 trial.

Induction

All patients with T-ALL enrolled in the COG AALL0434 trial received 28 days of induction therapy, which consisted of prednisone at 30 mg/m^2/ per dose twice daily; daunorubicin 25 mg/m^2 per dose on days 1, 8, 15, and 22; vincristine at 1.5 mg/m^2 per dose (maximum 2 mg) on days 1, 8, 15, and 22; and pegaspargase at a dose of 2,500 IU/m^2 per dose × 1 on days 4, or 5, or 6. Age-adjusted intrathecal cytarabine was given at the time of diagnostic lumbar puncture, or on day 1 (30 mg for patients aged 1 to 1.99 years, 50 mg for patients aged 2 to 2.99 years, and 70 mg for patients aged 3 years or older). Age-adjusted intrathecal methotrexate was given on days 1 and 29 for CNS1 and CNS2 disease, and additionally on days 15 and 22 for those with CNS3 disease (8 mg for patients aged 1 to 1.99 years, 10 mg for patients aged 2 to 2.99 years, 12 mg for patients aged 3 to 8.99 years, and 15 mg for patients aged 9 years or older).

Consolidation, Interim Maintenance, Delayed Intensification, and Maintenance

In the COG AALL0434 trial, the consolidation, interim-maintenance, delayed-intensification, and maintenance phases of treatment were started when peripheral counts recovered with an absolute neutrophil count equal to or greater than 750/µL, and platelets equal to or greater than 75,000/µL (whichever occurred later). However, patients with high-risk T-ALL and an MRD of greater than 1% and/or M2 marrow on day 29 were randomized and immediately switched to the consolidation and subsequent phases of treatment without waiting for count recovery.

In the initial safety phase of the COG AALL0434 trial,[17] 94 patients with high-risk T-ALL without CNS3 disease were randomly assigned to receive six 5-day courses of nelarabine at 650 mg/m^2 daily in addition to an aBMF regimen with C-MTX or HD-MTX. In the efficacy phase of COG AALL0434,[15] 659 patients with intermediate- or high-risk T-ALL were randomly assigned to receive six 5-day courses of nelarabine at 650 mg/m^2/dose in addition to an aBMF backbone with C-MTX or HD-MTX. Two courses of nelarabine were given on days 1 to 5 and 43 to 47 of the consolidation phase of treatment, 1 course was given on days 29 to 33 of the delayed-intensification phase of treatment, and 3 courses were given on days 29 to 33 of the first 3 maintenance

cycles. The duration of treatment was the same for all treatment arms: 2 years from the start of interim maintenance therapy for females and 3 years for males.

In the COG AALL0434 trial, all patients received prophylactic cranial radiation therapy at a dose of 12 Gy during delayed intensification therapy. All patients with CNS3 disease who received HD-MTX regimen with or without nelarabine (arms C and D) received cranial radiation therapy at a dose of 18 Gy during delayed intensification. All patients with persistent, postinduction testicular leukemia who received the HD-MTX regimen with or without nelarabine (arms C and D) received testicular radiation during consolidation at a dose of 24 Gy. Patients with testicular disease at a diagnosis that resolved by the end of induction therapy did not receive testicular radiation.

In the COG AALL0434 trial, any therapy was to be interrupted in patients with confirmed or suspected serious infection and then restarted after the signs of infection had disappeared. Treatment with nelarabine was discontinued if patients experienced neurologic toxicity before completion of 5 days of therapy, and the treatment could only be resumed if peripheral or central neurotoxicity was reduced to less than CTCAE grade 2 toxicity. Patients who were unable to receive a 5-day course of nelarabine because of toxicity proceeded to the next planned course of protocol therapy as soon as recovery allowed. In the event of the development of grade 4 neurologic toxicity related to nelarabine, the patient stopped taking nelarabine indefinitely. Treatment with nelarabine was discontinued in patients who developed signs or symptoms suggestive of an ascending polyneuropathy, including a Guillain-Barré–like syndrome, even if these symptoms resolve. If patients developed myalgia or myoglobinuria, they were evaluated for the potential of having rhabdomyolysis.

In the COG AALL0434 trial, the required or optional clinical, laboratory, and disease evaluations for patients with T-ALL included a history and physical examination; blood work and assessment of body surface area; bone marrow cytomorphology; bone marrow and peripheral blood MRD assessment; bilirubin, alanine transaminase, creatinine, and blood urea nitrogen assessment; varicella titre, and thiopurine methyltransferase testing.

In both the initial safety and efficacy phases of the COG AALL0434 trial, patients with induction failure were nonrandomly assigned to receive the HD-MTX regimen with nelarabine and could remain on study if M1 or M2 marrow was achieved by the end of consolidation; however, this arm was not included in this review. In addition, in the efficacy phase of the COG AALL0434 trial, 487 patients with seizure disorder or pre-existing peripheral neuropathy who were not eligible to receive nelarabine during the efficacy phase were nonrandomly assigned to receive C-MTX with or without nelarabine; however, these arms were not included in this report. About 4% of patients were excluded from the protocol therapy for a transplant by the investigator's choice, although the COG AALL0434 trial did not include an alloHSCT option.

Table 8: Treatment Details in COG AALL0434

Drug	Dose	Schedule
First-stage consent: induction, all arms		
Intrathecal cytarabine	Age-adjusted[a]	At diagnostic lumber puncture or day 1
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 22
Prednisone	30 mg/m^2/dose twice a day	Days 1 to 28
Daunorubicin	25 mg/m^2	Days 1, 8, 15, 22
Pegaspargase	2,500 units/m^2	Day 4, 5, or 6
Intrathecal methotrexate	Age-adjusted[a]	Days 8, 29 (CNS3: + days 15 and 22)
Second-stage consent: risk stratification and postinduction randomization to arm A, B, C, or D		
Consolidation[b]		
Courses without nelarabine (arms A and C)		
Cyclophosphamide	1,000 mg/m^2	Days 1 and 29
Cytarabine	75 mg/m^2	Days 1 to 4, 8 to 11, 29 to 32, 36 to 39
Mercaptopurine	60 mg/m^2	Days 1 to 14, 29 to 42
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 15, 22, 43, 50
Pegaspargase	2,500 units/m^2	Days 15 and 43
Intrathecal methotrexate	Age-adjusted[a]	Days 8, 15, 22, 29 (high risk); days 1, 8 (CNS3); days 1, 8,15, 22 (all others)
Cranial radiation therapy[c]	12 Gy (18 Gy for CNS3)	Start on day 15
Testicular radiotherapy[d]	24 Gy (persistent disease only)	Completed before day 15
Courses with nelarabine (arms B and D)		
Cyclophosphamide	1,000 mg/m^2	Days 8, 50
Cytarabine	75 mg/m^2	Days 8 to 11, 15 to 18, 50 to 53, 57 to 60
Mercaptopurine	60 mg/m^2	Days 8 to 21, 50 to 63
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 22, 29, 64, 71
Pegaspargase	2,500 units/m^2	Days 22, 64
Intrathecal methotrexate	Age-adjusted[a]	Days 15, 22, 57, 64 (omit day 22 for CNS3)
Cranial radiation therapy[c]	12 Gy (18 Gy for CNS3)	Start on day 22
Testicular radiotherapy[d]	24 Gy (persistent disease only)	Completed before day 15
Nelarabine	650 mg/m^2	Days 1 to 5, 43 to 47
Interim maintenance		
C-MTX (arms A and B)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Every 10 days 3 5 doses on days 1, 11, 21, 31, 41

Drug	Dose	Schedule
IV methotrexate[e]	100 mg/m^2	Every 10 days 3 5 doses on days 1, 11, 21, 31, 41
Pegaspargase	2,500 units/m^2	Days 2, 22
Intrathecal methotrexate	Age-adjusted[a]	Days 1, 31
HD-MTX (arms C and D)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 15, 29, 43
IV methotrexate[e]	5,000 mg/m^2	Days 1, 15, 29, 43
Leucovorin	15 mg/m^2	42, 48, 54 hours after IV methotrexate
Mercaptopurine (oral)	25 mg/m^2	Days 1 to 56
Intrathecal methotrexate	Age-adjusted[a]	Day 1, 29
Delayed intensification		
Without nelarabine (arms A and C)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 43, 50
Pegaspargase	2,500 units/m^2	Day 4 or 5 or 6 and 43
Dexamethasone	5 mg/m^2/dose twice a day	Days 1 to 7, 15 to 21
Doxorubicin	25 mg/m^2/d	Days 1, 8, 15
Cytarabine	75 mg/m^2	Days 29 to 32, 36 to 39
Cyclophosphamide	1,000 mg/m^2	Day 29
Thioguanine	60 mg/m^2/d	Days 29 to 42 (omit if patient receiving cranial radiation therapy)
Intrathecal methotrexate	Age-adjusted[a]	Days 1, 29, 36
Cranial radiation therapy[c]	12 Gy (18 Gy for CNS3)	Start on day 50 (arm C)
With nelarabine (arms B and D)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 8, 15, 50
Pegaspargase	2,500 units/m^2	Day 4 or 5, or 6 and 50
Dexamethasone	5 mg/m^2/dose twice a day	Days 1 to 7, 15 to 21
Doxorubicin	25 mg/m^2/d	Days 1, 8, 15
Cytarabine	75 mg/m^2	Days 36 to 39, 43 to 46
Cyclophosphamide	1,000 mg/m^2	Day 36
Thioguanine	60 mg/m^2/d	Days 36 to 49 (omit if patient receiving cranial radiation therapy)
Intrathecal methotrexate	Age-adjusted[a]	Days 1, 36, 43
Cranial radiation therapy[c]	12 Gy (18 Gy for CNS3)	Start on day 50 (arm C)
Nelarabine	650 mg/m^2	Days 29 to 33

Drug	Dose	Schedule
Maintenance[f]		
Without nelarabine (arms A and C)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 29, 57
Prednisone	20 mg/m^2/dose twice a day	Days 1 to 5, 29 to 33, 57 to 61
Mercaptopurine (oral)	75 mg/m^2/d	Daily/days 1 to 84
Methotrexate (oral)	20 mg/m^2/dose	Weekly (omit on day 29 for low-risk T-ALL and SR T-LLy)
Intrathecal methotrexate	Age-adjusted[a]	Day 1 (and day 29 first 4 cycles; low-risk patients only)
With nelarabine (arms B and D)		
Vincristine	1.5 mg/m^2 (2 mg maximum)	Days 1, 57
Prednisone	20 mg/m^2/dose twice a day	Days 1 to 5, 57 to 61
Mercaptopurine (oral)	75 mg/m^2/d	Days 1 to 28, 36 to 84
Methotrexate (oral)	20 mg/m^2/dose	Days 8, 15, 22, 36, 43, 50, 57, 64, 71, 78 weekly; omitted while taking nelarabine
Intrathecal methotrexate	Age-adjusted[a]	Day 1
Nelarabine	650 mg/m^2	Days 29 to 33 (first 3 cycles)

C-MTX = Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase; CNS1 = central nervous system disease with no blasts; CNS2 = central nervous system disease with a white blood cell count of 5 or lower with blasts; CNS3 = central nervous system disease with a white blood cell count greater than 5 with blasts; HD-MTX = high-dose methotrexate with leucovorin rescue; SR = standard risk; T-ALL = T-cell acute lymphoblastic leukemia.

Note: Treatment arms were as follows: arm A, C-MTX; arm B, C-MTX plus nelarabine; arm C, HD-MTX; and arm D, HD-MTX plus nelarabine.

[a]Intrathecal cytarabine: 1 to 1.99 years, 30 mg; 2 to 2.99 years, 50 mg; 3 or more years, 70 mg. Intrathecal methotrexate: 1 to 1.99 years, 8 mg; 2 to 2.99 years, 10 mg; 3 to 8.99 years, 12 mg; 9 years, 15 mg.

[b]In case of induction failure (bone marrow with greater than 25% blasts at day 29), begin arm D consolidation as soon as possible.

[c]Cranial radiation therapy: CNS1 or CNS2: 1.5 Gy/day over 8 fractions; CNS3: 1.8 Gy/day in 10 fractions for intermediate-risk and high-risk participants only. Intrathecal therapy is not held during the concomitant administration of cranial radiation therapy.

[d]Testicular radiation therapy: for biopsy-proven, persistent disease only: 2 Gy/day in 12 fractions.

[e]IV-MTX: 100 mg/m^2 (dose escalated by 50 mg/m^2 every 10 days for a total of 5 doses, adjusted for toxicity).

[f]Total duration of treatment from start of interim maintenance: female T-cell acute lymphoblastic leukemia, 2 years; male T-ALL, 3 years.

Source: Dunsmore et al. (2020).[15] Reprinted from Dunsmore KP, Winter SS, Devidas M, et al., Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia, J Clin Oncol, 38(28):3282 to 3293, https://doi.org/10.1200/JCO.20.00256, Copyright © 2020, by the American Society of Clinical Oncology.

Concomitant Therapy and Drug Interactions

Patients receiving certain antileukemic drugs, such as vincristine, anthracyclines, or etoposide, may experience increased toxicity when these drugs are used concomitantly. The concomitant use of enzyme-inducing anticonvulsants such as phenytoin, phenobarbital, and carbamazepine with antileukemic therapy, as well as rifampin, which also induces many drug-metabolizing enzymes, was limited in the COG AALL0434 trial; however, no further details are available. The concomitant use of the following drugs with C-MTX or HD-MTX should be avoided as they can cause methotrexate to precipitate in the urinary tract: nonsteroidal anti-inflammatory drugs, trimethoprim and sulfamethoxazole, penicillins, probenecid, IV contrast media, proton-pump inhibitors, phenytoin, and fosphenytoin. Azole antifungals, including

fluconazole, itraconazole, ketoconazole, posaconazole, and voriconazole, and the macrolide group of antibiotics, including erythromycin, clarithromycin, and azithromycin, can have strong inhibitory effects on drug-metabolizing enzymes.

Outcomes

A list of efficacy end points assessed in this clinical review report is provided in Table 9. These end points are further summarized in the following section. Summarized end points were identified as important to this review by stakeholders such as clinical experts, clinician groups, or patient groups.

Table 9: Outcomes Summarized From Pivotal Study

Outcome measure	COG AALL0434
Disease-free survival	Primary outcome
Overall survival	Secondary outcome
Central nervous system relapse	Secondary outcome
Bone marrow relapse	Secondary outcome

Source: Dunsmore et al. (2020).[15]

The primary end point of the efficacy phase of the COG AALL0434 trial was DFS, which was defined as the time from postinduction randomization to first event (relapse, second malignant neoplasm, or remission death) or date of last contact.

The secondary outcomes of the COG AALL0434 trial were OS and CNS relapse. OS was defined as the time from postinduction randomization to death, or date of last contact. Relapse was defined as any recurrence of disease, whether in marrow or extramedullary site. A relapse should be histologically confirmed. CNS relapse was defined by positive cytomorphology and a WBC count greater than 5/μL, or positive cytomorphology with a cerebral spinal fluid WBC count from 0 to 44/μL on 2 successive occasions 1 month apart. If any cerebral spinal fluid evaluation showed positive cytomorphology and a WBC count of less than 5/μL, a second cerebral spinal fluid evaluation was required in 4 weeks. Testicular relapse was to be documented by testicular biopsy if the testicular relapse was isolated. Bone marrow relapse was defined as an M3 marrow at any point after day 29.

A secondary malignant neoplasm was defined as a cancer caused by treatment for a previous malignancy (i.e., treatment with investigational intervention, radiation, or chemotherapy). A metastasis of the initial neoplasm was not considered a secondary malignancy. Three options were used to describe the event of secondary malignancy: leukemia secondary to oncology chemotherapy, myelodysplastic syndrome, and treatment-related secondary malignancy.

The following section describes the DFS outcome measure and summarizes evidence that examines the validity of DFS as surrogate for OS in patients with T-ALL.

DFS, also called recurrence-free survival,[54] is an end point based on a tumour assessment and has been frequently used as an efficacy outcome in clinical trials, particularly in curative-intent and adjuvant treatment

for cancers, including ALL.[1,55,56] Generally, DFS is defined as "the time from randomization until evidence of disease recurrence or death from any cause,"[57-60] or "time to development of new disease of tumour after curative treatment with surgery, radiotherapy or chemoradiotherapy."[54] DFS in the COG AALL0434 trial was defined as "the time from postinduction randomization to first event (relapse, second malignant neoplasm, or remission death) or date of last contact."[15] The DFS outcome values can be presented as the length of time (e.g., median survival time), or the probability of surviving over a prespecified time interval (e.g., 2-year or 5-year survival rate).[61] The common survival analysis (time-to-event analysis) approaches for DFS include the Kaplan-Meier method, the Cox proportional hazards regression model, and the log-rank test.[61-64]

Several benefits and drawbacks of DFS outcome have been noted.[54,57,58] Advantages of DFS include it being an objective measure based on quantitative assessment, the ability to evaluate it sooner (particularly when the survival period is expected to be prolonged), and the need for a smaller sample size compared with studies using OS as an end point.[54,57] Using DFS as an end point has disadvantages, such as certain inconsistent definitions across studies, the potential for assessment bias in open-label studies, inclusion of noncancer deaths, and not being statistically validated as a surrogate end point for OS. In addition, achieving a balanced timing of assessments across treatment groups is essential.[54,57] According to the FDA Oncology Drug Advisory Committee, DFS prolongation represents a clinical benefit if the magnitude of this benefit outweighs the toxicity of the adjuvant treatment.[57] The FDA guidelines recommend that sponsors clearly define the end point, outline the schedule for assessments, include an estimate of treatment-effect size, and ensure blinding of treatment assignments to help reduce the potential for bias.[57]

Treatment-related AEs were coded according to CTCAE version 4. A modified Balis scale was used to grade neurotoxic AEs that could be attributed to any bioactive drug used in the COG AALL0434 trial.

Peripheral motor neuropathy was graded as follows:[53]

- grade 1: subjective weakness, but no deficits detected on neurologic exam, other than abnormal deep tendon reflexes
- grade 2: weakness that alters fine motor skills (buttoning shirt, colouring, writing or drawing, using eating utensils) or gait without abrogating ability to perform these tasks
- grade 3: unable to perform fine motor tasks (buttoning shirt, colouring, writing or drawing, using eating utensils) or unable to ambulate without assistance
- grade 4: paralysis.

Peripheral sensory neuropathy was graded as follows:[53]

- grade 1: paresthesia, pain, or numbness that does not require treatment or interfere with extremity function
- grade 2: paresthesia, pain, or numbness that is controlled by non-narcotic medications (without causing loss of function), or alteration of fine motor skills (buttoning shirt, writing or drawing, using eating utensils) or gait, without abrogating ability to perform these tasks

- grade 3: paresthesia or pain that is controlled by narcotics, or interfere with extremity function (gait, fine motor skills as outlined above), or quality of life (loss of sleep, ability to perform normal activities severely impaired)
- grade 4: complete loss of sensation, or pain that is not controlled by narcotics.

Statistical Analysis

Initial Safety Phase of the COG AALL0434 Trial[17]

The initial safety phase of the COG AALL0434 trial was planned to last for no more than 3 years. AEs were studied in 94 patients with high-risk T-ALL who completed nelarabine therapy through maintenance cycle 3. AEs were compared between patients randomized to receive C-MTX or HD-MTX regimens with and without nelarabine, using 2-sided Fisher exact tests or chi-square analyses.

Efficacy Phase of the COG AALL0434 Trial[15]

Power calculations to compare a randomized group treated with nelarabine versus a group not treated with nelarabine were based on the 1-sided log-rank test with a significance level of 0.05. There was 80% power to detect an improvement in 4-year DFS from 82% to 89% between nelarabine and no-nelarabine groups in 659 patients, with a minimum follow-up time of 3 years. The accrual duration of the efficacy phase of the COG AALL0434 trial was driven by the time required to achieve accrual targets for the nelarabine randomization. A clinically important difference was assumed to be an improvement to a DFS of 85%, representing a relative DFS event reduction of approximately 41% for the better regimen. A total of 119 DFS events were expected with a 3-year follow-up after enrolment of the last randomized patient. The cumulative power to detect a difference by the final analysis was therefore expected to be 85.9%.

Five interim efficacy analyses were scheduled when approximately 20%, 40%, 60%, and 80% of the expected DFS events were observed. An alpha t^2 spending function for the stopping boundary with truncation at 3 standard deviations was used for interim monitoring to allocate greater importance to the later analyses. Futility-testing boundaries were used to compare nelarabine versus no-nelarabine groups to decide if stopping should occur for similarity of outcome. This was tested with a Pampallona-Tsiatis lower-monitoring boundary when approximately 20%, 40%, 60% and 80% of the DFS event information was available. In addition, stratified analysis was performed by intermediate- and high-risk T-ALL groups. In the high-risk group, the cumulative power to detect a change in DFS from 60% to 75% was expected to be 77.2%, while in the intermediate-risk group, the power to detect a change in DFS was expected to be less because those patients would only begin enrolling after the initial safety phase was complete.

Given the treatment regimens chosen and the factorial design of the COG AALL0434 trial, analyses were performed regularly to assess the possibility of a statistical interaction effect on DFS for the 2 main treatment factors (C-MTX versus HD-MTX, nelarabine versus no nelarabine). This was performed using a Cox regression likelihood ratio test, which assessed the 4 individual treatment regimens in a 2 × 2 design to examine the occurrence of a nonproportional hazards effect for combinations of the 2 main treatment factors. Separate analyses were planned of the effect of the regimen within each level of other treatment factors, if there was strong evidence of an interaction between the methotrexate and nelarabine factors.

The proportional hazards assumption underlying the log-rank test was regularly tested during treatment comparisons. The results of 2 predefined subgroup analyses by gender and race are not reported in this review as they were not considered important by CADTH.

The rates of DFS and OS were assessed using the Kaplan-Meier method[65] and standard errors,[66] with a significance level of 0.05 applied to all comparisons. A 2-sided log-rank test was used to compare survival curves. Cumulative incidence rates were computed using the cumulative incidence function for competing risks, with comparisons between groups made using the *k*-sample test. Another secondary end point was a comparison of CNS relapse rates between the nelarabine and no-nelarabine treatment groups. Proportions were compared between groups using a chi-square test or Fisher exact test.

The COG AALL0434 trial utilized the CTCAE of the NCI for toxicity and performance reporting. The toxicities experienced by patients who received nelarabine were examined in 2 primary ways: first, they were compared directly with those of patients who did not receive nelarabine, and second, with an additional comparison within separate subgroups of methotrexate regimen (C-MTX and HD-MTX). These comparisons focused on nonhematologic toxicities with a CTCAE grade of 3 or higher.

Table 10: Statistical Analysis of Efficacy End Points — COG AALL0434

End point	Statistical model	Adjustment factors	Handling of missing data	Sensitivity analyses
Disease-free survival	Kaplan-Meier method	NR	NR	NR
Overall survival	Kaplan-Meier method	NR	NR	NR
Central nervous system relapse	Chi-square test Fisher's exact test	NR	NR	NR
Bone marrow relapse	Chi-square test Fisher's exact test	NR	NR	NR

NR = not reported.

Source: Dunsmore et al. (2020).[15]

Analysis Populations

The ITT population (N = 659) consisted of all patients randomized or assigned to 1 of 4 treatment arms. The study was powered based on this population. Unless otherwise specified, all clinical efficacy end points were summarized and analyzed using the ITT population.

The initial safety analysis set (N = 94) consisted of patients with high-risk T-ALL who received at least 1 dose of randomized study drugs.

The safety analysis set in the efficacy phase of the COG AALL0434 trial (N = 659) consisted of all randomized or assigned patients who received at least 1 dose of randomized study drugs.

Results

Patient Disposition

In the COG AALL0434 trial, the first patient was randomized to study treatment in January 2007, and the last patient was randomized in July 2014. A total of 1,596 participants with T-ALL were screened, of whom 34 patients (2.1%) were screening failures. The main reasons for screening failures were inappropriate timing of start of protocol therapy (n = 13), followed by disease type or histology (n = 8), and stage or extent of disease (n = 3). Of the 1,562 patients, 373 patients were not eligible for postinduction therapy mainly because of receiving off-protocol therapy (n = 353). The main reasons for receiving off-protocol therapy were refusal of further protocol therapy by patient (n = 218), followed by physician decision (n = 60), having an alloHSCT (n = 32), and AEs or complications (n = 18).

Among 1,189 patients with T-ALL eligible for risk assessment at the end of induction, 109 patients (9.2%) were classified as having low-risk T-ALL, 808 patients (68.0%) as have intermediate-risk T-ALL, 229 patients (19.2%) as having high-risk T-ALL, and 43 (3.6%) as having induction failure. Out of 1,189 patients, 659 were successfully randomized to receive C-MTX or HD-MTX regimens with and without nelarabine, including 433 patients (65.7%) with intermediate-risk T-ALL, and 226 (34.3%) with high-risk T-ALL.

A total of 487 patients who were not eligible to receive nelarabine, including patients with seizure disorder or pre-existing peripheral neuropathy, were nonrandomly assigned to receive C-MTX or HD-MTX regimens, and 43 patients with induction failure were nonrandomly assigned to receive nelarabine with the HD-MTX regimen; these arms were not included in the report. Although the COG AALL0434 trial did not include an alloHSCT option, about 4% of patients were taken off protocol therapy for transplant.

Baseline Characteristics

A summary of baseline characteristics is presented in Figure 4. Baseline characteristics were well balanced between the treatment groups. Half of the patients (49.9%) were under the age of 10 years, 33.4% were between 10 and 15 years of age, and 16.7% were 16 years of age or older. A total of 74.8% of the patients were male, and 25.2% were female. A total of 70.6% of the patients had CNS1, 20.8% had CNS2, and 8.6% had CNS3 at diagnosis. Bone marrow M1 at the end of induction was found in 95.3% of patients, and M2 marrow in 4.7% of patients. A total of 83.3% of patients did not have an alloHSCT, while 3.2% had undergone an alloHSCT.

Figure 4: Summary of Baseline Characteristics of the Nelarabine Randomized Cohort — COG AALL0434

Characteristic	No. of Patients (%)	
	Nelarabine (n = 323)	No Nelarabine (n = 336)
Age, years		
< 10	151 (46.8)	178 (53.0)
10-15	116 (35.9)	104 (30.9)
≥ 16	56 (17.3)	54 (16.1)
Sex		
Male	238 (73.7)	255 (75.9)
Female	85 (26.3)	81 (24.1)
WBC (× 1,000/μL)		
< 50	130 (40.3)	116 (34.5)
≥ 50	193 (59.7)	220 (65.5)
CNS		
CNS1	232 (71.8)	233 (69.4)
CNS2	62 (19.2)	75 (22.3)
CNS3	29 (9.0)	28 (8.3)
Race		
American Indian or Alaska native	1 (0.3)	2 (0.6)
Asian	15 (4.7)	21 (6.3)
Native Hawaiian or other Pacific Islander	4 (1.2)	1 (0.3)
Black or African American	41 (12.7)	40 (11.9)
White	223 (69.0)	236 (70.2)
Unknown	39 (12.1)	36 (10.7)
Ethnicity		
Hispanic or Latino	51 (15.8)	46 (13.7)
Not Hispanic or Latino	260 (80.5)	279 (83.0)
Unknown	12 (3.7)	11 (3.3)
AlloHSCT		
Yes	8 (2.5)	13 (3.9)
No	275 (85.1)	274 (81.5)
Unknown	40 (12.4)	49 (14.6)
BM, induction day 29		
M1	306 (94.7)	322 (95.8)
M2	17 (5.3)	14 (4.2)
MRD, induction day 29, %		
< 0.01	160 (49.5)	174 (51.8)
0.01 to < 0.1	16 (5.0)	14 (4.2)
0.1 to < 1.0	38 (11.7)	32 (9.5)
1.0 to < 10.0	91 (28.2)	86 (25.6)
≥ 10	18 (5.6)	30 (8.9)

AlloHSCT = allogeneic hematopoietic stem-cell transplant; BM = bone marrow; MRD = minimal residual disease.

Source: Dunsmore et al. (2020).[15] Reprinted from Dunsmore KP, Winter SS, Devidas M, et al., Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia, J Clin Oncol, 38(28):3282 to 3293, https://doi.org/10.1200/JCO.20.00256, Copyright © 2020, by the American Society of Clinical Oncology.

Efficacy

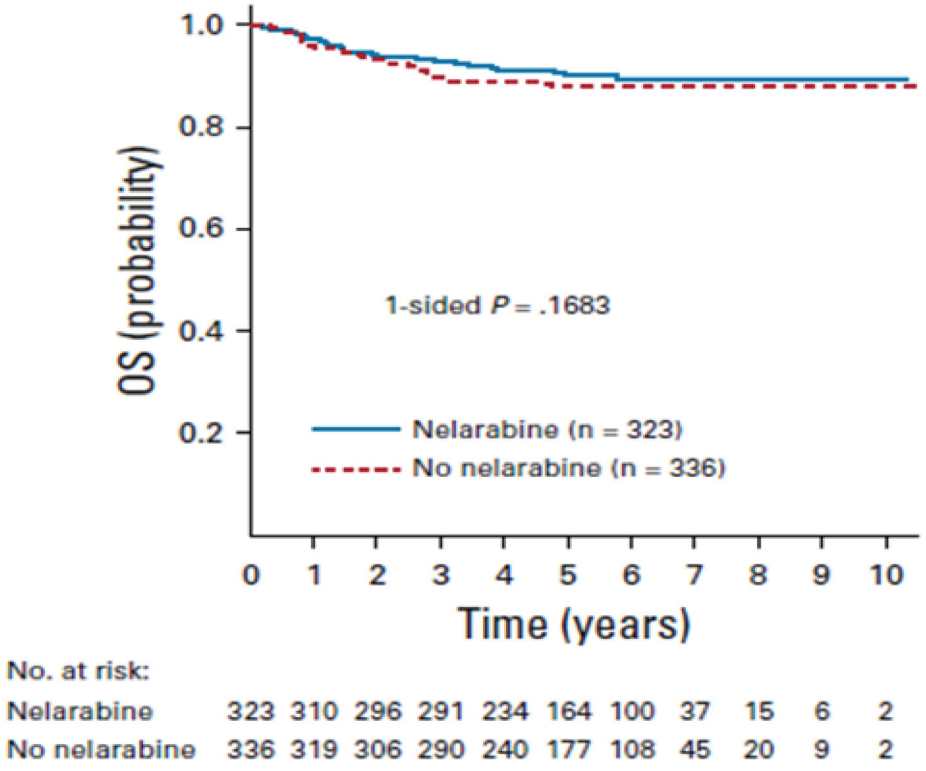
Table 11 presents a summary of key results from the efficacy phase of the COG AALL0434 trial.

Overall Survival[15]

Overall survival was the secondary end point of the COG AALL0434 trial. The 5-year OS rate was 90.3% (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) (Table 11, Figure 5).

In patients with intermediate-risk T-ALL who were randomly assigned to receive nelarabine or 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 nelarabine or not receive nelarabine, the 5-year OS rates were 88.5% (SE ± 3.8%) versus 79.2% (SE ± 4.6%), respectively (P = 0.051).

Figure 5: Kaplan-Meier Estimates of OS or Nelarabine Versus No Nelarabine — COG AALL0434



OS = overall survival.

Source: Dunsmore et al. (2020).[15] Reprinted from Dunsmore KP, Winter SS, Devidas M, et al., Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia, J Clin Oncol, 38(28):3282 to 3293, https://doi.org/10.1200/JCO.20.00256, Copyright © 2020, by the American Society of Clinical Oncology.

Progression-Free Survival

Progression-free survival was not measured or reported in the COG AALL0434 trial.

Events in Randomized Cohorts

In the COG AALL0434 trial, 70 patients experienced relapse, including 43 patients (12.8%) who received nelarabine compared with 27 (8.4%) who were treated without nelarabine. CNS relapse occurred in 14 patients (4.2%) who did not receive nelarabine compared with 1 (0.3%) who received nelarabine. Bone marrow relapse occurred in 14 patients (4.2%) who did not receive nelarabine compared with 12 (3.7%) who received nelarabine. CNS and bone marrow relapse marrow occurred in 8 patients (2.4%) who did not receive nelarabine compared with 2 (0.6%) who received nelarabine. A second malignant neoplasm occurred in 5 patients (1.5%) who did not receive nelarabine compared with 7 (2.1%) who received nelarabine, while remission death occurred in 10 patients (3.0%) who did not receive nelarabine compared with 5 patients (1.5%) who received nelarabine (Table 11).

Disease-Free Survival[15]

DFS was the primary end point of the COG AALL0434 trial. A total of 97 patients (14.7%) experienced any DFS events, including 39 who received nelarabine compared with 58 who did not receive nelarabine. 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) (Figure 6).

An analysis by treatment arm showed that 5-year DFS rates were 91.4% (SE ± 3.1%) in patients who received the C-MTX regimen with nelarabine (n = 147), 87.2% (SE ± 3.5%) in those who received the C-MTX regimen without nelarabine (n = 151), 85.5% (SE ± 3.6%) in those who received the HD-MTX regimen with nelarabine (n = 176), and 78.1% (SE ± 4.0) in those who received the HD-MTX regimen without nelarabine (n = 185) (P = 0.01) (Table 11, Figure 7).

Table 11: Summary of Key Results of Efficacy Phase of COG AALL0434 — ITT Population

Detail	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)

Detail	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
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 (%)	5 (1.5)	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; NR = not reported; OS = overall survival; SE = standard error.

[a]Percentage (SE) of patients alive from the Kaplan-Meier estimates.

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

[c]Percentage (SE) of disease-free events from the Kaplan-Meier 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 the COG AALL0434 trial.

[g]Common Terminology Criteria for Adverse Events grade of 3, 4, and 5.

[h]Common Terminology Criteria for Adverse Events grade of 3 and 4.

Source: Dunsmore et al. (2020).[15]

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).

Central Nervous System Relapse[15]

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) (Table 11). Among patients with CNS3 disease, CNS relapse occurred in 1 of 29 patients (3.4%) who were assigned to receive the HD-MTX regimen with nelarabine compared with 6 of 28 patients (21.4%) who were assigned to receive the HD-MTX regimen without nelarabine (P = 0.052).

Subgroup Analyses

Subgroups analyses by MRD response at the end of consolidation therapy or CNS status at diagnosis were not performed or reported in the COG AALL0434 trial.

Response Rate

Response rate was not measured or reported in the COG AALL0434 trial.

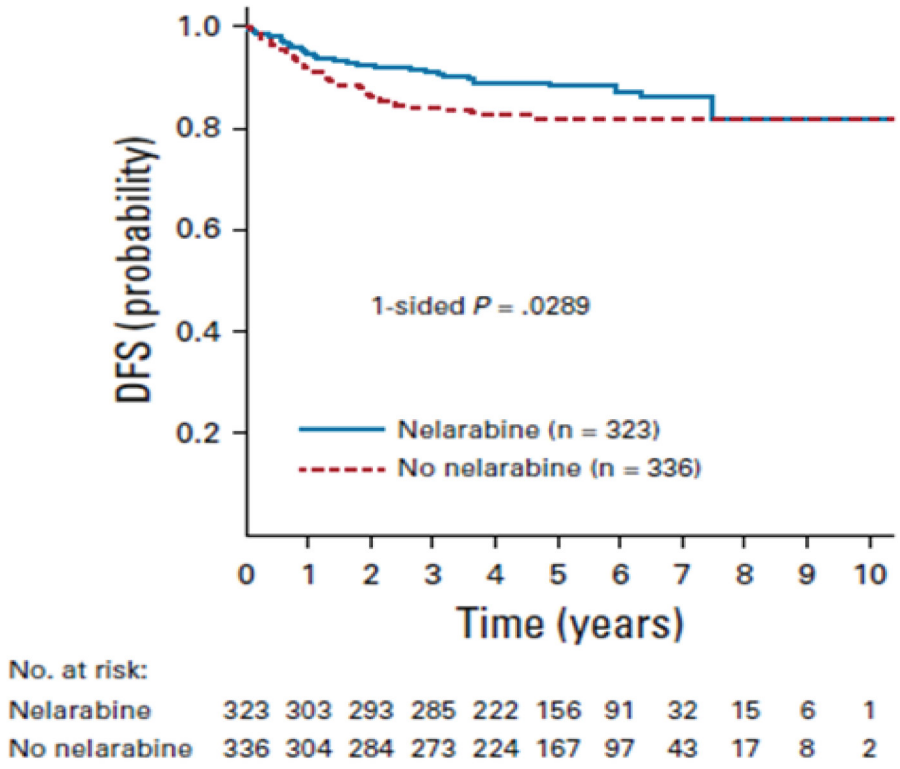
Duration of Response

Duration of response was not measured or reported in the COG AALL0434 trial.

Health-Related Quality of Life

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

Figure 6: Kaplan-Meier Estimates of DFS or Nelarabine Versus No Nelarabine — COG AALL0434



DFS = disease-free survival.

Source: Dunsmore et al. (2020).[15] Reprinted from Dunsmore KP, Winter SS, Devidas M, et al., Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia, J Clin Oncol, 38(28):3282 to 3293, https://doi.org/10.1200/JCO.20.00256, Copyright © 2020, by the American Society of Clinical Oncology.

Harms

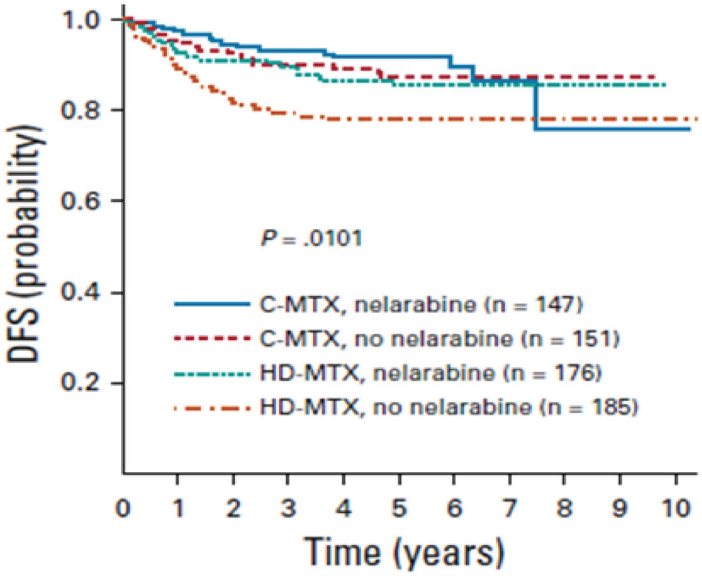
Initial Safety Phase of COG AALL0434[17]

Because nelarabine randomization occurred at the end of induction therapy, and nelarabine was not administered during induction, AEs from induction were excluded from analysis.

Sensory Neuropathy

Among 94 randomized patients with high-risk T-ALL, 49 (52.1%) experienced sensory neuropathy of any CTCAE grade, including 8 who received C-MTX without nelarabine (arm A), 14 who received C-MTX with nelarabine (arm B), 14 who received HD-MTX without nelarabine (arm C), and 13 who received HD-MTX with nelarabine (arm D). Only 1 of 6 CTCAE grade 3 sensory neuropathies was possibly attributable to treatment with nelarabine. No CTCAE grade 4 sensory neuropathy was reported during the safety phase of the COG AALL0434 trial.

Figure 7: Kaplan-Meier Estimates of DFS or Nelarabine Versus No Nelarabine by 4 Treatment Arms — COG AALL0434



No. at risk:

CMTX, nelarabine	147	141	136	132	103	76	41	14	5	3	1
CMTX, no nelarabine	151	141	136	131	108	82	51	25	11	3	0
HDMTX, nelarabine	176	162	157	153	119	80	50	18	10	3	0
HDMTX, no nelarabine	185	163	148	142	116	85	46	18	6	5	2

C-MTX = escalating-dose methotrexate without leucovorin rescue plus pegaspargase; DFS = disease-free survival; HD-MTX = high-dose methotrexate with leucovorin rescue.

Source: Dunsmore et al. (2020).[15] Reprinted from Dunsmore KP, Winter SS, Devidas M, et al., Children's Oncology Group AALL0434: A Phase III Randomized Clinical Trial Testing Nelarabine in Newly Diagnosed T-Cell Acute Lymphoblastic Leukemia, J Clin Oncol, 38(28):3282 to 3293, https://doi.org/10.1200/JCO.20.00256, Copyright © 2020, by the American Society of Clinical Oncology.

Motor Neuropathy

A total of 46 patients (48.9%) experienced motor neuropathy of any CTCAE grade, including 12 patients who received C-MTX without nelarabine, 18 patients who received C-MTX with nelarabine, 6 who received HD-MTX without nelarabine, and 10 who received HD-MTX with nelarabine. Only 3 of 7 CTCAE grade o3 motor neuropathies reported in the trial were possibly attributable to treatment with nelarabine: 1 occurred in a patient who received C-MTX with nelarabine, and 2 occurred in patients who received HD-MTX with nelarabine. The only case of CTCAE grade 4 motor neuropathy occurred in a patient who did not receive nelarabine. Most of the motor neuropathies associated with nelarabine occurred either during exposure of nelarabine or within 2 weeks of its administration.

Central Neurotoxicity

Encephalopathy, extrapyramidal tract symptoms, seizure, mental status, somnolence, and stroke were considered central neurotoxicities attributable to chemotherapeutic drugs, including nelarabine. The central neurotoxicities likely associated with nelarabine included 2 episodes of a CTCAE grade 2 tremor of during consolidation therapy, 1 episode of CTCAE grade 2 somnolence during delayed-intensification therapy, and 1 episode of CTCAE grade 3 cranial nerve V dysfunction of during delayed-intensification therapy. One case of CTCAE grade 4 central neurotoxicity was reported in a patient who did not receive nelarabine. Over 90% of reported neurotoxicities resolved during maintenance therapy. Only 2 CTCAE grade 1 central neuropathies persisted beyond maintenance cycle 3.

Non-Neurologic Toxicities

In general, the types and grades of hematological toxicities were similar between the 2 groups (nelarabine verses no nelarabine). Anemia and thrombocytopenia with a CTCAE grade of 3 and 4 were more commonly reported in patients who did not receive nelarabine during delayed-intensification therapy. Other toxicities, including febrile neutropenia, and elevations of aspartate aminotransferase or alanine transferase were similar between the nelarabine and no-nelarabine arms.

Death as a First Event

Among 94 patients with high-risk T-ALL, 1 died during induction therapy, and 8 died after randomization to 1 of 4 treatment arms at the end of induction therapy. One patient who received the C-MTX regimen without nelarabine died from an opportunistic infection during consolidation therapy. Among patients who received the HD-MTX regimen without nelarabine, 2 patients died from progressive disease, and 1 from transplant-related complications. Three patients died on arm D (HD-MTX regimen with nelarabine), including 2 patients from progressive disease, and 1 patient from a superior sagittal sinus thrombosis associated with pegaspargase during consolidation therapy. No patients died from complications related to nelarabine.

Safety Analysis of the Efficacy Phase of COG AALL0434[15]

The rate of nontargeted toxicity with a CTCAE grade of 3 or higher was 41.2% in patients who received nelarabine compared with 46.1% in patients who did not receive nelarabine.

The targeted neurotoxicity and neuropathy rates were acceptable and similar between 2 groups (nelarabine versus no nelarabine) (Table 11). Of 323 patients who received nelarabine, 11 (3.4%) experienced central

neurotoxicity of CTCAE grade 3 or higher, 26 (8.0%) experienced peripheral motor neuropathy of CTCAE grade 3 or 4, and 29 (9.0%) experienced peripheral sensory neuropathy of CTCAE grade 3 or 4. Of 336 patients who did not receive nelarabine, 7 (2.1%) patients experienced central neurotoxicity of CTCAE grade 3 or higher, 19 (5.7%) experienced peripheral motor neuropathy of CTCAE grade 3 or 4, and 27 (8.0%) experienced peripheral sensory neuropathy of CTCAE grade 3 or 4.

Critical Appraisal

Internal Validity

The COG AALL0434 trial was an open-label, phase III, 2 × 2 pseudofactorial randomized trial comparing nelarabine and an aBFM backbone in pediatric and AYA patients with newly diagnosed intermediate- and high-risk T-ALL. Detailed information on randomization and treatment allocation is not available. The study also included 2 additional treatment arms, including patients who were not eligible to receive nelarabine and who were nonrandomly assigned to receive C-MTX and HD-MTX without nelarabine, and patients with induction failure who were nonrandomly assigned to received HD-MTX with nelarabine. However, these 2 treatment arms were not relevant to this review and were not included in this report. The open-label design of the trial was most likely due to the nature of treatment administration, which made blinding infeasible. For example, patients with CNS3 disease were nonrandomly assigned to receive HD-MTX and then randomized to receive or not receive nelarabine. This bias, due to the open-label design, would not be introduced into the measurement of objective outcomes such as DFS or OS, which are the primary and secondary outcomes of the trial. 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. Although the COG AALL0434 trial was amended to include patients with T-LBL in 2010, the study design was not affected because there was a separate analysis and reporting plan for these patients. Patients in the COG AALL0434 trial received 28-day induction therapy consistent with clinical practice, after which they were randomly assigned to receive nelarabine with a C-MTX or HD-MTX regimen. The duration of treatment with nelarabine was 2 years for females and 3 years for males. The clinical experts consulted for this review noted that the longer duration of treatment in men could be explained by the increased risk of relapse in men compared to women. The clinical experts indicated that if patients experience neurotoxicity with a CTCAE grade of 3 or higher, the drug may be temporarily discontinued until the neurotoxicity resolves. No information is available regarding the treatment-discontinuation rates and the proportion of protocol deviations.

The primary outcome (DFS) and key secondary outcomes (OS and CNS relapse) were considered appropriate for this disease setting. DFS, also called recurrence-free survival,[54] is an end point based on tumour assessment and has been frequently used as an efficacy outcome measure in clinical trials, especially in curative-intent and adjuvant treatment for cancers, including ALL.[1,55,56] The analyses of primary and key secondary outcomes were conducted using the ITT population, which maintained randomization and minimized the risk of bias by comparing groups with similar prognostic factors. The clinical experts consulted noted that the results of the primary outcome (DFS) were clinically meaningful based on the absolute event-rate reduction within the selected study population. The clinical experts further noted that there is no known or accepted MID for DFS or OS rates in this population. The clinical experts noted that inclusion of a second malignant neoplasm event as a criterion to define DFS could bias the results; however,

only a small group (1.8%) of patients in the trial had second malignant neoplasms, which may not affect the results of the study. No information was available regarding the dropout rates and how missing values were handled in the trial. A risk-stratified DFS analysis (intermediate-risk versus high-risk T-ALL) was prespecified in the study protocol; however, randomization was not stratified by risk, and no information was provided on how well the populations belonging to these 2 risk groups were balanced.

The COG AALL0434 trial utilized 2 × 2 pseudofactorial randomization to compare 2 separate treatments: C-MTX versus HD-MTX, and nelarabine versus no nelarabine. Because 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 2-stage procedure, including methotrexate and nelarabine randomizations. Interim efficacy analyses were scheduled when approximately 20%, 40%, 60%, 80%, and 100% of the expected events were observed; however, the results of interim analyses are not available. An alpha t^2 spending function for the stopping boundary was used for interim monitoring to allocate greater importance to the later analyses; however, no further details were provided. No adjustments were made for multiple comparisons among participant subsets, such as comparisons of DFS by 4 treatment arms, and risk groups (intermediate-risk versus high-risk). Based on the enrolled sample size, the study was powered to test its primary end point based on the ITT population. The proportional hazards assumption underlying the log-rank test was planned during treatment comparisons; however, no further details were provided. The secondary outcomes of the study, including OS and CNS relapse, produced findings consistent with those of DFS. It is unknown if the interim efficacy analyses on these outcomes are also in support of the findings on primary outcome. Subgroups analyses by MRD response at the end of consolidation therapy, or CNS status at diagnosis, which were identified as important by the clinical experts consulted for this review, were not performed in the COG AALL0434 trial. Although HRQoL was identified as an important outcome by both clinicians and patients, it was not evaluated or reported in the COG AALL0434 trial.

External Validity

In general, the clinical experts consulted for this review confirmed that the population of the COG AALL0434 trial was similar to that of the patients seen in clinics, and they raised no concerns about generalizing the findings from the trial to the Canadian clinical setting. The COG AALL0434 trial was a multicentre study; the population was drawn from 215 sites in the US, Australia, Canada, New Zealand, and Switzerland. In the COG AALL0434 trial, 373 of 1,572 patients were not eligible for postinduction therapy, including 353 patients who discontinued protocol therapy, which further reduced the generalizability of the trial results. The main reason for discontinuation of protocol therapy after induction therapy was the refusal of further protocol therapy by patient, parent, or guardian (61.7%). The clinical experts noted that failure to continue protocol therapy after induction may be related to the fact that some patients may already have experienced neurotoxicity events and were reluctant to take more medication that could cause more such events. The clinical experts added that all patients in the trial received prophylactic cranial radiation, which may not be helpful and may cause more harm to the patient, especially in children younger than 5 years of age.

In the COG AALL0434 trial, out of the 1,189 patients with T-ALL eligible for risk assessment at the end of induction therapy, 109 (9.2%) patients were classified as having low-risk T-ALL, 808 (68.0%) as having intermediate-risk T-ALL, and 229 (19.2%) as having high-risk T-ALL. The clinical experts consulted noted that this is reflective of Canadian clinical practice. In the efficacy phase of the COG AALL0434 trial, only patients with intermediate- and high-risk T-ALL were randomized to receive or not receive nelarabine in addition to the multidrug chemotherapy. The clinical experts consulted noted that patients with low-risk T-ALL were excluded from the nelarabine randomization due to concerns about neurotoxicity and therefore did not receive nelarabine in the trial; however, the neurotoxicity rates reported in the study were minimal. According to clinical experts, some centres across Canada are successfully prescribing nelarabine to all patients with newly diagnosed T- ALL, including those at low risk. Both clinician groups and clinical experts highlighted the importance of ensuring successful first-line treatment in patients with newly diagnosed T-ALL to minimize the relapse rate, as there is no standard of care for patients with relapsed T-ALL other than a TBI-based stem-cell transplant, and less than half of patients with relapsed or refractory T-ALL are cured by a transplant due to the significant risk of early or morbidity (i.e., graft-versus-host disease) and late morbidity (i.e., neurocognitive impairment) morbidity.

The COG AALL0434 trial included patients aged 1 to 30 years, and most patients were aged younger than 15 years. The clinical experts consulted indicated that this is reflective of Canadian clinical practice, and most patients with newly diagnosed T-ALL are young. While there is no relevant clinical evidence available, the clinical experts further noted that, although most patients with newly diagnosed T-ALL are young, 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. According to the clinician groups' input, patients between the age of 1 and 30 years with newly diagnosed T-ALL are most likely to respond to treatment with nelarabine and are the most in need of this intervention. Most patients (74.8%) in the trial were male; the clinical experts indicated that there is a higher predisposition for the disease in men than in women. In the COG AALL0434 trial, an aBMF backbone containing either a C-MTX or HD-MTX regimen was considered standard of care for patients with newly diagnosed T-ALL and it was selected as an appropriate active comparator in the trial. According to the clinical experts, in clinical practice, most patients receive C-MTX without leucovorin rescue, while patients with CNS3 disease or testicular disease generally receive HD-MTX with rescue treatment with leucovorin. The clinical experts consulted for this review indicated that the criteria used in the trial to determine risk (low, intermediate, or high) in patients with T-ALL after induction therapy are reflective of Canadian clinical practice.

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 highlighted that the clinicians would prefer to use triple intrathecal therapy over cranial radiation therapy in patients with CNS3 disease, particularly in those aged younger than 5 years due to the neurocognitive complications of cranial radiation therapy. The clinical experts further mentioned that different centres in Canada may take different approaches to the use of cranial radiation therapy. The clinical experts emphasized 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. While there is

no relevant clinical evidence available, the clinical experts noted that upfront treatment with nelarabine can prevent patients from receiving radiation therapy. In the COG AALL0434 trial, patients with a pre-existing, medication-dependent seizure disorder were not eligible for nelarabine randomization. However, the clinical experts noted that this exclusion criterion is not typical of clinical practice.

The clinical experts indicated that nelarabine is currently considered the standard of care in addition to an aBFM backbone therapy for patients with newly diagnosed T-ALL, and it is reimbursed in some formularies through a hospital budget.

Long-Term Extension Studies

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

Indirect Evidence

No studies with indirect evidence were identified for this review.

Studies Addressing Gaps in the Pivotal and Randomized Controlled Trial Evidence

No studies addressing gaps in the pivotal and randomized controlled trial evidence were identified for this review.

Discussion

Summary of Available Evidence

The COG AALL0434 trial was a phase III, 2 × 2 pseudofactorial randomized, open-label trial that 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 the C-MTX or HD- MTX regimen. During the initial safety phase, only patients with high-risk T-ALL were randomized to receive the aBFM backbone with randomization to 1 of 4 treatment arms after completion of induction therapy. After 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,[15] and patients with intermediate- and high-risk T-ALL were randomized to 1 of 4 treatment arms after completion of induction therapy. Patients with low-risk T-ALL did not participate in the nelarabine randomization in either the initial safety or efficacy phases. Patients with intermediate-risk T-ALL were eligible for the nelarabine randomization during the efficacy phase but did not participate in the nelarabine randomization during the initial safety phase. Patients with high-risk T-ALL were eligible to receive nelarabine during both the safety and efficacy phases of the trial.

Baseline characteristics were well balanced between the treatment groups. Half of the patients (49.9%) were under the age of 10 years, 33.4% 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. M1 bone marrow at the end of induction therapy was

found in 95.3% of patients, and M2 bone marrow was found in 4.7% of patients. A total of 83.3% of patients did not have an alloHSCT, while 3.2% underwent alloHSCT.

In the efficacy phase of COG AALL0434, 659 patients were successfully randomized to receive the C-MTX or HD-MTX regimen with and without nelarabine at the end of induction therapy, including 433 patients (65.7%) with intermediate-risk T-ALL, and 226 (34.3%) with high-risk T-ALL. The primary efficacy end point was DFS, and the secondary efficacy end points were OS and CNS relapse. The safety end points included sensory neuropathy, motor neuropathy, central neuropathies (encephalopathy, seizure, stroke, extrapyramidal tract symptoms, acute mental status changes and somnolence), non-neurologic toxicities, and mortality. Although HRQoL was identified as an important outcome by both patients and clinicians, it was not evaluated or reported in this trial. Harms and notable harms (identified in the CADTH systematic review protocol) were assessed.

Interpretation of Trial Results

Efficacy

As a secondary outcome in the COG AALL0434 trial, analysis of OS was exploratory in nature and there was no adjustment for multiplicity. The clinical experts consulted for this review indicated that OS is an important outcome to assess treatment response in patients with newly diagnosed T-ALL. The 5-year OS rate was similar across the groups who received versus those who did not receive nelarabine in the COG AALL0434 trial (90.3% [SE ± 2.2%] versus 87.9% [SE ± 2.3%], respectively; P = 0.168). The clinical experts consulted noted that, in the COG AALL0434 trial, the between-group difference of 2.1% in the 5-year OS rate was modest but clinically meaningful, as the duration of treatment exposure and follow-up period were likely too short to observe any beneficial effect of nelarabine on mortality. The clinical experts further noted that it is unknown if the deaths reported in the trial were related to nelarabine treatment, radiation therapy received during the trial, relapse, or comorbidities.

The superiority of nelarabine over an aBFM backbone including C-MTX or HD-MTX regimens was demonstrated for DFS, with a between-group difference of 6.1% in the 5-year DFS rate (88.2% [SE ± 2.4%] versus 82.1% [SE ± 2.7%] in the nelarabine and non-nelarabine groups, respectively; P = 0.029), and this was considered a clinically meaningful difference by the clinical experts consulted for this review. However, there is no known or accepted MID for DFS rates in this population. The median follow-up duration and the median DFS rate were not reported; the longer-term efficacy of nelarabine for DFS is therefore unknown for upfront therapy of newly diagnosed T-ALL. Among patients who received C-MTX regimen, the 5-year DFS rates were higher in those who received nelarabine versus those who were treated without nelarabine (91.4% [SE ± 3.1%] and 87.2% [SE ± 3.5%], respectively). Among patients who received the HD-MTX regimen, the 5-year DFS rates were higher in those who received nelarabine versus those who were treated without nelarabine (85.5% [SE ± 3.6%] and 78.1% [SE ± 4.0%], respectively). The clinical experts consulted for this review noted that C-MTX is more accessible to patients because patients do not require hospitalization to receive it. The clinical experts further noted that, in clinical practice, HD-MTX is mainly prescribed to patients with CNS3 disease as HD-MTX penetrates to the CNS and reduces CNS relapse.

The between-group difference in the 5-year CNS relapse was 5.6% (1.3% [SE ± 0.63%] versus 6.9% [SE ± 1.4%] in the nelarabine and non-nelarabine groups, respectively; P = 0.0001), which was considered clinically meaningful by the clinical experts consulted for this review. The CNS relapse analysis was exploratory in nature as there was no adjustment for multiplicity. The clinical experts mentioned that the number of patients who developed a second malignant neoplasm was marginally higher in the trial than they would expect for this population in 5 years. However, they noted that this difference was not significant and not many of the second malignant neoplasms would be associated with nelarabine treatment.

Although HRQoL was identified as an important outcome by both clinicians and patients, it was not evaluated or reported in the COG AALL0434 trial. According to the patient input received from the LLSC, patient respondents with T-ALL indicated that the impact of treatment with nelarabine on quality of life was neutral or less challenging than other treatments for acute lymphoblastic leukemia.

Harms

In the initial safety phase of the COG AALL0434 trial, only 1 of the 6 grade 3 sensory neuropathies was possibly attributable to nelarabine. For the 6 patients who received nelarabine, 3 CTCAE grade 3 motor neuropathies were attributed to nelarabine. The only CTCAE grade 4 motor neuropathy occurred in a patient who did not receive nelarabine. Most of the neuropathies associated with nelarabine occurred either during exposure of nelarabine or within 2 weeks of its administration. There were 4 episodes of central neurotoxicity possibly related to treatment with nelarabine. Among 94 patients with high-risk T-ALL, 1 patient died during induction therapy and 8 patients died after being randomized at the end of induction into the 4 treatment arms. No patients died from complications related to treatment with nelarabine.

In the efficacy phase of the COG AALL0434 trial, neurotoxicity and overall toxicity were marginally higher among patients who received nelarabine. Central neurotoxicity was reported in 11 patients (3.4%) who received nelarabine, and 7 patients (2.1%) who did not receive nelarabine. A total of 55 patients (17.0%) who received nelarabine and 46 patients (13.7%) who did not receive nelarabine experienced peripheral sensory or motor neuropathies. The clinical experts consulted for this review indicated that, because the patients in the trial received multidrug chemotherapy, it is difficult to determine if reported neuropathies or neurotoxicity were related to treatment with nelarabine. The number of deaths observed during remission was minimal, and it was lower in patients who received nelarabine compared to those who did not receive nelarabine, and it is unknown if deaths observed during this phase of the trial were related to treatment with nelarabine.

Conclusion

Based on data from the COG AALL0434 trial, nelarabine in combination with an aBFM backbone demonstrated a clinically meaningful and statistically significant benefit compared to an aBFM backbone alone in improving DFS in patients with newly diagnosed intermediate- and high-risk T-ALL. Because the median DFS was not reported in either treatment group, the longer-term efficacy of nelarabine for DFS is unknown for upfront therapy for newly diagnosed T-ALL. Compared with placebo, treatment with nelarabine (when added to an aBFM backbone) was associated with a reduction in CNS relapse rates. According to

clinical experts, nelarabine could help optimize upfront treatment of T-ALL to improve outcomes in terms of disease recurrence and CNS relapse. In the COG AALL0434 trial, the improvement in OS was modest; however, the duration of treatment exposure and follow-up period were likely too short to observe the beneficial effect of nelarabine on mortality. While notable AEs (central neurotoxicity and peripheral motor and sensory neuropathies) were not insignificant in the COG AALL0434 trial, the clinical experts consulted considered the safety profile of nelarabine to be expected and manageable in patients with newly diagnosed T-ALL. Although HRQoL was identified as an important outcome by both clinicians and patients, it was not evaluated or reported in the COG AALL0434 trial. The clinical experts consulted for this review indicated that nelarabine is currently considered the standard of care in addition to aBFM backbone therapy for patients with newly diagnosed T-ALL.

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Appendix 1: Literature Search Strategy

Note that this appendix has not been copy-edited.

Clinical Literature Search

Overview

Interface: Ovid

Databases:

- MEDLINE All (1946–)
- Embase (1974–)
- Note: Subject headings and search fields have been customized for each database. Duplicates between databases were removed in Ovid.

Date of search: March 31, 2023

Alerts: Bi-weekly search updates until project completion

Search filters applied: No filters were applied to limit the retrieval by study type.

Limits:

- Publication date limit: none
- Language limit: none
- Conference abstracts: excluded

Table 12: Syntax Guide

Syntax	Description
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ot	Original title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.dq	Candidate term word (Embase)
.pt	Publication type

Syntax	Description
.rn	Registry number
.nm	Name of substance word (MEDLINE)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

Multi-Database Strategy

1. (nelarabin* or nelzarabin* or atriance* or arranon* or zygara* or 506U78 or 506-U-78 or gw506U78 or gw-506U78 or 506U or 506-U or bw506u or bw-506u or gw506u or gw-506u or gi262250 or gi-262250 or gr262250 or gr-262250 or nsc686673 or nsc-686673 or 60158CV180).ti,ab,kf,ot,hw,rn,nm.
2. 1 use medall
3. *nelarabine/ or (nelarabin* or nelzarabin* or atriance* or arranon* or zygara* or 506U78 or 506-U-78 or gw506U78 or gw-506U78 or 506U or 506-U or bw506u or bw-506u or gw506u or gw-506u or gi262250 or gi-262250 or gr262250 or gr-262250 or nsc686673 or nsc-686673).ti,ab,kf,dq.
4. 3 use oemezd
5. or/2,4
6. 5 not (conference abstract or conference review).pt.
7. remove duplicates from 6

Clinical Trials Registries

ClinicalTrials.gov

Produced by the US National Library of Medicine. Targeted search used to capture registered clinical trials.

[Search -- Studies with results | nelarabine OR atriance OR arranon OR zygara OR 506U78]

WHO ICTRP

International Clinical Trials Registry Platform, produced by the WHO. Targeted search used to capture registered clinical trials.

[Search terms -- nelarabin* OR atriance* OR arranon* OR zygara*]

Health Canada's Clinical Trials Database

Produced by Health Canada. Targeted search used to capture registered clinical trials.

[Search terms -- nelarabine OR atriance]

EU Clinical Trials Register

European Union Clinical Trials Register, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- nelarabine OR atriance OR arranon OR zygara OR 506U78]

EU Clinical Trials Information System (CTIS)

European Union Clinical Trials Information System, produced by the European Union. Targeted search used to capture registered clinical trials.

[Search terms -- nelarabine OR atriance OR arranon OR zygara OR 506U78]

Grey Literature

Search dates: March 21, 2013 – April 3, 2023

Keywords: [nelarabine, atriance, arranon, zygara, lymphocytic leukemia, lymphoblastic leukemia, lymphoid leukemia, lymphatic leukemia, lymphocyte leukemia, TCell leukemia, T-cell leukemia, lymphocytic leukemia, lymphoblastic leukemia, lymphoid leukemia, lymphatic laeukemia, lymphocyte leukemia, TCell leukemia, T-cell leukemia, or lymphoma]

Limits: Publication years: none

Relevant websites from the following sections of the CADTH grey literature checklist Grey Matters: A Practical Tool for Searching Health-Related Grey Literature were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings An analysis by treatment arm showed that 5-year DFS rates were 91.4% (SE ± 3.1%) in p
- Drug Class Reviews
- Clinical Trials Registries
- Databases (free)
- Internet Search

Appendix 2: Excluded Studies

Note that this appendix has not been copy-edited.

Table 13: Excluded Studies

Reference	Reason for exclusion
Agrawal et al. (2021) Cohen et al. (2008) Gandhi et al. (2001) Muffly et al. (2012)	Not relevant study design
Dunsmore et al. (2012) Abaza et al. (2018)	Not relevant intervention
Kanayama et al. (2017)	Not relevant outcome
Hayashi et al. (2020) Monita et al. (2021)	Not relevant study population

Pharmacoeconomic Review

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Abbreviations

aBFM	augmented Berlin-Frankfurt-Münster
AE	adverse event
ALL	acute lymphoblastic leukemia
BIA	budget impact analysis
BSA	body surface area
C-MTX	Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase
COG	Children's Oncology Group
DFS	disease-free survival
Hyper-CVAD	hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone
ICER	incremental cost-effectiveness ratio
OS	overall survival
QALY	quality-adjusted life-year
RR	relative risk
SOC	standard of care
T-ALL	T-cell acute lymphoblastic leukemia

Executive Summary

The executive summary comprises 2 tables (Table 1 and Table 2) and a conclusion.

Table 1: Submitted for Review

Item	Description
Drug product	Nelarabine (Atriance), IV infusion
Submitted price	Nelarabine, 5 mg/mL, 50 mL vial: $545.42[a] per single-use vial
Indication[b]	For the treatment of patients with T-ALL and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens
Health Canada approval status	Unlabelled indication
Health Canada review pathway	NA
NOC date	NA
Reimbursement request	For the addition to front-line multidrug therapy of pediatric, adolescents, and young adult patients (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL
Sponsor	Pediatric Oncology Group of Ontario
Submission history	Previously reviewed: No

NA = not applicable; NOC = Notice of Compliance; T-ALL = T-cell acute lymphoblastic leukemia.

[a]Price submitted by the sponsor based on correspondence with Novartis Pharmaceuticals in 2021.[1]

[b]Approved Health Canada indication.[2]

Table 2: Summary of Economic Evaluation

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
Comparator	SOC, defined as aBFM multidrug chemotherapy protocol
Perspective	Canadian publicly funded health care payer
Outcomes	QALYs, life-years
Time horizon	Lifetime (90 years)
Key data source	COG AALL0434
Submitted results	ICER = $39,206 per QALY gained (incremental costs: $77,311; incremental QALYs: 1.97)
Key limitations	• Long-term efficacy of nelarabine plus 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

Component	Description
	was associated with a 5-year DFS benefit in the trial (between-group difference of 6.1%); however, as the 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 centres across Canada and that a patient's age should not exclude a patient from being eligible for nelarabine. The cost-effectiveness of nelarabine plus SOC in low-risk T-ALL and in adult patients aged 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-old's over the entire treatment duration (i.e., ranging from 2 to 3 years, based on gender). • Clinical efficacy data comparing nelarabine plus 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 plus aBFM SOC to hyper-CVAD is unknown.
CADTH reanalysis results	• CADTH revised the unit price for several drugs, including nelarabine, to address 1 of the identified key limitations as part of its reanalysis. • In the CADTH reanalysis, the ICER for nelarabine plus SOC was $26,362 per QALY gained compared to SOC alone. No price reduction is required for nelarabine plus SOC to be 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 plus SOC. Should a smaller OS difference be observed for nelarabine plus SOC vs. SOC alone as a first-line treatment for children, adolescents, and young adults with newly diagnosed intermediate- or high-risk T-ALL, a smaller QALY benefit would be expected, leading to a higher ICER for nelarabine plus SOC vs. 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 = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; ICER = incremental cost-effectiveness ratio; OS = overall survival, QALY = quality-adjusted life-year; SOC = standard of care; T-ALL = T-cell acute lymphoblastic leukemia; vs. = versus.

Conclusions

Evidence from the Children's Oncology Group (COG) AALL0434 study suggests that nelarabine as an add-on to first-line augmented Berlin-Frankfurt-Münster (aBFM) multidrug chemotherapy demonstrated a clinically meaningful and statistically significant benefit compared to an aBFM backbone alone in improving disease-free survival (DFS) for newly diagnosed pediatric, adolescent, and young adult patients (aged 1 to 30 years) with intermediate- and high-risk T-cell acute lymphoblastic leukemia (T-ALL). Overall survival (OS) was reported as a secondary outcome. While the clinical experts consulted by CADTH for this review noted that the between-group difference of 2.1% in the 5-year OS rate was modest but clinically meaningful, they pointed out that the duration of treatment and the follow-up period were likely too short to observe any beneficial effect of nelarabine on OS. Similarly, nelarabine was associated with a clinical benefit over the aBFM backbone regimen for DFS at 5 years (the between-group difference in the 5-year DFS rate was 6.1%), but the long-term efficacy of nelarabine remains unknown as the median DFS was not reported.

CADTH undertook reanalysis to address inaccuracies in unit prices of nelarabine, cytarabine, doxorubicin, methotrexate, and pegaspargase. The CADTH reanalysis resulted in an incremental cost-effectiveness

ratio (ICER) for nelarabine plus standard of care (SOC) versus SOC alone of $26,362 per quality-adjusted life-year (QALY) gained (incremental costs = $51,573, incremental QALYs = 1.96). CADTH results were consistent with those of the sponsor in that no price reduction would be required for nelarabine plus SOC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained when compared to SOC alone. The majority of the incremental QALYs associated with nelarabine were driven by an assumed survival benefit, with approximately 74% of the incremental QALYs for nelarabine accruing after the observed follow-up period of the COG AALL0434 trial (minimum follow-up time of 3 years). This corresponds to an estimated additional 2.87 life-years, which occurred during the post-trial period compared to SOC; however, as previously noted, the true long-term effect of nelarabine on OS is unknown due to the short duration of treatment and follow-up period in the COG AALL0434 trial.

Clinical expert feedback received by CADTH noted that some centres across Canada are prescribing nelarabine as an add-on to aBFM backbone therapy to all patients with T-ALL, including those with low-risk disease. They further stated that factors such as a patient's age should not affect patient eligibility for nelarabine; however, the cost-effectiveness of nelarabine in addition to SOC versus SOC alone for low-risk and adult patients 30 years and older with T-ALL is unknown. Last, the cost-effectiveness of nelarabine plus aBFM versus hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) for adult patients with intermediate- and high-risk T-ALL also remains unknown.

Stakeholder Input Relevant to the Economic Review

This section is a summary of the feedback received from the patient groups, registered clinicians, and drug plans that participated in the CADTH review process.

Patient input was jointly submitted by the Leukemia & Lymphoma Society of Canada, Advocacy for Canadian Childhood Oncology Research Network, Ontario Parents Advocating for Children with Cancer, and Childhood Cancer Canada. Information was gathered via 2 online surveys conducted in 2019 and 2023 from patients under the age of 30 with acute lymphoblastic leukemia (ALL) at the time of their diagnosis or their caregivers. A total of 66 responses were collected over the 2 surveys, and from 1 one-on-one interview conducted in 2019. Respondents from both surveys noted that ALL has a significant impact on both patient and their caregiver quality of life, specifically surrounding daily routines, physical and mental functioning, and the work life of caregivers. The majority of survey respondents agreed that the most important factors to consider when making decisions about currently available treatments were physician recommendation, side effects, quality of life, and the possible impact of treatment on disease. The surveys' participants expressed the hope that any new treatment would come with improved prognosis (increased survival), fewer and/or less-severe long-term adverse effects, improved treatment logistics (e.g., fewer trips to the hospital, removing steroids from treatment, and shortening the maintenance period), and provision for associated mental health supports. Direct experience with nelarabine was reported by 3 and 7 respondents in the 2019 and 2023 surveys, respectively. Of respondents with experience with nelarabine treatment, the majority noted that nelarabine positively affected their treatment and had minimal side effects compared with other

ALL treatments. Of the side effects, respondents indicated they were generally minor and manageable, with low platelet counts, low red blood cell counts, anemia, low white blood cell counts, and extreme sleepiness causing side effects with the greatest impacts.

Separate clinical input was received from 3 clinician groups: the Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee, the Pediatric Hematology/Oncology program at the Janeway Children's Health and Rehabilitation Centre in St. John's, Newfoundland and Labrador, and the Department of Hematology, Oncology, and Bone Marrow Transplant at the British Columbia Children's Hospital. Clinician input noted that current treatment largely consists of pediatric intensive multidrug chemotherapy regimens with a curative intent; however, relapse-free survival rates in pediatric patients with T-ALL are suboptimal and not all patients respond to currently available treatments. 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 the addition of nelarabine as a front-line drug and are the most in need of this intervention.

In their feedback, the drug plans asked whether patients with low-risk T-ALL and those over the age of 30 years should be eligible for front-line treatment with nelarabine in combination with multidrug chemotherapy. The plans also asked about the feasibility of re-treatment with nelarabine in a later line of therapy in cases of relapsed disease. Last, the drug plans raised concerns about the low likelihood of vial sharing but noted that, with published extended stability data, this could allow more than 1 daily dose of nelarabine to be compounded, which would reduce vial wastage.

Three of these concerns were addressed in the sponsor's model:

- The impact of T-ALL on patient quality of life was captured by utility values. The utility-measurement scale used in this model was based on Health Utility Index 3, which includes assessments of attributes relating to ambulation, emotion, cognition, and pain.
- The sponsor's model compared nelarabine as an add-on to SOC with SOC alone. This reflects its anticipated use for children, adolescents, and young adult patients between the age of 1 to 30 years with intermediate- or high-risk T-ALL.
- Vial sharing was not considered in the analysis.

CADTH was unable to address the following concerns raised from stakeholder input:

- As the clinical data informing the treatment effect of nelarabine plus SOC was based on the COG AALL0434 trial, the clinical effectiveness and cost-effectiveness of nelarabine plus SOC in low-risk T-ALL and adults over 30 years of age are unknown.
- Adverse events (AEs) were not included within the analyses. However, feedback from clinical experts consulted by CADTH indicated that no significant difference in AEs would be expected in clinical practice between nelarabine plus SOC versus SOC alone, which was aligned with the findings from the COG AALL0434 trial.

Economic Review

The current review is for nelarabine (Atriance) as an add-on to front-line aBFM multidrug therapy for pediatric and adolescent patients, and young adults (aged 1 to 30 years at diagnosis) with intermediate- or high-risk T-ALL.

Economic Evaluation

Summary of Sponsor's Economic Evaluation

Overview

The Health Canada indication for nelarabine (Atriance) is for the treatment of adults and children with T-ALL and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least 2 chemotherapy regimens.[2] The sponsor, the Pediatric Oncology Group of Ontario, is seeking a review of nelarabine as an add-on to first-line treatment in children, adolescents, and young adults (aged 1 to 30.99 years) with newly diagnosed intermediate- or high-risk T-ALL, and it has submitted a cost-utility model comparing nelarabine in addition to SOC with SOC alone for this population. SOC was defined as a COG multidrug regimen, referred to as the aBFM chemotherapy protocol. This modelled population differs from the Health Canada indication and represents the reimbursement request.[1]

Nelarabine is available in 50 mL single-use vials.[2] The Health Canada–recommended dose of nelarabine as a monotherapy is 650 mg/m^2 per day administrated intravenously over 1 hour on days 1 to 5, repeated every 21 days, for pediatric patients under 15 years of age or 1,500 mg/m^2 per day administered intravenously over 2 hours on days 1, 3, and 5, repeated every 21 days, for adults.[2] An optimal monotherapy dosing regimen has not been established for patients aged 16 to 21 years.[2] Due to the unlabelled indication, there is no product monograph dosing. For use in the reimbursement requested population, nelarabine is an add-on therapy to aBFM for which dosing is expected to align with the protocol of the COG AALL0434 trial (i.e., 650 mg/m^2 on days 1 to 5 and days 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).[1,3] Based on correspondence with Novartis Pharmaceuticals in 2021, the submitted price of nelarabine used by the sponsor was $545.42 per 50 mL vial (the model uses a price of $582.49 based on an inflation adjustment to derive 2022 values).[1] The comparator for this analysis was SOC (i.e., the aBFM chemotherapy protocol), which was associated with a total drug acquisition cost ranging from approximately $168,225 to $171,163 (depending on the patients' sex and body surface area [BSA]). The cost of aBFM when added to nelarabine ranged from $167,853 to $170,791, depending on the patient's sex and BSA and given the slight dosing variations to the aBFM protocol with the addition of nelarabine.

Outcomes of the model included QALYs and life-years, reported over a lifetime time horizon of 90 years. The analysis was conducted from the perspective of a publicly funded health care payer. Discounting at 1.5% per year was applied to both costs and outcomes and a cycle length of 30 days was used.[1]

Model Structure

The sponsor submitted a patient-level microsimulation model consisting of 3 health states: relapse-free, postrelapse, and death (Figure 1).[1] The model simulated patients with unique health profiles using baseline characteristic data from the COG AALL0434 trial. Each individual entered the model individually in a relapse-free health state following a previous diagnosis of T-ALL and completion of the induction phase of treatment. A patient could remain in this health state or transition to either the postrelapse or death state. Regardless of prior first-line treatment assignment, those in the postrelapse health state were assumed to have identical survival rates that would be equal to those of the SOC-plus-nelarabine arm. Patients could transition to death at any point.

Model Inputs

Baseline characteristics (i.e., proportion female = 25.2%; and proportion of patients who were positive for central nervous system disease with a white blood cell count greater than 5 with blasts at diagnosis = 8.6%) were informed by the COG AALL0434 trial[3] whereas the mean age at diagnosis (8.77 years) was informed by the Pediatric Oncology Group of Ontario Networked Information System dataset.[4]

Parametric survival curves were fitted to individual patient-level data from the randomized portion of the COG AALL0434 trial for patients treated with Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase (C-MTX) in the interim maintenance phase to inform transition probabilities between health states. Curve selection was based on goodness of fit and clinical plausibility. In the sponsor's base-case analysis, the Gompertz distribution was selected to inform the relapse-free–to–relapse, relapse-free–to–death, and relapse-to-death transitions in both the SOC and nelarabine-plus-SOC groups.[1]

The sponsor applied Canadian age- and gender-specific general population mortality rates throughout the modelled time horizon.[5] To account for the increased risks of premature mortality in long-term ALL survivors, the sponsor further adjusted the background all-cause mortality rates using age-specific relative risk (RR) of death (i.e., age ≤ 40 years, RR = 3.2; 40 < age ≤ 50, RR = 2.7; 50 < age ≤ 60, RR = 1.8; age > 60. RR = 1.4)[6] up to 15 years postinduction. Beyond 15 years postinduction, patients in all alive health states were assumed to be cured, with their mortality risk based on Canadian age- and gender-specific general population mortality rates.

The sponsor did not consider treatment adherence in the model as it was assumed the rates of discontinuation for SOC and nelarabine would be similar.[1] It was further assumed that there was no significant difference in AE rates between SOC and SOC plus nelarabine; therefore, AEs were not included in the model.[1]

Health-state utility values in the model were informed by published literature.[7,8] Patients in the relapse-free health state were assumed to have a higher utility value the longer they remained in the relapse-free health state. For the first 6 months, patients were assumed to have a utility of 0.79, which would increase to 0.87 for months 7 to 9. Patients who remained in the relapse-free health state would be assigned a utility value of 0.90 after treatment (after month 10).[1] Utilities in the relapse state were not dependent on time spent within this health state.[1]

Drug acquisition cost, administration costs, and health care resource use costs were included in the analysis and informed by Novartis Pharmaceuticals Canada, the Ontario Schedule of Benefits, and published literature.[9,10] Drug acquisition and administration frequency for all treatment stages beyond induction therapy (i.e., consolidation, interim maintenance, delayed intensification and maintenance) were informed primarily by the COG AALL0434 trial (Appendix 1).[3] The sponsor identified minor deviations from the AALL0434 protocol (i.e., dexamethasone in maintenance versus prednisone) guided by expert opinion.[1] Additional dosing information is provided in Appendix 1. The cost of cranial radiation was considered for patients with central nervous system involvement at diagnosis, as informed by the Ontario Schedule of Benefits.[11] Health care costs for the postrelapse state were informed by Gupta et al., reflecting patients in Ontario diagnosed with ALL between 2002 and 2012.[12] All costs were expressed in 2022 Canadian dollars.[1]

Summary of Sponsor's Economic Evaluation Results

All analyses were run probabilistically for 1,000 iterations, each with 5,000 simulated patients. Probabilistic findings are presented in the following section.

Base-Case Results

When comparing nelarabine plus SOC to SOC alone for first-line treatment in children, adolescents, and young adults (aged 1 to 30.99 years) with intermediate- or high-risk T-ALL, the sponsor's base-case analysis found that the addition of nelarabine to SOC was associated with an additional 1.97 QALYs at an additional cost of $77,311. Therefore, the ICER of SOC plus nelarabine was $39,206 per QALY gained compared to SOC alone. The majority (approximately 74%) of the incremental QALYs for nelarabine plus SOC were found to accrue during the extrapolation period, which was affected by the additional 3.41 life-years gained for nelarabine plus SOC compared to SOC alone.

Table 3: Summary of the Sponsor's Economic Evaluation Results

Drug	Total costs ($)	Incremental costs ($)	Total QALYs	Incremental QALYs	ICER vs. SOC ($ per QALY)
SOC	194,942	Reference	29.26	Reference	Reference
SOC plus nelarabine	272,253	77,311	31.23	1.97	39,206

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care; vs. = versus.
Source: Sponsor's pharmacoeconomic submission.[1]

Sensitivity and Scenario Analysis Results

The sponsor conducted several scenario analyses using alternative inputs to inform postrelapse survival, different statistical distributions for SOC, different definitions for time of cure, and discounting. While the base case assumed all patients in the postrelapse health state would have identical survival rates, a scenario analysis in which arm-specific postrelapse survival in the COG AALL0434 trial was used to inform the economic analysis had the largest impact on results, with an ICER of $149,719 per QALY gained.[1]

CADTH Appraisal of the Sponsor's Economic Evaluation

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the economic analysis:

- **Long-term efficacy of nelarabine as an add-on therapy for first-line treatment of children, adolescents, and young adults (aged 1 to 30.99 years) with newly diagnosed intermediate- or high-risk T-cell ALL is unknown**. The treatment efficacy for nelarabine plus SOC in the sponsor's base case was informed by parametric extrapolations fitted to patient-level data from the COG AALL0434 trial. As noted in the CADTH clinical review, the 5-year OS rates were similar between groups (nelarabine = 90.3% [standard error = 2.2] and no nelarabine = 87.9% [standard error = 2.3]; P = 0.168). Clinical expert feedback sought by CADTH stated that the 2.1% between-group difference observed in the 5-year OS rate was modest but clinically meaningful. The feedback received by clinical experts also noted that the duration of treatment explored and follow-up period were likely too short to observe any beneficial effect of nelarabine on OS. Similarly, although nelarabine was associated with a clinical benefit over the aBFM backbone regimen for DFS at 5 years (between-group difference in the 5-year DFS rate of 6.1%); the long-term efficacy of nelarabine remains unknown as median DFS was not reported.

  The primary efficacy outcome of the COG AALL0434 trial was DFS while relapse-free survival (including time to relapse) was the primary outcome used to inform the economic analysis. However, while CADTH requested the individual patient-level data used to inform the model from COG directly, the data were not received in time to inform this review. CADTH validated the predicted OS outcomes produced by the model against the reported OS outcomes of the COG AALL0434 trial, finding a slight OS benefit compared to SOC alone (i.e., the trial reported a 5-year OS of 90.3% versus the model prediction of 89.8%).

  - CADTH was unable to resolve the issue surrounding the uncertainty in the comparative long-term efficacy due to limitations in data availability. Should a smaller OS benefit be observed over time for nelarabine plus SOC versus SOC alone, this would bias the cost-effectiveness against nelarabine due to a smaller QALY benefit.
- **Exclusion of low-risk and adult (30 years and older) patients is not appropriate**. The sponsor's economic evaluation was specifically conducted to reflect the requested reimbursement population (i.e., pediatric and young adult [aged 1 to 30] patients with intermediate- or high-risk T-ALL). This requested reimbursement population reflected the trial population studied in the COG AALL0434 trial, which excluded low-risk patients from nelarabine randomization due to potential concerns with neurotoxicity associated with nelarabine. Patients on nelarabine had minimal neurotoxicity documented in the trial, and clinical expert feedback obtained by CADTH noted that some centres across Canada are currently using nelarabine in addition to SOC for all pediatric patients with T-ALL as front-line therapy. The low-risk cohort would represent approximately 10% to 15% of T-ALL patients. The clinical experts also noted that nelarabine may be used in adult patients older then 30 years if deemed appropriate. Factors such as patient age and disease-risk status should not affect a

patient's eligibility for nelarabine, according to the feedback received by clinical experts consulted by CADTH, despite the reimbursement requested indication being more restrictive.

  - CADTH was unable to resolve this issue due to limitations in the clinical data availability as neither direct nor indirect comparative evidence is available for these other patient populations. The cost-effectiveness of nelarabine plus SOC in low-risk T-ALL and in adult patients aged 30 years or older is unknown.

- **Drug acquisition costs may be underestimated.** The price of nelarabine was informed by communications with Novartis in 2021, which were then inflated to 2022 Canadian dollars based on the Consumer Price Index using the Bank of Canada inflation calculator.[13] The remaining drug prices in the sponsor's submitted analysis were informed by the Ontario Schedule of Benefits or published literature.[9,10] There were some inaccuracies regarding the unit drug price of nelarabine, cytarabine (the sponsor based its estimate on a Health Quality Ontario publication),[10] doxorubicin (the sponsor based its estimate on a Health Quality Ontario publication),[10] methotrexate PO (IV unit costs were used to inform the costs of the oral product) and pegaspargase.

  Furthermore, to align with the starting age of the population, the average BSA (i.e., 1.07 m^2) for a patient aged 9 years was used to inform drug costs for the entire duration of treatment. Given that the dosing of some of the treatments within the regimen, including nelarabine, is based on BSA, and assuming treatment may be provided for up to 3 years, total drug costs are highly dependent on patient age and size. Over time, as the cohort ages and some proportions of the patients become young adults, the total drug costs would be underestimated if the dosing still reflects that given to a patient 9 years of age over the entire duration of the treatment regimen.

  - In the CADTH base-case analysis, the unit price for nelarabine, cytarabine, doxorubicin, oral methotrexate, and pegaspargase were corrected.
  - To explore how alternative BSA values may affect the cost-effectiveness of nelarabine plus SOC, CADTH conducted a scenario analysis using a starting age of 18 years and a BSA of 1.8 m^2.

- **Exclusion of hyper-CVAD as a comparator for adult patients with intermediate- or high-risk T-ALL was inappropriate**. In the sponsor's submitted analysis, the included comparator was the aBFM multidrug chemotherapy regimen used in the COG AALL0434 trial. While feedback from clinical experts received by CADTH noted that this was the most relevant comparator for children and adolescents with newly diagnosed, intermediate- or high-risk T-ALL, the feedback also noted that hyper-CVAD may be used as a chemotherapy regimen in adult T-ALL patients. There has been no head-to-head trial or indirect comparison of the addition of nelarabine to aBFM versus hyper-CVAD in adult patients with newly diagnosed intermediate- or high-risk T-ALL. As such, the cost-effectiveness of nelarabine plus SOC against this comparator is unknown.

  - CADTH was unable to resolve this issue due to limitations in data availability. However, the clinical experts consulted by CADTH expected only a small subset of patients newly diagnosed with intermediate- or high-risk T-ALL to receive hyper-CVAD.

- **Health-state utility values used in the sponsor's base case were overestimated.** In the sponsor's base case, health-state utility values for the relapse-free health state were informed by Furlong et al., (2012), which was a study examining the health-related quality of life of children treated for ALL.[8] The sponsor assumed that patients would have a higher health-state utility value the longer they remained in the relapse-free state. Utilities of 0.79, 0.87, and 0.9 were therefore used to inform the utility values for the relapse-free health state between 0 and 6 months, 7 to 9 months, and 10 months and longer, respectively. However, a Canadian Community Health Survey estimated that the average Canadian utility in children aged 12 to 19 was 0.886.[14] Clinical experts consulted by CADTH noted that it was unlikely that patients with T-ALL would have a quality of life similar to that of the average patient in Canada given the advanced, biologically aggressive disease in this subset of patients. The absolute utility values from Furlong et al., (2012) therefore may have overestimated the absolute QALYs estimated by the economic model; however, clinical expert feedback received by CADTH noted that the relative difference between each health-state utility value may be reasonable.
    - CADTH was unable to resolve this issue due to limitations in available data. The impact of this limitation on the cost-effectiveness of nelarabine plus SOC may have inflated the absolute QALYs reported for each treatment; however, the reported ICER may be reasonable as the relative differences between each health-state utility value may be reasonable.

Additionally, the following key assumptions made by the sponsor were appraised by CADTH (Table 4).

Table 4: Key Assumptions of the Submitted Economic Evaluation (Not Noted as Limitations to the Submission)

Sponsor's key assumption	CADTH comment
All patients entered the model at the age of 8.77 years, which aligns with the average age of diagnosis from the POGONIS dataset.	Potentially reasonable. Feedback from clinical experts received by CADTH noted that the average age of diagnosis in the POGONIS dataset may be reflective of Canadian clinical practice. However, given that drug dosing and costs are highly dependent on the assumed patient age and BSA, it would have been more appropriate to model the age parameter as a distribution from the POGONIS dataset. The average age of diagnosis is expected to affect the cost-effectiveness of nelarabine plus SOC, as it may be correlated with a patient's BSA.
Mortality risks for patients in the relapse-free or postrelapse health state 15 years after induction were based on Canadian background mortality (adjusted to account for the risk of premature mortality in long-term T-ALL survivors).	Reasonable. Clinical expert feedback received by CADTH noted that patients with T-ALL often relapse within approximately 1 to 5 years in their treatment course. While adult patients stop follow-up at around 5 years, pediatric patients are often followed for life to monitor late effects of the disease. Those who survive past 15 years may be deemed cured by clinicians as disease-specific mortality risks are expected to be low.
Nelarabine efficacy data from the C-MTX arm of the COG AALL0434 trial were used to inform the model.	Reasonable. Clinical expert feedback received by CADTH noted that, although methotrexate dose is centre-dependent across Canada, low-dose methotrexate (as aligned with the C-MTX arm of the COG AALL0434 trial) is generally more reflective of Canadian SOC for pediatric, adolescent, and young adult patients with intermediate-or

Sponsor's key assumption	CADTH comment
	high-risk T-ALL, while high-dose methotrexate is more commonly used in CNS patients.
Postrelapse survival for SOC is equal to postrelapse survival in the nelarabine plus SOC arm of the COG AALL0434 trial.	Uncertain. The sponsor assumed that patients who relapsed without having received nelarabine in first-line treatment would be more likely to receive nelarabine as part of their subsequent therapy. The clinical experts consulted by CADTH noted that patients who failed first-line nelarabine plus SOC may have worse survival outcomes than do patients who fail SOC due to more severe underlying disease. CADTH conducted a sensitivity analysis that set the treatment arm's postrelapse survival to be equal to their respective observations from the COG AALL0434 trial.
Adherence rates between nelarabine plus SOC vs. SOC alone were assumed to be equal.	Reasonable. Although adherence is not reported in COG AALL04343, clinical expert feedback received by CADTH suggested that the addition of nelarabine is not expected to affect treatment adherence rates.
Assumed no AE disutility.	Reasonable. The CADTH clinical review noted that no significant differences in AEs between the SOC and nelarabine plus SOC arms in the COG AALL0434 trial.
Patients were assumed to have a higher health-state utility value the longer they remained in the relapse-free state.	Reasonable. Clinical expert feedback received by CADTH stated that patients who progress through the various courses of SOC for the treatment of T-ALL (i.e., induction through to maintenance) while remaining relapse-free may experience slight improvements in quality of life given that treatment intensity subsides as the treatment course continues. This may allow patients to participate in many activities similar to those of their peers.
Cranial radiation was included as part of first-line therapy for patients diagnosed with CNS3 disease.	Reasonable and confirmed by clinical expert feedback received by CADTH.

AE = adverse events; CNS = central nervous system; COG = Children's Oncology Group; C-MTX = Capizzi escalating-dose methotrexate without leucovorin rescue plus pegaspargase; POGONIS = Pediatric Oncology Group of Ontario Networked Information System; SOC = standard of care; T-ALL = T-cell acute lymphoblastic leukemia; vs. = versus.

CADTH Reanalyses of the Economic Evaluation

Base-Case Results

The CADTH base case was derived by making changes in model parameter values in consultation with clinical experts. The changes summarized in Table 5 involved updating certain drug unit prices to better reflect the current list price. CADTH was unable to address the other identified limitations with the submitted model.

Table 5: CADTH Revisions to the Submitted Economic Evaluation

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
Dosing frequency	Dosing frequencies of the following were inaccurately captured in the costing calculations: Nelarabine plus SOC • Dexamethasone (delayed intensification and cycle 1 to 3 of maintenance) • Vincristine, mercaptopurine, methotrexate, and nelarabine (maintenance, cycle 3) SOC alone • Vincristine, dexamethasone, and pegaspargase (delayed intensification) • Mercaptopurine (maintenance)	Corrected to align with dosing frequency as specified in COG AALL0434 (Table 10 provides more details)
Changes to derive the CADTH base case		
Unit price of drug treatments	• Nelarabine (informed by internal communications with Novartis 2021) • Cytarabine (costed per vial) • Doxorubicin • Methotrexate PO • Pegaspargase	• Nelarabine (DeltaPA) = $579.5400 • Cytarabine (costed per mL, DeltaPA) = $15.3250 • Doxorubicin (ODB) = $50 • Methotrexate PO (ODB) = $0.2513 • Pegaspargase (OHQ report) = $6,570.17
CADTH base case	Reanalysis 1	

COG = Children's Oncology Group; ODB = Ontario Drug Benefit; OHQ = Ontario Health Quality; PO = oral.

CADTH base-case results are presented in Table 6, with the disaggregated clinical outcomes estimated by the economic model reported in Table 9 of Appendix 4. Additional reanalyses are presented in Appendix 4.

In the CADTH base case, nelarabine plus SOC was associated with an estimated total cost of $269,137 and 31.21 QALYs, compared with total costs of $217,565 and 29.25 QALYs for patients on SOC alone. The ICER for nelarabine compared to SOC alone was therefore $26,362 per QALY gained (incremental costs = $51,573; incremental QALYs = 1.96). The probability that nelarabine plus SOC would be a cost-effective treatment at a willingness-to-pay threshold of $50,000 per QALY gained was 69%.

Aligned with the sponsor's submitted base-case results, nelarabine was associated with an additional 3.41 life-years for nelarabine plus SOC compared to SOC alone. The majority (approximately 73%) of the incremental QALYs for nelarabine plus SOC were found to accrue during the extrapolation period, which was driven by the expected survival benefits associated with nelarabine, as it was estimated to be associated with additional 2.87 life-years, which occurred during the post-trial period, compared to SOC (Table 9).

Table 6: Summary of the Stepped Analysis of the CADTH Reanalysis Results

Stepped analysis	Drug	Total costs ($)	Total QALYs	ICER ($ per QALY)
Sponsor's base case	Standard of care	194,942	29.26	Reference
	Nelarabine plus standard of care	272,253	31.23	39,206
Sponsor's corrected base case	Standard of care	218,522	29.25	Reference
	Nelarabine plus standard of care	270,949	31.21	26,702
CADTH base case (Reanalysis 1)	Standard of care	217,565	29.25	Reference
	Nelarabine plus standard of care	269,137	31.21	26,362

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year.

Scenario Analysis Results

Given that treatment dosing is based on BSA and the presence of uncertainties in the BSA of the patient cohort, a scenario analysis was conducted on the CADTH base case to investigate the impact of using an average adult BSA to inform drug costing. This analysis resulted in an ICER of $44,139 per QALY gained (incremental cost = $86,813; incremental QALYs = 1.97) for nelarabine plus SOC versus SOC alone. In this scenario, the main difference observed in the results was that it would be associated with higher incremental costs given that a higher dose of nelarabine would be required. As such, this highlights how the cost-effectiveness of nelarabine plus SOC is sensitive to a patient's BSA, which may be correlated with age.

CADTH also conducted a scenario analysis that explored the impact of selecting the postrelapse survival for each treatment arm with the respective treatment data from the COG AALL0434 trial as an alternative to the sponsor's base case, in which the postrelapse survival for SOC was equal to the postrelapse survival for nelarabine plus SOC. This analysis resulted in an ICER of $99,572 per QALY gained (incremental cost = $45,619; incremental QALYs = 0.46) for nelarabine plus SOC versus SOC alone. While this analysis suggests that nelarabine plus SOC would be associated with fewer incremental QALYs, due to limitations in data reporting in COG AALL0434, it is unclear if patients on SOC received nelarabine as part of their subsequent therapy and therefore the true impact of postrelapse survival on the cost-effectiveness of nelarabine plus SOC is unknown.

Based on the CADTH base-case analysis, nelarabine does not require a price reduction to be cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained when compared to SOC alone at current list prices.

Issues for Consideration

- Nelarabine is currently used across Canada as an add-on to first-line SOC (aBFM chemotherapy) for the treatment of pediatric and young adult patients with intermediate- or high-risk T-ALL. Funding varies across jurisdictions as it may be reimbursed by hospital budgets or clinicians may be required, for each patient, to apply for special access within their provincial drug reimbursement program.
- Feedback received by CADTH from clinical experts noted that the use of nelarabine could be considered part of reinduction or reconsolidation treatment before allogeneic hematopoietic stem

cell transplant in patients with relapsed T-ALL. However, the economic model did not consider re-treatment with nelarabine.

- As noted previously, some centres in Canada are currently using nelarabine as an add-on to first-line therapy for the treatment of pediatric and young adult patients with low-risk T-ALL. A future COG trial is anticipated to explore the comparative efficacy and safety of nelarabine as an add-on treatment to SOC in newly diagnosed patients with low-risk T-ALL.

Overall Conclusions

Evidence from the COG AALL0434 study suggests that nelarabine as an add-on to first-line aBFM multidrug chemotherapy demonstrated a clinically meaningful and statistically significant benefit compared to an aBFM backbone alone in improving DFS for newly diagnosed pediatric, adolescent, and young adult patients (aged 1 to 30 years) with intermediate- and high-risk T-ALL. OS was reported as a secondary outcome and was exploratory in nature. While the clinical experts consulted by CADTH noted that the between-group difference of 2.1% in the 5-year OS rate was modest but clinically meaningful, they also noted that the duration of treatment and the follow-up period were likely too short to observe any beneficial effect of nelarabine on OS. Similarly, nelarabine was found to be associated with a clinical benefit over the aBFM backbone regimen for DFS at 5 years (with a between-group difference in the 5-year DFS rate of 6.1%), but the long-term efficacy of nelarabine remains unknown as median DFS was not reported.

CADTH undertook reanalysis to address inaccuracies in unit prices of nelarabine, cytarabine, doxorubicin, methotrexate and pegaspargase. The CADTH reanalysis resulted in an ICER for nelarabine plus SOC versus SOC alone of $26,362 per QALY (incremental costs = $51,573, incremental QALYs = 1.96). CADTH results were consistent with those of the sponsor in that no price reduction would be required for nelarabine plus SOC to be considered cost-effective at a willingness-to-pay threshold of $50,000 per QALY gained when compared to SOC alone. The majority of the incremental QALYs associated with nelarabine were driven by an assumed survival benefit, with approximately 74% of the incremental QALYs for nelarabine accruing after the observed follow-up period of the COG AALL0434 trial (minimum follow-up time of 3 years). This corresponds to an estimated additional 2.87 life-years (which occur during the post-trial period) compared to SOC alone; however, the true long-term effect of nelarabine on OS is unknown due to the short duration of treatment and follow-up period in the COG AALL0434 trial.

The cost-effectiveness of nelarabine plus SOC was sensitive to assumptions on BSA. Specifically, CADTH conducted a scenario analysis exploring the impact of assuming an average adult BSA of 1.8 m^2, which resulted in an ICER of $44,139 per QALY gained (incremental cost = $86,813; incremental QALYs = 1.97) for nelarabine plus SOC versus SOC alone. Therefore, no price reduction is required to achieve cost-effectiveness at a willingness-to-pay threshold of $50,000 per QALY gained.

While clinical expert feedback received by CADTH noted that some centres across Canada are prescribing nelarabine as an add-on to aBFM backbone therapy to all patients with T-ALL, including those with low-risk disease, the cost-effectiveness of nelarabine is unknown in this patient population. Clinical expert feedback further stated that factors such as a patient age should not affect eligibility for nelarabine. Last, although hyper-CVAD is a chemotherapy regimen sometimes used to treat adult patients with intermediate and high-

risk T-ALL, the cost-effectiveness of nelarabine plus SOC versus SOC alone for patients 30 years and older and the cost-effectiveness of nelarabine plus aBFM versus hyper-CVAD for adult patients with intermediate- and high-risk T-ALL are unknown.

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Appendix 1: Cost Comparison Table

Table 7: CADTH Cost Comparison Table for the First-Line Treatment of Children, Adolescents, and Young Adults With Newly Diagnosed Intermediate- or High-Risk T-ALL

Treatment	Strength or concentration	Form	Price	Typical dosage	Cost per 28 days ($)	Course cost ($)
Nelarabine (Atriance)	5 mg/mL	50 mL vial	579.5400[a]	650 mg/m^2 on days 1 to 5 and 43 to 47 (consolidation), days 29 to 33 (delayed intensification), and days 29 to 33 (first 3 cycles; maintenance) as an add onto to aBFM backbone[b]	Consolidation: 8,693 Delayed intensification: 3,864 maintenance: 2,898	Consolidation: 17,386 delayed intensification: 8,693 maintenance: 8,693
Augmented Berlin-Frankfurt-Münster						
Consolidation						
Cyclophosphamide (Procytox)	20 mg/mL	500 mg vial 1,000 mg vial Powder for IV infusion	97.8000[a] 177.2700[a]	1,000 mg/m^2 IV on days 1 and 29	275	550
Cytarabine (generic)	100 mg/ mL	5 mL vial 20 mL vial for IV infusion	76.8500[a] 306.5000[a]	75 mg/m^2 IV on days 1 to 4, 8 to 11, 29 to 32 and 36 to 39[c]	615	1,230
Mercaptopurine (generic)	50 mg	Tab	2.8610	60 mg/m^2 PO on days 1 to 14 and 29 to 42	80	160
Methotrexate IT[b]	10 mg/ mL 25 mg /mL	2 mL vial Injectable solution	12.5000 8.9200	15 mg/m^2 IT on days 1, 8, 15 and 22[d]	25	50

Treatment	Strength or concentration	Form	Price	Typical dosage	Cost per 28 days ($)	Course cost ($)
Vincristine (generic)	1 mg/ mL	1 mg vial 2 mg vial for IV infusion	30.6000 63.3650	1.5 mg/m^2 IV on days 15, 22, 43 and 50	127	253
Pegaspargase	750 IU/mg	Vial	6,570.1700[e]	2,500 units/m^2 IM on days 15 and 43	26,281	52,561
Total cost for consolidation					27,403	54,804
Interim maintenance						
Vincristine (generic)	1 mg/ mL	1 mg vial 2 mg vial for IV infusion	30.6000 63.3650	1.5 mg/m^2 IV on days 1, 11, 21, 31 and 41	153	306
Methotrexate IV[f]	10 mg/ mL 25 mg /mL	2 mL vial Injectable solution	12.5000 8.9200	100 to 300 mg/m^2 IV on days 1, 11, 21, 31 and 41	67	134
Methotrexate IT[c]	10 mg/ mL 25 mg /mL	2 mL vial Injectable solution	12.5000 8.9200	15 mg/m^2 IT on days 1 and 31	13	25
Pegaspargase	750 IU/mg	Vial	6,570.1700[e]	2,500 units/mg/m^2 IM on days 2 and 22	26,281	52,561
Total cost for interim maintenance					26,514	53,026
Delayed intensification						
Vincristine (generic)	1 mg/ mL	1 mg vial 2 mg vial for IV infusion	30.6000 63.3650	1.5 mg/m^2 IV on days 1, 8, 15, 43 and 50	136	306
Dexamethasone (generic)	0.5 mg 4 mg	Tab Tab	0.1564 0.6112	5 mg/m^2 PO twice daily on days 1 to 7 and 15 to 21	13	30
Doxorubicin (generic)	2 mg /mL	10 mg vial 50 mg vial for IV infusion	50.0000 255.0000	25 mg/m^2 IV on days 1, 8 and 15	200	450

Treatment	Strength or concentration	Form	Price	Typical dosage	Cost per 28 days ($)	Course cost ($)
Pegaspargase	750 IU/mg	Vial	6,570.1700[e]	2,500 units/m^2 IM on days 4 [OR 5 OR 6] and 43	23,361	52,561
Methotrexate IT[c]	10 mg/ mL 25 mg /mL	2 mL vial Injectable solution	12.5000 8.9200	15 mg/m^2 on IT days 1, 29, and 36	17	38
Cyclophosphamide (Procytox)	20 mg/mL	500 mg vial 1,000 mg vial Powder for IV infusion	97.8000[a] 177.2700[a]	1,000 mg/m^2 IV on day 29	122	275
Cytarabine (generic)	100 mg/ mL	5 mL vial 20 mL vial for IV infusion	76.8500[a] 306.5000[a]	75 mg/m^2 IV on days 29 to 32 and 36 to 39	273	615
Thioguanine	40 mg	Tab	5.3676	60 mg/m^2 PO on days 29 to 42	67	150
Total cost for delayed intensification					24,189	54,425
Maintenance (Cycle 1 to 8 or 1 to 12)[f]						
Methotrexate IT[c]	10 mg/ mL 25 mg /mL	2 mL vial	12.5000 8.9200	15 mg/m^2 IT on day 1	4	13
Vincristine (generic)	1 mg/ mL	1 mg vial 2 mg vial for IV infusion	30.6000 63.3650	1.5 mg/m^2 IV on days 1, 29, and 57	61	184
Dexamethasone (generic)	0.5 mg 4 mg	Tab Tab	0.1564 0.6112	3 mg/m^2 PO twice daily for 5 days every 4 weeks	6	18
Mercaptopurine (generic)	50 mg	Tab	2.8610	75 mg/m^2 PO on days 1 to 84	160	481
Methotrexate PO	2.5 mg	Tab	0.2513	20 mg/m^2 PO on days 8, 15, 22, 29, 36, 43, 50, 57, 64, 71 and 78	8	25

Treatment	Strength or concentration	Form	Price	Typical dosage	Cost per 28 days ($)	Course cost ($)
Total cost for maintenance					239	721
Total cost for aBFM regimen					**78,345**	**162,976**
Hyper-CVAD[h]						
Course A						
Cyclophosphamide (Procytox)	20 mg/mL	500 mg vial 1,000 mg vial Powder for IV infusion	97.8000[a] 177.2700[a]	300 mg/m^2 IV every 12 hours on days 1 to 3	587	587
Doxorubicin (generic)	2 mg /mL	10 mg vial 50 mg vial for IV infusion	50.0000 255.0000	50 mg/m^2 IV on day 4	305	305
Vincristine (generic)	1 mg/ mL	1 mg vial 2 mg vial for IV infusion	30.6000 63.3650	1.4 mg/m^2 IV on day 4 and 11	122	122
Dexamethasone (generic)	0.5 mg 4 mg	Tab Tab	0.1564 0.6112	40 mg PO days 1 to 4 and 11 to 14	49	49
Total cost for Course A					1,014	1,014
Course B						
Methotrexate IV	10 mg/ mL 25 mg /mL	2 mL vial Injectable solution	12.5000 8.9200	1,000 mg/m^2 IV on day 1	196	196
Cytarabine (generic)	100 mg/ mL	5 mL vial 20 mL vial for IV infusion	76.8500[a] 306.5000[a]	3 g/m^2 IV every 12 hours on days 2 and 3	2,148	2,148
Total cost for Course B					2,344	2,344
Total cost for hyper-CVAD regimen[h]					**1,014 to 2,344**	**13,432**

Hyper-CVAD = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; IM = intramuscular; IT = intrathecal; PO = oral.

The comparators presented in the following table have been deemed to be appropriate based on feedback from clinical expert(s). Comparators may be recommended (appropriate) practice or actual practice. Existing Product Listing Agreements are not reflected in the table and as such, the table may not represent the actual costs to public drug plans.

Notes: All prices are from the Ontario Drug Benefit Formulary (accessed April 2023), unless otherwise indicated, and do not include dispensing fees. Calculations assume a patient body surface area of 1.07m^2, unless otherwise stated. Wastage of partially used vials was assumed in calculations.

Note that this table has not been copy-edited.

[a]Wholesale price from IQVIA Delta PA (accessed April 2023).[3,15]

[b]Informed by the COG AALL0434 trial, aligned with clinical practice based on clinical expert feedback received by CADTH.[3] Note that the aBFM backbone varies slightly with the addition of nelarabine.

[c]Dosing is age-based, dosage presented reflects the require dose for patients aged 9 years old and older.

[d]Dosing schedule may vary for high risk or CNS3 patients.

[e]Health Quality Ontario (2016).[10] Reported cost inflated to CAD 2022.

[f]IV methotrexate dose in the interim maintenance therapy phase, starts at 100 mg/m^2 and escalates by 50 mg/m^2 every 10 days for a total of 3 doses.

[g]Maintenance therapy for girls is repeated until the total duration of therapy is 2 years from the start of interim maintenance, for an approximate total of eight 12-week cycles. For boys, Maintenance therapy is repeated until the total duration of therapy is 3 years from the start of interim maintenance, for an approximate total of twelve 12-week cycles.

[h]Primarily used for adult patients. Regimen consists of 8 alternative courses of Course A and Course B, given every 21 to 28 days. Dosing informed by Cancer Care Ontario[16] and UHN clinical practice guidelines.[17]

Appendix 2: Submission Quality

Note that this appendix has not been copy-edited.

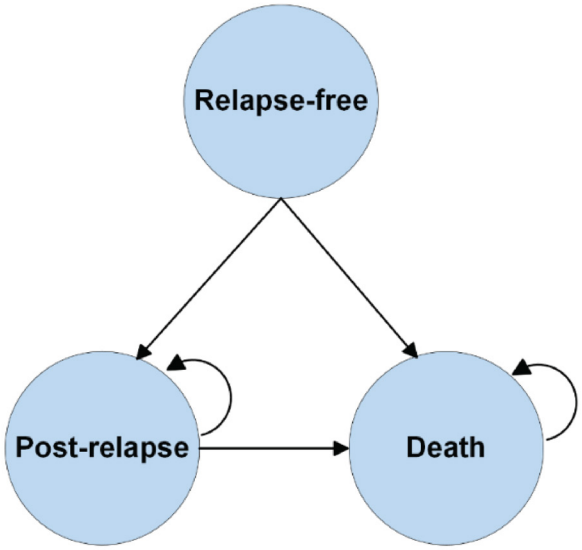
Table 8: Submission Quality

Description	Yes/No	Comments
Population is relevant, with no critical intervention missing, and no relevant outcome missing	No	While the submission reflects the reimbursement requested population, input from clinical experts consulted by CADTH and drug plans noted subpopulations of interest to consider that are outside the reimbursement requested population (e.g., older patients greater than 30 years of age; low-risk T-ALL). Refer to CADTH critical appraisal.
Model has been adequately programmed and has sufficient face validity	Yes	No comment.
Model structure is adequate for decision problem	Yes	No comment.
Data incorporation into the model has been done adequately (e.g., parameters for probabilistic analysis)	Yes	Largely conducted adequately. CADTH identified a few errors related to how dosing frequency were incorporated into the model. Corrections were made in the CADTH base-case analysis.
Parameter and structural uncertainty were adequately assessed; analyses were adequate to inform the decision problem	Yes	No comment.
The submission was well organized and complete; the information was easy to locate (clear and transparent reporting; technical documentation available in enough details)	Yes	No comment.

Appendix 3: Additional Information on the Submitted Economic Evaluation

Note that this appendix has not been copy-edited.

Figure 1: Model Structure



Source: Sponsor's pharmacoeconomic submission.[1]

Table 9: Disaggregated Summary of Clinical Outcomes From the Sponsor's Economic Evaluation (Corrected)

Parameter	Nelarabine plus standard of care	Standard of care	Incremental
Discounted LYs			
Overall	54.93	51.47	3.46
Relapse-free	54.81	51.32	3.49
In trial	9.90	9.31	0.58
Out of trial	45.04	42.16	2.88
Discounted QALYs			
Overall	31.21	29.25	1.96
Relapse-free	31.21	29.12	2.09
In trial	8.17	7.69	0.48
Out of trial	23.04	21.56	1.48

Appendix 4: Additional Details on the CADTH Reanalyses and Sensitivity Analyses of the Economic Evaluation

Note that this appendix has not been copy-edited.

Table 10: Dosing Frequency Corrections Made to the Sponsor's Base Case

Treatment phase	Treatment	Sponsor-submitted value	CADTH correction
Nelarabine plus standard of care			
Delayed intensification	Dexamethasone	Month 5: 3 Month 6: 0	Month 5: 20 Month 6: 8
Maintenance	Vincristine	Month 14: 1 Month 15: 1	Month 14: 0 Month 15: 1
	Dexamethasone	Month 7 to 15: 0	Month 7 to 15: 10
	Mercaptopurine	Month 13: 4 Month 14: 0 Month 15: 0	Month 13: 30 Month 14: 23 Month 15: 28
	Methotrexate	Month 13: 28 Month 14: 25 Month 15: 24	Month 13: 3 Month 14: 3 Month 15: 4
	Nelarabine	Month 13: 2 Month 14: 3	Month 13: 0 Month 14: 5
Maintenance	Mercaptopurine	Month 16plus: 85	Month 7+: 84
Standard of care			
Delayed intensification	Vincristine	Month 6: 0	Month 6: 2
	Dexamethasone	Month 4: 7 Month 5: 7	Month 4: 20 Month 5: 8
	Pegaspargase	Month 6: 0	Month 6: 1
Maintenance	Mercaptopurine	Month 7+: 85	Month 7+: 84

SOC = standard of care.

Detailed Results of the CADTH Base Case

Table 11: Disaggregated Summary of Clinical Outcomes From CADTH's Economic Evaluation

Parameter	Nelarabine plus standard of care	Standard of care	Incremental
Discounted LYs			
Overall	54.93	51.47	3.46
Relapse-free	54.81	51.32	3.49
In trial	9.90	9.314	0.58
Out of trial	45.04	42.16	2.88
Discounted QALYs			
Overall	31.21	29.25	1.96
Relapse-free	31.21	29.12	2.09
In trial	8.17	7.69	0.48
Out of trial	23.04	21.56	1.48

Scenario Analyses

Table 12: Summary of CADTH's Economic Evaluation Results — Scenario Analyses

Treatment	Total costs ($)	Total QALYs	ICER ($ per QALY gained)
Adult BSA			
SOC	311,018	29.25	Reference
Nelarabine plus standard of care	397,831	31.21	44,139
Postrelapse as informed by treatment arm in the COG AALL0434 trial			
SOC	223,566	30.75	Reference
Nelarabine plus standard of care	269,184	31.21	99,572

COG = Children's Oncology Group; ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SOC = standard of care.

Appendix 5: Submitted Budget Impact Analysis and CADTH Appraisal

Note that this appendix has not been copy-edited.

Table 13: Summary of Key Take-Aways

Key take-aways of the budget impact analysis
• CADTH identified the following key limitations with the sponsor's budget impact analysis (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 3-year budget impact was $6,587,091.

Summary of Sponsor's Budget Impact Analysis

The sponsor submitted a BIA to estimate the impact of reimbursing nelarabine as an add-on therapy to current SOC (aBFM chemotherapy) for the first-line treatment of patients aged 1 to 30.99 with intermediate- or high-risk T-ALL. The analysis was taken from the perspective of the Canadian public drug plans using an epidemiological approach. A 3-year time horizon was used with 2021 as the base year. Data from the POGONIS and the AALL0434 trial was used to inform the patient population eligible for treatment each year.

The BIA compared 2 scenarios to determine the incremental budget impact of reimbursing nelarabine. The reference case scenario assumed that 100% of eligible patients would receive the current SOC (aBFM), while the new scenario assumed a proportion of these patients would receive nelarabine added to SOC. In the sponsor's base case, costs related to drug acquisition and administration were considered. Key inputs to the BIA are documented in Table 15.

Key assumptions include:

- Proportion of male to female to inform drug costs was obtained from the COG AALL0434 trial.
- Incidence rates were constant over the BIA time horizon.
- Treatment discontinuation was not considered.

Summary of the Sponsor's Budget Impact Analysis Results

In the sponsor's base-case analysis, the estimated incremental budget impact of funding nelarabine for the first-line treatment of patients aged 1 to 30.99 with intermediate- or high-risk T-ALL was $3,076,415 in Year 1, $3,640,893 in Year 2, and $3,664,474 in Year 3. Therefore, the 3-year incremental budget impact was $10,381,782 (CADTH corrected values based on ensuring the same number of patients in each annual cohort between the reference and new drug scenario).

Table 14: Summary of Key Model Parameters

Parameter	Sponsor's estimate (reported as Year 1 / Year 2 / Year 3 if appropriate)
Target population	
Number of incident patients (aged 15 years or younger)[a]	40/ 40/ 40
Young adult estimation factor[b]	1.2/ 1.2/ 1.2
Number of patients eligible for drug under review	49/ 49/ 49
Market Uptake (3 years)	
Uptake (reference scenario) SOC Alone	 100% / 100% / 100%
Uptake (new drug scenario) SOC Alone Nelarabine + SOC	 15% / 10% / 10% 85% / 90% / 90%
Cost of treatment (per patient)	
Cost over the treatment course (approximately 40 months) SOC Alone Nelarabine + SOC	 $139,635 (male)/ $135,754 (female) $218,008 (male)/ $214,128 (female)

SOC = standard of care.

[a]informed by POGONIS.

[b]informed by the proportion of patients in the AALL0434 trial who were 16 years or older (i.e., approximately 20%).

CADTH Appraisal of the Sponsor's Budget Impact Analysis

CADTH identified several key limitations to the sponsor's analysis that have notable implications on the results of the BIA:

- **Market share of nelarabine may be underestimated.** In the sponsor's submitted budget impact analysis, it was assumed that in the current scenario the market share of nelarabine + SOC was 0% as nelarabine is not currently publicly funded for the first-line treatment of newly diagnosed patients aged 1 to 30.99 with intermediate- or high-risk T-ALL. While true, this may be an underestimation of the nelarabine + SOC market share in the current scenario as drug program input received by CADTH noted that many jurisdictions currently do fund nelarabine for pediatric patients on a per case basis. In the new scenario, the sponsor assumed that, once approved, nelarabine + SOC would account for 85%, 90%, and 90% of the market share in years 1, 2, and 3, respectively based on feedback from consultations with their clinical experts. They assumed that all pediatric patients aged 1 to 17 would receive treatment while only 20% of patients aged 18 to 30 (expanding to 25% in year 3) would receive nelarabine + SOC due to many young adults being treated in adult cancer units. Feedback from clinical experts received by CADTH noted that these values may be underestimated as treatment in adult cancer units would not hinder nelarabine + SOC uptake in patients aged 18 to 30.
    - CADTH explored the impact of this limitation in a scenario analysis where it was assumed that nelarabine + SOC accounted for 5% of the market in all the years of the reference scenario and

90%, 95%, and 95% of the market share in year 1, 2, and 3 respectively for the new scenario. As nelarabine may already be funded in some jurisdictions for certain pediatric patients on a per case basis, the true budget impact of reimbursing nelarabine for as an add-on therapy to current SOC (aBFM chemotherapy) for the first-line treatment of patients aged 1 to 30.99 with intermediate- or high-risk T-ALL may be smaller.

- **Drug costs may be underestimated due to utilizations of incorrect unit drug costs and patient BSA dependent assumptions.** In the sponsor's base-case analysis, the drug acquisition cost of nelarabine was informed by communications with Novartis in 2021 (with price inflated to CAD 2022). The remaining drug unit costs in the sponsor's submitted analysis were informed by the Ontario Schedule of Benefits or published literature.[9,10] As noted in greater detail within the economic evaluation section, there were some inaccuracies regarding the unit drug price of nelarabine, cytarabine, cyclophosphamide IV, and methotrexate PO based on a review of Delta PA. Furthermore, to align with the starting age of the population, the average body surface area for a 9-year-old was assumed to be 1.07 m^2 and this constant value was applied over the entire analytical time horizon. Given that dosing is based on body surface area and treatment may be provided for up to 3 years, total drug costs are highly dependent on a patient's age. Given that the cohort ages over time and some proportions of the patients are young adults, total drug costs would be underestimated by assuming dosing based on a fixed BSA of a 9 year-old.
    - In the CADTH base-case analysis, unit drug costs were updated to align with values used in the CUA.
    - A scenario analysis was conducted to explore the budget impact of assuming an BSA of 1.8 m^2 due to the cost dependency on a patient's BSA.

CADTH Reanalyses of the Budget Impact Analysis

Based on 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 in year 3. Therefore, the 3-year budget impact was $6,587,091.

Two CADTH scenario analyses were conducted to explore the impact of account for current nelarabine use as a first-line treatment and an adult BSA to inform drug costs. Results of these analyses estimated a 3-year budget impact of $6,537,039 and $10,683,909, respectively.

Table 15: CADTH Revisions to the Submitted Budget Impact Analysis

Stepped analysis	Sponsor's value or assumption	CADTH value or assumption
Corrections to sponsor's base case		
1. Dosing frequency	Dosing frequencies of the following were inaccurately captured in the costing calculations: Nelarabine + SOC: • dexamethasone (delayed intensification and cycle 1 to 3 of maintenance) • vincristine, mercaptopurine, methotrexate, and nelarabine (maintenance, cycle 3) SOC alone: • vicereine, dexamethasone, and pegaspargase (delayed intensification) • mercaptopurine (maintenance)	Corrected to align with dosing frequency as specified in COG AALL0434 (see Table 10 for more details)
Changes to derive the CADTH base case		
1. Drug unit costs	Unit costs of the following were inaccurately captured: • Nelarabine (informed by internal communications with Novartis 2021) • Cytarabine (costed per vial) • Cyclophosphamide IV (informed by cyclophosphamide PO) • Methotrexate IV and IT (informed by methotrexate PO)	Drug unit costs were updated as follows: • Nelarabine (DeltaPA) = $579.5400 • Cytarabine (costed per mL, ODB) = $15.3250 • Cyclophosphamide IV (updated to IV cost, DeltaPA) = $97.8000 per 500 mg vial and $177.2700 per 1,000 mg vial • Methotrexate IV (updated to IV cost, costed per vial, DeltaPA) = $12.5000
CADTH base case	Reanalysis 1	

COG = Children's Oncology Group, IT = intrathecal, ODB = Ontario Drug Benefit; PO = oral, SOC = standard of care.

Table 16: Summary of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Three-year total
Sponsor's base case	$10,381,782
Sponsor's corrected base case	$7,002,485
CADTH base case	$6,587,091

Table 17: Detailed Breakdown of the CADTH Reanalyses of the Budget Impact Analysis

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
Sponsor's base case	Reference	$6,236,855	$6,682,980	$6,853,715	$6,929,381	$26,702,930
	New drug	$6,236,855	$9,759,395	$10,494,608	$10,593,855	$37,084,712
	Budget impact	$0	$3,076,415	$3,640,893	$3,664,474	$10,381,782
Sponsor's base case (corrected)	Reference	$7,447,723	$7,944,301	$8,115,036	$8,190,703	$31,697,764

Stepped analysis	Scenario	Year 0 (current situation)	Year 1	Year 2	Year 3	Three-year total
	New drug	$7,447,723	$9,963,519	$10,596,096	$10,692,911	$38,700,249
	Budget impact	$0	$2,019,218	$2,481,059	$2,502,208	$7,002,485
CADTH base case	Reference	$8,013,828	$8,491,113	$8,622,541	$8,680,787	$33,808,270
	New drug	$8,013,828	$10,379,754	$10,962,580	$11,039,198	$40,395,361
	Budget impact	$0	$1,888,641	$2,340,039	$2,358,411	$6,587,091
CADTH scenario analysis (alternative market shares)	Reference	$8,300,901	$8,639,916	$8,769,733	$8,826,440	$34,536,989
	New drug	$8,300,901	$10,488,517	$11,101,207	$11,183,403	$41,074,028
	Budget impact	$0	$1,848,602	$2,331,474	$2,356,964	$6,537,039
CADTH scenario analysis (1.8 m^2 BSA)	Reference	$12,089,008	$12,805,140	$12,999,862	$13,086,159	$50,980,168
	New drug	$12,089,008	$15,852,386	$16,800,898	$16,921,785	$61,664,077
	Budget impact	$0	$3,047,246	$3,801,036	$3,835,626	$10,683,909

BSA = body surface area.

Stakeholder Input

List of Tables

List of Figures

Patient Input

The Leukemia and Lymphoma Society of Canada

About The Leukemia and Lymphoma Society of Canada

The Leukemia and Lymphoma Society of Canada — bloodcancers.ca

LLSC is a national charitable status organization dedicated to finding a cure for blood cancers and its ability to improve 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 Leukemia and Lymphoma Society of Canada is the largest charitable organization in Canada dedicated to blood cancer, our focus includes:

- funding research from bench to bedside
- Rethinking how a person navigates their blood cancer experience
- Providing targeted blood cancer information
- Offering tools for psychological and emotional support
- Empowering Canadians to take charge of their blood cancer experience through practical support and advocacy.

Advocacy for Canadian Childhood Oncology Research Network (Ac2orn)

Ac2orn is committed to advocating for translational research and effective treatments to realize the goal of curing childhood, adolescent, and young adult cancers.

http://www.curesforourkids.com/

Ontario Parents Advocating for Children with Cancer (OPACC)

OPACC will be the leading voice and expert resource for families and organizations navigating the childhood cancer journey.

http://www.opacc.org/

Childhood Cancer Canada

Childhood Cancer Canada's mission is to create victories for Canadian children with cancer through investment in national, collaborative, lifesaving research, empowering education, and community programs.

https://www.childhoodcancer.ca/

Information Gathering

Two online surveys were created through SurveyMonkey. Information was gathered between two time periods. The first period was June 2019, and the second period was March 2023. Respondents who indicated that they were not an ALL patient or a caregiver of an ALL patient were disqualified from the surveys. Respondents who were ALL patients who indicated that they were over the age of 30 at the time of their diagnosis were disqualified from the surveys.

Survey 2019

The first survey was developed and distributed collectively by LLSC, Ac2orn and OPACC, in both English and French, in June 2019. The survey was distributed through various social media channels and directly by email.

The survey asked for input from patients and families who were treated for childhood ALL and who may or may not have had experience with nelarabine. 20 respondents participated in this survey. There was a total of 3 respondents with direct experience with nelarabine. The majority of respondents indicated that they were the parent of the patient (16 responses). 4 respondents were patients. 1 respondent was an immediate family member of the patient.

The following is a breakdown of the ages of the ALL patients at their time of diagnosis:

1-4 years old (10), 5-14 years old (6), 15-19 years old (1), 20-30 years old (2), age 30+ (1).

The majority of respondents identified the location of their primary residence as Ontario (11 responses). British Columbia (4 responses), Alberta (3 responses), and Quebec (1 response) were also represented. 2 respondents indicated that they were residents of the United States.

Survey 2023

The second survey was fielded by LLSC between March 7, 2023, and March 15, 2023, in English only. In total, 46 respondents participated in this survey. 1 one-on-one French was also conducted.

In this survey, respondents were led into two different streams of questions based on their answer to the question, “Has the ALL patient taken nelarabine (Atriance) as a treatment for ALL?” If the respondents answered yes, they were led down a path of questions directly related to their experience with nelarabine treatment and were also asked questions about other treatments that they have experienced and were asked to draw comparisons. If respondents answered no, they were led down a stream of questions that asked about their experiences with ALL treatments that they have used. A total of 7 respondents answered that they have had direct experience with nelarabine.

The majority of respondents indicated that they were the caregiver of the ALL patient (26 respondents).19 respondents were the ALL patient themselves.

The majority of respondents indicated that the ALL patient was between the ages of 20-30 at the time of their diagnosis (10 respondents), followed by 5-14 years old (9 respondents), Age 30 years+ (7 respondents), age 1-4 (4 respondents) and age 15-19 (4 respondents).

The majority of respondents identified the location of their primary residence as Ontario (22 responses).

Alberta (6 responses), British Columbia (4 responses), and Quebec (1 response) were also represented. 1 respondent indicated that they were a resident of the United States. 12 respondents did not indicate their geographic location.

Open-ended responses to both the 2019 and 2023 surveys that reflected the sentiment of a majority are included verbatim to provide a deeper understanding of patient perspectives.

As both surveys were anonymous, we were not able to determine whether participants in the 2023 survey had previously participated in the 2019 survey.

The survey results explained below reflect the feelings and opinions of patients and their families who have experienced nelarabine and/or other treatments for ALL. The responses recorded reflect the real-life impact that illness and treatment issues can cause families to experience when a loved one or they themselves are going through ALL. These issues are not limited to their physical health but include themes regarding effects on their financial well-being, their personal relationships, social lives and their emotional and mental health.

Disease Experience

Pediatric ALL is a difficult, disruptive experience in all aspects of life including physical and mental health, financial well-being, social life, relationships, etc.

The difficulties of ALL affect patients' and caregivers' lives even before diagnosis. The disease has a significant impact on quality of life and the symptoms associated with ALL affect patients and caregivers in many ways.

The pathway to diagnosis was one that was described as not being a straight line, and in many cases took multiple visits to a physician before the diagnosis was made. One parent noted:

(2019) "In the 2 months or so before my son (2.5 years at the time) was diagnosed, he was getting sick often (colds, ear infections, fevers with night sweats) and was feeling tired often. He complained of pain in his legs/foot one weekend. We took him to the doctor with each illness, but nothing was a red flag since he was a small child in daycare. We took him back to the doctor after several days with a fever thinking he had another ear infection, and there was no ear infection but the doctor noticed other concerning symptoms (paleness, tachycardia, enlarged spleen I think) and our doctor was concerned enough (our doctor at this point suspected ALL) to send us immediately to the ER at Sick Kids that evening where the diagnosis of ALL was made."

(2023) "Parent A" recounted her experience in a one-on-one interview, stating that she noticed a large lump ("the size of half a golf ball") on her son's neck. She suspected an allergic reaction and took him to the local ER where she was told that it was a swollen lymph node and sent home. 12 days later, her son (under 2 years old at this time) was gasping for air. She took him again, to the local ER and x-rays showed a 9.4cm mass in his chest, displacing his heart and obstructing his airway. ALL diagnosis was made within hours.

The Symptoms of ALL impeded patients' ability to participate in regular life activities. The most critical physical effects that individuals with ALL experienced prior to diagnosis were fatigue, pain and nausea/vomiting. Responses regarding physical effects prior to diagnosis were consistent within both surveys (2019 and 2023)

Child patients were particularly distressed by the instability, disruptions and changes to their home and family life that they experienced due to ALL. Many changes made a “large” or “extremely large” impact on child patients and their families; (2023)

- Change to their regular daily schedule – 15/24 (63%)
- Behavioural changes (clingy, impulsive, withdrawn/distant, angry, sad, scared) -- 11/24 (46%)
- Change in appearance – 11/24 (46%)
- Change in living environment/travel/separation due to hospital stays -- 8/24 (33%)

Family relationships and dynamics were/are seriously impacted for many ALL patients and their family as a whole:

(2023) One parent commented, “Being hospitalized for extended periods of time alienated his brother and affected our couple's relationship. There is no aspect of life that isn't affected and very, very few people can possibly understand how deeply impacted everyone is.”

ALL had a significant effect on patients’ and their families’ quality of life in several areas which included much more than just physical impacts. The most significant detrimental impacts were to patients and caregivers.

- Daily routines: 30/34 (88%)
- Physical functioning: 29/34 (85%)
- Mental functioning: 29/34 (85%)
- Work life: 28/34 (82%)
- Social life: 27/34 (79%)
- Lifestyle: 25/34 (74%)
- Family life: 24/34 (71%)

(2023) ALL diagnosis and treatment have had significant mental health and psychosocial impacts on both ALL patients and caregivers. Respondents were asked about feelings they’ve experienced throughout ALL diagnosis and treatment and asked to rate the impact of these feelings on their mental health. Scale was from 1 (no impact) to 5 (extremely large impact). We used “weighted average” to measure their collective responses.

- Sadness – 3.8/5 (76%)
- Fear – 3.7/5 (74%)
- Nervous, Anxious, Depressed – 3.7/5 (74%)
- Frustration – 3.6/5 (72%)
- Stress/Worry – 3.6/5 (72%)
- Overwhelmed/Feeling out of control – 3.5/5 (70%)
- Loneliness/Isolation – 3.5/5 (70%)
- Post Traumatic Stress – 3.4/5 (68%)

- Helplessness/Hopelessness – 3.3/5 (66%)

There have been considerable consequences for ALL patients and their families regarding their financial stability and the ability to maintain employment/financial status due to ALL diagnosis and treatment schedules. Considering patients who are young adults just starting out in their careers, and parents and caregivers in the prime of their careers, inability to maintain a stable work schedule, or to work at all, can have dire impacts on career development. (All responses in this section are from Survey 2023)

9/24 (38%) of patient respondents and 7/24 (29%) of caregiver respondents noted that they have endured missed career development/advancement opportunities due to their experience with ALL.

7/24 (29%) of patient respondents and 7/24 (29%) of caregiver respondents stated that they have had to take a leave of absence from work due to ALL.

Respondents described ALL's effect on their employment. Many noted that they had to either change jobs or leave their job:

> "Moved to Calgary and transferred jobs (was luckily able to work anywhere and her team she worked with was based in Calgary, so we got lucky)"
>
> "Had to leave my position."
>
> "Having a child with cancer affects all aspects of life. Being in treatment for 4 years caused both parents to quit work in staggered increments to care for him."

19/24 (79.17%) patients and/or caregivers said that they experienced a decrease in income as a direct result of diagnosis and treatment of ALL.

Several caregivers and patients stated that they have had to depend on government financial support and assistance programs such as CPP Disability 8/20 (40%) and Employment Insurance 7/20 (35%) at times during their experience with ALL.

One patient shared, "I am also now on AISH ((Alberta's social assistance program/income support)) as I try to find jobs that suit my ability which is often part time or short term work."

Overall, it was clear that respondents felt that several areas of their lives (physical/social/psychosocial) were/are significantly affected by ALL. This is the case not just for ALL patients themselves, but for their families and caregivers as well.

Experiences with Currently Available Treatments

Survey respondents had varying experiences with currently available treatments.

49 respondents in both surveys (2019 and 2023 responses combined) shared which forms of ALL treatment they have received since their diagnosis. Responses were as follows:

- Chemotherapy - 46/49 (94%)
- High dose chemotherapy - 33/49 (67%)
- Maintenance Therapy - 25/49 (51%)

- Radiation – 21/49 (43%)
- Stem cell/bone marrow transplant - 11/49 (22%)
- Immunotherapy - 6/49 (12%)
- Surgery – 3/49 (6%)
- 2 (4%) patients noted under "other" that they received steroids as part of their treatment

Treatment created difficulties and challenges in all areas of life for patients, caregivers and their families.

Though length of treatment and treatment experiences varied for each patient and their caregivers based on their situation, it was clear through respondent answers that a wide array of difficulties and challenges come along with currently available pediatric ALL treatments. These difficulties and challenges arose in all areas of life for patients, caregivers and their families. (All responses under this section are from Survey 2019)

One respondent's quote plainly summed up their feelings regarding the impact of their treatment experience: "Everything is impacted. Mental health, income, socially, health."

Other respondents also shared the effects of their treatment experiences on themselves and their families.

> "It's been a very long and tough journey. Almost feels like a prison sentence at some points."
>
> "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."
>
> "Most of treatment was in hospital. Numerous complications including pleural effusion and cellulitis. Stopped walking completely."
>
> "We were unprepared for how harsh induction would be. We were not properly explained the horrible side effects of steroids and when my son was unrecognizable, we were devastated. Front line treatment was very difficult. We spent 80% of our time inpatient with numerous complications."
>
> "He handled all of the frontline treatment relatively well however had an anaphylactic reaction to the second round of Pegasparganes which resulted in 24 Erwinia needles (the hardest part on his journey so far)."

The need to travel to and from treatment where necessary was a significant barrier for patients and caregivers.

Those who had to travel away from home for ALL treatment and care expressed that this task negatively influenced their mental health, physical health, finances and family life. (All responses under this section are from Survey 2023)

Of those who did not have nelarabine treatment but received other forms of treatment for ALL,

- 11/19 (58%) did not have to travel to receive treatment as it was available at their home hospital.
- 7/19 (37%) had to travel long distances by car in their province/state.
- 1/19 (5%) answered "other" and specified, "Hour drive to hospital by car."

The distance from the ALL-treatment facility to home affected both the patients' and caregivers' quality of life.

> "It is physically draining getting in the car for an hour when I am nauseous or going through headaches."
>
> "Hospital is within 1 hour drive, but caregiver had to work fully remotely in order to escort me to appointments and maintain a job/income."
>
> "Greatly affected caregivers' quality of life. Did not affect patient's ability to follow through with treatment plans."

Regarding treatment location, respondents also commented,

> "Dramatically my son and I had to leave and move to Toronto at RMH. I had to quit my job. My mom had to take a few months leave from work so she could drive and support me. For me the patient the drive was horrible, it was painful, I often had lots of headaches and back pain and was nauseous. We ended up staying in Calgary where my treatments were for most of the time, and I barely got to go home. It was depressing."
>
> "As a single mom of two kids, my mother had to temporarily move to Calgary to help with my other child while I was full-time at the hospital with my sick child. I had to apply for long term disability from work as there was no option to have paid leave. I did not have a disability, but I had to exaggerate mental health difficulties."

Families experiencing ALL treatment had additional financial costs as a result of treatment.

(2023) Both those who had nelarabine treatment, and those who had not, were asked if they had incurred additional financial costs as a result of ALL diagnosis and treatment.

14/18 (78%) of those who did not have nelarabine treatment had to pay out of pocket for drugs not covered by provincial providers.

Only 1/5 (20%) of nelarabine users incurred the same expense.

Those who did not experience nelarabine treatment but received other forms of treatment for ALL expressed how severely the quality-of-life of patients, caregivers and their families were impacted by their ALL treatment (All responses under this section are from Survey 2019)

> "Horrible stress and feeling sick has led to depression, inability to participate in life, no physical activity, hair loss has resulted in her not wanting to leave the house & low self-esteem."
>
> "As the parent of a child with ALL (currently 3.5 years old and in maintenance treatment) my goal is to minimize the effects of treatment on his quality of life. During his initial treatment, my son experienced pain and fatigue that prevented him from being active and playing as a young child should. We also took him out of his preschool due to his treatment and concerns with him getting sick, so he missed out on educational and developmental opportunities. Now that he is in maintenance treatment, he is feeling better and back at preschool. We as parents now try to make his life as "normal"

as possible while he finishes treatment. It's stressful and difficult as a parent to manage our son's treatment while trying to minimize any negative effects on his quality of life, but we're trying to have him live a normal kid's life while still in chemo treatment."

"My daughter has had periods of not being able to walk. She has 2 fractured ankles right now from nothing. All routines in our family have been disrupted. I am a single parent with 4 kids. Everyone has exhibited PTSD type symptoms. It is horrible and there has got to be a better way."

"Life turned on its head. Increased daycare needs, increased wear and tear on vehicle to get to treatment, high level of stress/anxiety, breakdown of marriage, not able to travel, give up work to be with child, impact on non- sick children, sleepless nights, guilt for restraining your child for treatment, friends/family that don't understand, this is a part of our lives forever, will my son be able to have children, will he have long term effects, what lies ahead?"

Those who did not experience nelarabine treatment but received other forms of treatment for ALL experienced significant physical side effects as a result of ALL treatment.

Respondents (2023) who did not have treatment with nelarabine rated how their ALL-treatment side effects impacted the patient's quality of life during their ALL treatments, on a scale from 1 (no impact/not applicable) to 5 (extremely large impact). 19 respondents answered this question. **Please refer to** Figure 1 **for respondent ratings.**

For comparison purposes, those who had experience with nelarabine treatment answered the same question. (Please refer to Figure 2.)

Symptoms rated as most significant by those who did not experience nelarabine treatment were, in order of severity:

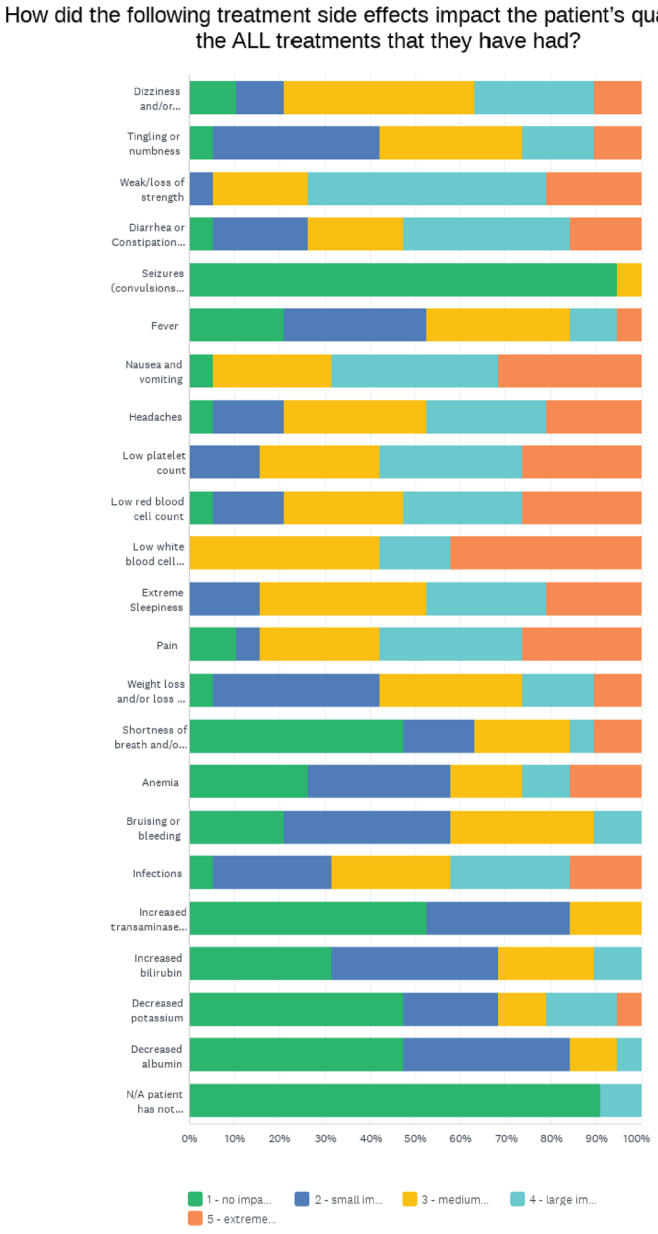
- Nausea and Vomiting
- Weakness/Loss of Strength
- Low white blood cell count
- Low platelet count
- Pain

Resources and supports provided necessary respite for patients and caregivers during treatment. Parents expanded on their importance in helping their families to get through: (2019)

"The support systems and expertise at SickKids were vital to us at that point and we relied entirely on them. We stayed at the Ronald McDonald house as well which was critical to us at the time. Son was in PICU and in serious danger for the first few days. The steroids and chemo drugs had various effects on him, mood, weight loss and nausea being the most common. He required an NG tube to administer medications for two months as the chemos and medicines are extremely unpalatable and he would refuse, spit out or vomit them up immediately. This is an important and ongoing challenge through treatment. The medicines are disgusting, high in volume and number, and it is impossible to rationalize with a 2-year-old child. Having a POGO Satellite Clinic in our city was such an advantage to

our family as well."

Figure 1: Treatment Side Effects on Patient's Quality of Life During ALL Treatment



"Our experience with leukemia treatment was difficult as parents dealing with the treatment and side effects on our 2.5-year-old son. It was a difficult time to navigate as parents, but the support from family, Sick Kids staff (doctors, nurses etc), Sick Kids volunteers, Camp Ooch staff and volunteers and everyone else was and is what helps us get through treatment with our son. The resources and

support from all those around us are invaluable to us as a family to get through this together for our son. Negative experiences can't be avoided when someone is going through a cancer diagnosis and treatment but having those resources and support easily available to patients and their family/caregivers is what is going to get everyone through this experience. Volunteers in hospital to give parents a break, support groups, parent groups, financial assistance, Camp Ooch for the kids - all these things and more are what brings some positive experiences to the overall negative experience of chemo."

Improved Outcomes

ALL patients and caregivers crave the comfort of the normalcy and quality of life they had before ALL. This is reflected in responses below regarding the most important factors they consider when making decisions about currently available treatments. (2023)

- Physician recommendation – 28/34 (82%)
- Side effects – 27/34 (79%)
- Quality of life 27/34 (79%)
- Possible impact on disease – 26/34 (76%)

Patients and caregivers would like to see changes in new treatments that are not available in current front-line therapies.

Many commented (2019 and 2023) on the ***need to address the long-term effects of treatment*** and the devastating effect that treatment can have on a child when they are young, and their bodies are developing:

(2019) "If improved odds of survival or improved quality of life or the possibility of fewer late effects."

(2019) "Concerned about future health issue or long-term effects."

(2019) "While treatment has come a long way, we need to look at the overall impact it has on children. Physically and cognitive side effects are not something that should be accepted because overall survival has increased."

(2019) "It's great that it's a cure, but the lifetime effects get ignored by the medical field and this is a gross injustice for our children."

(2023) "Increased survival with less toxic risks."

Others (2023) commented on what they'd like to see in terms of ***changes regarding side effects and treatment logistics***:

"No neuropathy as a side effect"

"Less nausea causing treatments."

"Less trips to the hospital and shortening of wait times while there."

"Removing steroids from treatment. Ideally shortening the maintenance period"

"I am still under 2 years out from my transplant so effectiveness at eliminating relapse is still a concern, chronic graft vs host is still a concern, and even though I wasn't as affected the possible other side effects of the chemotherapy required can have a large impact on quality of life.

> "There has got to be a better way to treat this disease. The chemo has been horrible for my daughter. It is an extremely long process and "maintenance" is terrible.

Other comments (2023) pointed out the ***importance of addressing mental health effects:***

> "The physicians do not do a good job preparing us for what we are going to have to go through. Not enough emotional support available for caregivers & siblings."
>
> "Please recognize that the kids need emotional aftercare and trained therapists that know how to deal with PTSD."

Experience With Drug Under Review

Those who used nelarabine treatment relayed their thoughts around the treatment and its results. Those who used nelarabine were pleased with the fact that there were minimal side effects during nelarabine treatment in comparison to other ALL treatments that they have experienced.

9 patients combined (Survey 2019 and Survey 2023) who were treated with nelarabine answered the question, "How did nelarabine treatment affect your illness?"

4 respondents from Survey 2019 answered this question:

- 2/4 (50%) - results are unknown at this time.
- 1/4 (25%) - nelarabine (Atriance) eliminated the disease for some time before relapsing (refer to Figure 2), this respondent also noted in a comment, "Nelarabine eliminated my son's Disease his first diagnosis but because of the many complications my son suffered he did not receive the number of treatments that he needed and relapsed 4 years and 8 months post first treatment. My son received Nelarabine again when he relapsed due to the history of his Autonomic Neuropathy and Nelarabine quickly helped to eradicate my son's disease (2019)
- 1/4 (25%) - nelarabine kept the disease stable.

5 respondents from Survey 2023 answered this question:

- 4/5 (80%) - nelarabine eliminated the disease with no relapse.
- 1/5 (20%) - results are unknown at this time.

Those treated with nelarabine relayed that they felt that the side effects of nelarabine treatment were manageable. Respondent answers indicated that any side-effects experienced were generally minor or not experienced at all when being treated with nelarabine.

Respondents (2023) rated how treatment side effects impacted the patient's quality of life during nelarabine treatment, on a scale from 1 (no impact/not applicable) to 5 (extremely large impact). 5 respondents answered this question. Please refer to Figure 2 for respondent ratings.

Figure 2: Treatment Side Effects on Patient's Quality of Life During Nelarabine Treatment

Summary (2023): Treatment symptoms in general were reported as being more significant in impact for those who were not given nelarabine treatment but were given other forms of treatment for ALL.

Though the number of respondents for the two questions varied significantly (19 respondents and 5 respondents respectively), comparisons of the responses between the 2 groups of patients shows that patients who were treated with nelarabine experienced less severe and impactful symptoms than those who did not have nelarabine treatment but experienced other treatments for ALL.

(2019) One caregiver of a nelarabine user commented: “He had no side effect to the drug.”

(2023) 5/5 (100%) nelarabine users surveyed indicated that they would rate the severity of the following potential treatment symptoms during their nelarabine treatment as a 1 (no impact, not applicable):

- Seizures
- Fever
- Headaches
- Shortness of breath/persistent cough
- Infections
- Increased transaminase
- Increased bilirubin
- Decreased albumin

(2023) 2/5 (40%) of nelarabine users surveyed rated each of the following symptoms as having either a “large impact” or “extremely large impact” on the patient during nelarabine treatment. These were their highest rated symptoms in terms of impact.

- Low platelet count
- Low red blood count
- Anemia
- Low white blood count
- Extreme sleepiness

Comments from respondents regarding nelarabine treatment:

> (2023) “It was one of the easiest chemos he had with few side effects at all.”
>
> (2023) “My son felt pretty good during nelarabine week. Many other chemos were far worse.”

Respondents throughout both surveys had numerous positive comments about their experiences with nelarabine...

> (2023) “Nelarabine saved my sons life. Nothing else matters.”
>
> (2023) “Pediatric Cancer made life difficult and Nelarabine saved my son's life.”
>
> (2023) “Nelarabine treatment improved my quality of life compared to other treatments I have received.”
>
> (2019) “Treatment was done in hospital as my son had allergic reactions to erwinia and peg. No reaction or issues with Nelarabine other than drop in counts. It brought mrd to lowest level to proceed with bone marrow transplant. He is 3 years post-transplant and doing well. Incredibly thankful for this drug as without it his disease was too high to have the transplant.”

The distance from the treatment facility to home and having to travel for nelarabine treatment affected both the patients’ and caregivers’ quality of life.

> (2023) One parent stated "We had to travel to my son's treatment hospital 2-3 hours away for it, but we also had to do that for many other chemos. It had a big effect on our daily lives and finances, but we would never have considered not getting Nelarabine (or any other chemo) because of the distance. We endured.
>
> (2023) Another parent commented, "Having to live for longer and shorter times such a far distance from home was beyond difficult. My son saw much larger improvements in his physical and mental health when he was able to be at home with his brothers than when we were stuck living near his treating hospital for nelarabine and other treatments."

Respondents felt that though travel was difficult, they were willing to endure because the treatment works.

When asked how the patient accessed nelarabine treatment, 3 respondents answered the question: (2019)

- Compassionate use – 1/3
- Clinical trial – 2/3

Patients and caregivers drew comparisons between patients' quality of life during nelarabine treatments and other treatments they received for ALL. In general, respondents found that the quality-of-life effects of nelarabine treatment were neutral or less challenging than other treatments they had experienced for ALL. (2023)

- 2/5 (40%) felt that treatment with nelarabine was "neutral" in comparison to other treatments.
- 2/5 (40%) felt that nelarabine treatment was "less challenging" than their other ALL treatments.
- 1/5 (20%) felt that nelarabine was "more challenging" than other treatments.

Regarding nelarabine treatment, "Parent A" commented in a one-on-one interview (2023).

> "On nelarabine weeks my son was still happy, playing, eating and seemed fine. That's how I isolate nelarabine from his other treatments. That was the contrast. We would look forward to nelarabine weeks."

Companion Diagnostic Test

Not applicable.

Anything Else?

Treatment options that are effective in stabilizing and/or eliminating disease, that are accessible, affordable, and that have minimal physical side effects for patients during treatment can minimize the difficulties, significant burden and trauma of illness and treatment, and make these unfortunate experiences more manageable for patients and their families. Responses from those who have used nelarabine reflect that nelarabine gave back life, hope and normalcy to patients and their families after treatment.

Direct quotes from caregivers:

> (2023) "It potentially saved my sons life. Every single T cell patient should have access to this chemo. It has been proven to be safe and increase survival rates measurably. We were "lucky" to have

begun treatments right as the results of COGs 0434 trial were published and our oncologist immediately changed my son's treatment plan to include Nelarabine. I have no doubt that my son's chance at being alive today, alive ten years from now is directly, positively influenced by having had Nelarabine specifically. It is also responsible for removing prophylactic cranial radiation from the standard treatment of T cell ALL patients which would have had a dramatic, tragic effect on my son's quality of life had he had to have done radiation instead of Nelarabine. Nelarabine is hope, life itself for T cell patients".

(2023) "The benefit of nelarabine for us, outweighed anything else."

Overall, respondents who had experience with nelarabine felt positive about the time they or their loved one were on treatment with the drug and the results that nelarabine had on their disease upon completion of treatment. The results of nelarabine (Atriance) treatment speak for themselves. Nelarabine treatment works to eliminate Pediatric ALL with minimal side effects for patients and therefore relatively minimal disruptions to quality-of-life and psychosocial aspects for patients and their families.

In 2007, Health Canada approved nelarabine (Atriance) for use in treating T-Cell Lymphoblastic Leukemia as well as T-Cell Lymphoblastic Lymphoma in both adults and children. However, nelarabine (Atriance) has yet to be recommended for reimbursement for children. Nelarabine is soon to be off patent and therefore will be a cost-effective option when it comes to cancer treatment.

We would strongly advise CADTH to recommend reimbursement of nelarabine (Atriance) treatment for front-line therapy of pediatric, adolescent, and young adult patients (aged 1–30 years at diagnosis) with intermediate- or high-risk T-cell acute lymphoblastic leukemia (T-ALL), during upfront therapy.

Conflict of Interest Declaration — The Leukemia and Lymphoma Society of Canada (LLSC)

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

Did you receive help from outside your patient group to complete this submission?

Not applicable.

Did you receive help from outside your patient group to collect or analyze data used in this submission?

Not applicable.

List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures for Leukemia and Lymphoma Society of Canada (LLSC)

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
No COI	–	–	–	–

Clinician Input

Division Hem/Onc/BMT BC Children's Hospital

About Division Hem/Onc/BMT BC Children's Hospital

Department of Hematology, Oncology, and Bone Marrow Transplant, British Columbia Children's Hospital

We are a division of 16 attending pediatric hematologist and oncologist who together, treat all pediatric hematology, oncology, and bone marrow transplant patients from the province of British Columbia and the Yukon Territory.

https://pediatrics.med.ubc.ca/divisions-centres/hematology/

Information Gathering

Review of the literature, and discussion with T-ALL experts within and external to our Clinician Group.

Current Treatments and Treatment Goals

Nelarabine is a prodrug of arabinosylguanine nucleotide triphosphate and has demonstrated activity against T-cell acute lymphoblastic leukemia (T-ALL). T-ALL represents 10-15% of newly diagnosed pediatric acute leukemia, and with standard therapy, cure can be achieved in the majority of children. However, for those who relapse or have refractory disease, outcomes are dismal, resulting in less than 25% overall survival despite maximal therapy. Therefore, preventing relapse before it occurs by optimizing therapy in newly diagnosed patients will be of tremendous over-all benefit. Standard treatment for pediatric T-ALL includes multi-agent chemotherapy delivered over approximately 3 years, with additional craniospinal radiation therapy for patients with central nervous system (CNS) disease. The Children's Oncology Group (COG) conducted a phase III, randomized clinical trial that studied pediatric patients with T-ALL who were treated on a standard augmented Berlin-Frankfurt-Muenster regimen of chemotherapy, and compared 323 patients who additionally received nelarabine to 336 patients who did not receive nelarabine. The 5-year Disease Free Survival (DFS) rate for those receiving nelarabine was 88.2% +/- 2.4%, compared with 82.1% +/-2.7% for those who did not receive nelarabine (P =0.029). Moreover, the rates of CNS disease relapse were significant decreased in the nelarabine patients (1.3% +/- 0.63%), compared with those who did not receive nelarabine (6.9% +/- 1.4%; P = 0.0001). This is particularly clinically significant, as children who have relapsed CNS T-ALL must be treated with additional cranial radiation, which is associated with significant risk of chronic neurocognitive sequelae, particularly in young children.

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Relapse-free survival rates in pediatric T-ALL are suboptimal, with nearly 20% of patients experiencing relapsed or refractory disease. Salvage of relapsed or refractory disease is dismal, with less than 25% overall survival (Raetz EA, Teachey DT. T-cell acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2016 Dec 2;2016(1):580-588). Therefore, the unmet need is to improve event-free survival

by incorporating effective agents such as nelarabine in frontline therapy, and decreasing the risk of relapse. Additionally, patients who have detectable central nervous system (CNS) disease must include radiation therapy as part of their treatment, either at diagnosis, or at the time of relapse. Therefore, another unmet need is the prevention of CNS relapse.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

The use of nelarabine for newly diagnosed pediatric T-ALL would be incorporated into a multi-agent chemotherapy backbone similar to that used in the phase III COG study AALL0434. As an example, in this protocol, Nelarabine is given as follows: 1) Consolidation cycle - IV 650 mg/m2/dose (650 mg) on Days 1-5 and 43-47 - cycle total of 10 doses. 2) Delayed Intensification cycle - IV 650 mg/m2/dose (650 mg) on Days 29-33 - cycle total of 5 doses. 3) Maintenance - IV 650 mg/m2/dose (650 mg) on Days 29-33 X 3 cycles - cycle total of 15 doses.

The goal of this treatment would be to improve response to the underlying disease by improving treatment response rates, decrease relapse rates, and improve survival of children with T-ALL. This therapy is not a symptomatic management therapy. This is a proposal for the use of Nelarabine in the context of newly diagnosed disease, not as a second line therapy for those who have responded poorly to first line therapy, or as a sequential therapy.

Is the drug under review the first treatment approved that will address the underlying disease process rather than being a symptomatic management therapy?

Yes, it will address the underlying T-ALL disease process.

Would the drug under review be used as a first-line treatment, in combination with other treatments, or as a later (or last) line of treatment?

The use of nelarabine for newly diagnosed pediatric T-ALL would be incorporated into a multi-agent chemotherapy backbone similar to that used in the phase III COG study AALL0434 (see above).

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated?

No, this application is for all pediatric T-ALL.

Is the drug under review expected to cause a shift in the current treatment paradigm?

Yes, this drug is expected to be used as frontline standard of care for pediatric T-ALL.

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective.

No, Nelarabine is not intended to be used as monotherapy in the frontline setting; therefore, the recommendation would be to combine Nelarabine with multiagent chemotherapy. It would not be recommended to be used sequentially, as there is no data for this practice in the upfront setting.

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

Patients between the age of 1 -30 years of age inclusive with newly diagnosed T-cell acute lymphoblastic leukemia will be most likely to respond to nelarabine and are most in need of an intervention. Diagnosis of this disease follows standard laboratory and clinical evaluation, including the confirmation of an abnormal clonal population of immature T-lymphoblasts in bone marrow, circulating blood, cerebral spinal fluid, or tissue. This is not dependent on any specific cytogenetic or molecular testing. Patients with non-T-ALL forms of hematological malignancies are least suitable for nelarabine treatment.

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Pediatric patient undergoing standard treatment for T-ALL will routine undergo repeat disease evaluations all sites of initial disease after Induction and Consolidation cycles of chemotherapy. This 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. Further re-evaluations after these time points are conducted at the discretion of the treating physician, and informed by the status of disease or at any point that relapse or progression is suspected.

A clinically meaningful response to treatment is 1) the achievement of remission (ie. no detectable leukemic disease), and 2) the persistence of disease remission over time without relapse.

What factors should be considered when deciding to discontinue treatment with the drug under review?

Nelarabine has been associated with rare cases of neurotoxicity, including but not limited to myelopathy, sensory changes, central neurocognitive decompensation, Guillan-Barre-like syndrome, and paralysis. Fatal cases have been reported. Mild cases can be managed with supportive care only, but should severe or progressive neurotoxicity occur, nelarabine would be discontinued.

Other known side effects, such as myelosuppression of the bone marrow, are anticipated and can be supported through standard supportive care measures without the need for discontinuation of nelarabine.

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Nelarabine should be administered under the direction and supervision of a pediatric hematologist-oncologist who is familiar with treating pediatric T-ALL and is equipped to anticipate and support the potential side effects of nelarabine.

Conflict of Interest Declarations — Division Hem/Onc/BMT BC Children's Hospital

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the

clinician group input. CADTH may contact your group with further questions, as needed. Please refer to the Procedures for CADTH Drug Reimbursement Reviews (section 6.3) for further details.

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

No.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Declaration for Clinician 1
Name: Amanda Li

Position: Clinical Assistant Professor, Attending Physician

Date: 24/03/2023

Table 2: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 1

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Novartis	X	—	—	—

Declaration for Clinician 2
Name: Caron Strahlendorf

Position: Division Head, Dept. of Hematology, Oncology, and BMT, BCCH. Attending Physician.

Date: 24/03/2023

Table 3: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 2

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	—	—	—	—

Declaration for Clinician 3
Name: Jessica Halparin

Position: Pediatric Hematologist/Oncologist

Date: 24/03/2023

Table 4: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 3

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 4
Name: Juliette Hukin

Position: Clinical Associate Professor, Attending Physician

Date: 24/03/2023

Table 5: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 4

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
Novartis	X	–	–	–
Astra Zeneca	X	–	–	–

Declaration for Clinician 5
Name: Rebecca J Deyell

Position: Clinical Associate Professor, Pediatric Oncologist

Date: 24/03/2023

Table 6: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 5

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 6
Name: Sylvia Cheng

Position: Clinical Assistant Professor, Pediatric Oncologist

Date: 24/03/2023

Table 7: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 6

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 7
Name: George Michaiel

Position: Attending Pediatric Hematologist/Oncologist

Date: 24/03/2023

Table 8: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 7

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 8
Name: Mark Belletrutti

Position: Attending Pediatric Hematologist/Oncologist

Date: 24/03/2023

Table 9: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 8

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 9
Name: Kirk Schultz

Position: Attending Pediatric Hematologist/Oncologist

Date: 24/03/2023

Table 10: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 9

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 10
Name: Natasha Datoo

Position: Attending Pediatric Hematologist/Oncologist

Date: 24/03/2023

Table 11: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 10

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 11
Name: Rod Rassekh

Position: Attending Pediatric Hematologist/Oncologist

Date: 24/03/2023

Table 12: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 11

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 12
Name: Jacob Rozmus

Position: Attending Pediatric Hematologist/Oncologist

Date: 24/03/2023

Table 13: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 12

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 13
Name: Melissa Harvey

Position: Attending Pediatric Hematologist/Oncologist

Date: 24/03/2023

Table 14: COI Declaration for Division Hem/Onc/BMT BC Children's Hospital — Clinician 13

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

About Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
OH-CCO's Cancer Drug Advisory Committees provide 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.

Information Gathering
Information was gathered via video conferencing and email.

Current Treatments and Treatment Goals
Current treatment: Pediatric-inspired intensive chemotherapy regimens.

Treatment goal: Curative

Treatment Gaps (Unmet Needs)

Considering the treatment goals, please describe goals (needs) that are not being met by currently available treatments.

Not all patients respond to available treatments.

Place in Therapy

How would the drug under review fit into the current treatment paradigm?

As an additive treatment, as per study (COG AALL0434).

Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As per study (COG AALL0434)

What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Standard lymphoma and leukemia response measures

What factors should be considered when deciding to discontinue treatment with the drug under review?

Disease progression or significant intolerance

What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Setting: Outpatient

Specialist: Leukemia specialists

Additional Information

Not applicable.

Conflict of Interest Declarations — Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

OH-CCO provided secretariat function to the group.

Did you receive help from outside your clinician group to collect or analyze any information used in this submission.

No.

List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review.

Declaration for Clinician 1
Name: Dr. Tom Kouroukis

Position: Lead, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 16-02-2023

Table 15: COI Declaration for OC-CCO Hematology Cancer Drug Advisory Committee — Clinician 1

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 2
Name: Dr. Lee Mozessohn

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 16-02-2023

Table 16: COI Declaration for OC-CCO Hematology Cancer Drug Advisory Committee — Clinician 2

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Declaration for Clinician 3
Name: Dr. Pierre Villeneuve

Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee

Date: 16-02-2023

Table 17: COI Declaration for OC-CCO Hematology Cancer Drug Advisory Committee — Clinician 3

Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In Excess of $50,000
No COI	–	–	–	–

Eastern Health
February 3, 2023

Re: Application to CADTH for Nelarabine

To Whom It May Concern:

I am writing on behalf of the Pediatric Hematology/Oncology program at the Janeway Children's Health and Rehabilitation Centre in St. John's, Newfoundland and Labrador, to support the application to CADTH regarding Nelarabine.

Nelarabine is an important drug in intermediate and high-risk T-cell acute lymphoblastic leukemia, with a survival benefit that has been proven in a large randomized clinical trial conducted by the Children's Oncology Group. The safety profile of Nelarabine was also demonstrated in this trial. (See attached papers.)

Nelarabine has been considered standard of care at our site for several years. We fully support the application to CADTH regarding Nelarabine, and we hope that this important drug will be recommended for funding so that patients across Canada can benefit.

I would be happy to discuss our position further.

Sincerely,

Paul Moorehead MD FRCPC

Pediatric Hematologist/Oncologist

ISSN: 2563-6596

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