FDA Arranon (Nelarabine)
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Clinical and Statistical
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Established Name	Nelarabine
(Proposed) Trade Name	ARRANON®
Therapeutic Class	Antineoplastic
Applicant	GlaxoSmithKline
Priority Designation	(P)

Formulation:

ARRANON (nelarabine) Injection is supplied as a clear, colorless, sterile solution in glass vials. Each vial contains 250 mg of nelarabine (5 mg nelarabine per mL) and the inactive ingredient sodium chloride (4.5 mg per mL) in 50 mL Water for Injection, USP. Hydrochloric acid and sodium hydroxide may have been used to adjust the pH. The solution pH ranges from 5.0 to 7.0. Nelarabine is intended for intravenous infusion.

Dosing Regimen:

Adults: The recommended adult dose of nelarabine is 1,500 mg/m² administered intravenously over 2 hours on days 1, 3, and 5 repeated every 21 days.

Children: The recommended pediatric dose of nelarabine is 650 mg/m² administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days.

The recommended duration of treatment has not been clearly established. In clinical trials, treatment was generally continued until there was evidence of disease progression, the patient experienced unacceptable toxicity**,** or the patient became a candidate for bone marrow transplant.

Supportive Care: Appropriate measures (e.g., hydration, urine alkalinization, and prophylaxis with allopurinol) must be taken to prevent hyperuricemia of tumor lysis syndrome.

Dose Modification: Nelarabine should be discontinued at the first sign of neurologic events of NCI Common Toxicity Criteria grade 2 or greater. Dosage may be delayed for other toxicity including hematologic toxicity. Dose reductions for hematologic and non-hematologic toxicities may be considered.

Indication:

Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

Intended Population:

Adults and pediatric patients $\leq$21 years of age

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1. EXECUTIVE SUMMARY

1.1 Recommendation On Regulatory Action

Recommendation is deferred pending the advice of the ODAC. Nelarabine has been studied in pediatric and adult patients with T-cell ALL and T-cell LBL who had relapsed or were refractory to two or more prior induction regimens. One Phase 2 non-comparative study was conducted in adults and one in children. The CR rate in the adult CALGB study was 18% and the CR rate in the pediatric COG study was 13%. The CR + CR* (complete response without full hematologic recovery) rate was 21% and 23%, respectively in the two studies. Response duration evaluation is confounded by the fact that patients in nelarabine induced complete remission may have received additional therapy, including stem cell transplantation, prior to disease progression or recovery of normal peripheral blood cell counts. This additional therapy is considered to be standard of care.

Support for the conclusion that nelarabine treatment is of benefit to patients with T-ALL/T-LBL comes from CR and CR* rates for patients who had received only 1 prior induction regimen. In the COG study the CR rate was 42% (13 of 31 patients) and the CR plus CR* rate was 48%. (15 of 31 patients). In the CALGB adult study there were 11 patients who had received only 1 prior treatment regimen. There were 2 CR's (18%) and 3 CR's plus CR*'s (27%). Similar to patients whose disease had relapsed or was refractory to two or more prior induction regimens remission duration and survival evaluation was confounded by the fact that patients frequently received additional cytotoxic therapy and stem cell transplant prior to disease progression or recovery of peripheral blood counts..

Dose limiting toxicity of nelarabine is neurotoxicity. Most neurologic AE's were grade 1 or 2 in severity with grade 3 neurotoxicity occurring in 10% of adults and in 14% of pediatric patients. Grade 4 neurotoxicity occurred in 3% and 8%, respectively. Most neurologic toxicity resolved over time. Other common toxicities related to bone marrow suppression, to the gastrointestinal system and to fatigue.

1.22 Required Phase 4 Commitments

Further investigation of the integration of nelarabine into treatment regimens for T-cell acute leukemia and T-cell lymphoblastic lymphoma would be required if the application is granted accelerated approval.

1.3 SUMMARY OF CLINICAL FINDINGS

1.3.1 Brief Overview of Clinical Program

Pediatric Clinical Study: The safety and efficacy of nelarabine in pediatric patients was studied in a phase II clinical trial conducted by the Children's Oncology Group (COG P9673). This study had 4 strata and included 151 patients 21 years of age and

younger, 149 of whom had relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four (84) patients were treated with 650 mg/m^2/day of nelarabine administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days. Thirty-nine of the above patients had received two or more prior induction regimens (stratum 2) , and 31 had received one prior induction regimen (stratum 1). The remaining 14 patients were in strata 3 and 4.

Baseline patient and disease characteristics of the 70 stratum 1 and stratum 2 patients treated with 650 mg/m^2/day of nelarabine were consistent with those generally observed for patients with these diseases. Patients ranged in age from 2.5-21.7 years (overall mean, 11.9 years), 52% were 3 to 12 years of age and most were male (74%) and Caucasian (62%). The majority (77%) of patients had a diagnosis of T-ALL.

Complete response (CR) in this study was defined as bone marrow blast counts ≤5%, no other evidence of disease, and full recovery of peripheral blood counts. Complete response without full hematologic recovery (CR*) was also assessed. Five of 39 patients (13%) achieved a CR and an additional 4 patients (10%) had a CR*.

For the 31 patients who had received only one prior induction there was a 42% (13/31) CR rate. Nine of these 31 patients had failed to respond to the prior induction. Four (44%) of these 9 refractory patients experienced a complete response to nelarabine.

Adult Clinical Study: This phase II clinical trial was conducted by the Cancer and Leukemia Group B (CALGB). This study included 39 treated patients, 26 of whom had T-cell acute lymphoblastic leukemia (T-ALL) and 13 of whom had T-cell lymphoblastic lymphoma (T-LBL). Twenty-eight patients had relapsed following or were refractory to at least two prior induction regimens. Nelarabine 1,500 mg/m^2 was administered intravenously over 2 hours on days 1, 3 and 5 repeated every 21 days. Complete response (CR) in this study was defined as bone marrow blast counts ≤5%, no other evidence of disease, and full recovery of peripheral blood counts. Complete response without complete hematologic recovery (CR*) was also assessed. Five of 28 patients (18%) with ≥2 prior inductions achieved a CR and an additional patient (3%) achieved a CR*.

1.3.2 Efficacy

Adult and pediatric patients with relapsed/refractory T-ALL/T-LBL, whose disease had relapsed or was refractory to two or more prior induction regimens have no established treatment options and have a poor prognosis. The CR rate in the adult CALGB study was 18% and the CR rate in the pediatric COG study was 13%. The CR + CR* (CR with incomplete hematologic recovery) rate was 21% and 23%, respectively in the two studies. Remission duration and survival evaluation is confounded by the fact that patients in nelarabine induced CR or CR* may have received additional intrathecal and systemic cytotoxic therapy with or without stem cell transplant including marrow, peripheral blood stem cells and cord blood. This represents the standard of care in the disease under study.

1.3.3 Safety

The most common adverse events in pediatric patients, regardless of causality, were hematologic disorders (decreased hemoglobin, decreased white blood cell count, decreased neutrophil count, and decreased platelet count,). Of the non-hematologic adverse events in pediatric patients, the most frequent events reported were headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin, and vomiting.

The most common adverse events in adults, regardless of causality, were fatigue, gastrointestinal (GI) disorders (nausea, diarrhea, vomiting, and constipation), hematologic disorders (decreased hemoglobin, decreased platelet count, and decreased neutrophil count), respiratory disorders (cough and dyspnea), nervous system disorders (somnolence and dizziness), and pyrexia.

Neurologic toxicity was often dose limiting for both pediatric patients and adults. For pediatric patients grade 3/4 neurotoxicity consisted of headache (6%), peripheral sensory neuropathy (6%) hypoesthesia (4%), somnolence (2%), peripheral neuropathy (2%). For adults grade grade 3/4 neurotoxicity consisted of headache (1%), peripheral motor neuropathy (1%) hypoesthesia (2%), depressed consciousness (1%), peripheral neuropathy (1%) and ataxia (1%).

1.3.4 Dosing Regimen and Administration

Adults: The recommended adult dose of nelarabine is 1,500 mg/m² administered intravenously over 2 hours on days 1, 3, and 5 every 21 days.

Children: The recommended pediatric dose of nelarabine is 650 mg/m² administered intravenously over 1 hour daily for 5 consecutive days every 21 days.

The recommended duration of treatment has not been clearly established. In clinical trials, treatment was generally continued until there was evidence of disease progression, the patient experienced unacceptable toxicity or the patient became a candidate for bone marrow transplant.

Supportive Care: Appropriate measures (e.g., hydration, urine alkalinization, and prophylaxis with allopurinol) must be undertaken to prevent hyperuricemia of tumor lysis syndrome.

Dose Modification: Nelarabine should be discontinued at the first sign of neurologic events of NCI Common Toxicity Criteria grade 2 or greater. Dosage may be delayed for other toxicity including hematologic toxicity. Dose reductions for hematologic and non-hematologic toxicity should be considered.

1.3.5 Drug-Drug Interactions

In a pharmacokinetic study in 13 adult patients receiving 1,200 mg/m^2 of nelarabine,

fludarabine administration at 30 mg/m^2 4 hours prior to nelarabine administration did not affect the plasma pharmacokinetics of nelarabine and ara-G or the intracellular accumulation of ara-GTP in leukemic blasts.

Nelarabine and ara-G did not significantly inhibit the activities of the major hepatic cytochrome P450 (CYP) enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4 in vitro of nelarabine and ara-G concentrations up to 100 μM.

1.3.6 Special Populations

Gender: The effect of gender on nelarabine and ara-G pharmacokinetics has not been specifically studied. There was no apparent difference in efficacy or safety observed by gender in clinical trials.

Race: The effect of race on nelarabine and ara-G pharmacokinetics has not been specifically studied.

Geriatrics: Nelarabine and ara-G pharmacokinetics have not been specifically studied in an elderly population. Decreased renal function, which is more common in the elderly, may reduce ara-G clearance.

Renal Impairment: Nelarabine and ara-G pharmacokinetics have not been specifically studied in renal impairment or hemodialysis patients. Nelarabine is excreted by the kidney to a small extent (5 to 10% of the administered dose). Ara-G is excreted by the kidney to a greater extent (20 to 30% of the administered nelarabine dose). In a pharmacokinetic/pharmacodynamic cross-study analysis with a limited number of renally impaired patients (n = 2 with CLcr <50 mL/min), baseline calculated creatinine clearance (CLcr) was a significant predictor of ara-G apparent clearance (CL/F). Ara-G apparent clearance was 7% lower in patients with mild renal impairment (CLcr 50 to 80 mL/min) than in patients with normal renal function (>80 mL/min). Because the risk of adverse reactions to this drug may be greater in patients with decreased renal function (CLcr <50 mL/min), these patients should be closely monitored for toxicities when treated with nelarabine.

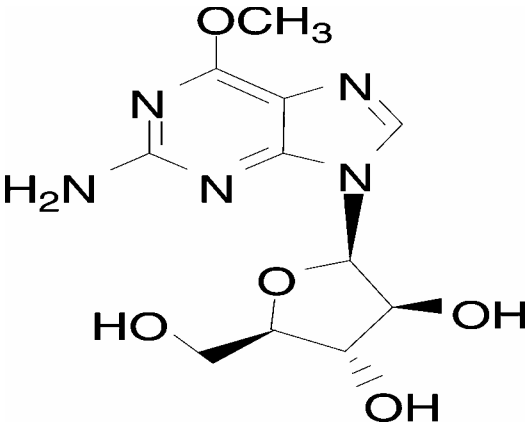
Hepatic Impairment: The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated.

2.0 INTRODUCTION AND BACKGROUND

2.1 Product Information

ARRANON (nelarabine) is a pro-drug of the cytotoxic deoxyguanosine analogue, 9-β-*D*-arabinofurosanylguanine (ara-G). The chemical name for nelarabine is 2-amino-9-β-*D*-arabinofuranosyl-6-methoxy-9*H*-purine. It has the molecular formula $C_{11}H_{15}N_5O_5$ and a molecular weight of 297.27. Nelarabine has the following structural formula:

Figure 1 Nelarabine structural formula



2.2 Currently Available Treatment for Indication(s)

There are no approved therapies. Numerous drugs can be employed in the setting of relapsed-refractory T-ALL/LBL

2.3 Availability of Proposed Active Ingredient In The United States

Available from the sponsor GlaxoSmithKline

2.4 Important Issues With Pharmacologically Related Products

Ara-C and Fludarabine also cause neurotoxicity at high doses.

2.5 Presubmission Regulatory Activity

Table 1: Regulatory Activity

Date	Event
9-Jun-93	Initial IND filed by Dr. Joanne Kurtzberg (Duke University)
16-Aug-96	IND transferred to Glaxo Wellcome
18-Jun-97	End-of-Phase I meeting re: COG protocol endpoints
23-Jun-03	CMC development teleconference
24-Nov-03	End-of-Phase II meeting/Pre-NDA meeting
23-Jun-04	CMC Pre-NDA meeting
30-Jun-04	Teleconference to discuss plans to evaluate neurological events
10-Aug-04	Orphan drug designation

22-Sep-04	Pre-NDA meeting (content and format)
17-Dec-04	Initiate rolling NDA submission (Nonclinical and CMC components)
18-Feb-05	Pre-NDA- clinical
29-Apr-05	Complete NDA submission

2.6 Other Relevant Background Information

None

3.0 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (And Product Microbiology. If Applicable)

See CMC Review

3.2 Animal Pharmacology/Toxicology

See pharmacology/toxicology Review

3.3 Clinical Pharmacology

Nelarabine is a pro-drug of the deoxyguanosine analogue 9-β-*D*-arabinofuranosylguanine (ara-G). Nelarabine is rapidly demethylated by adenosine deaminase (ADA) to ara-G and then phosphorylated intracellularly by deoxyguanosine kinase and deoxycytidine kinase to its 5'-monophosphate. The monophosphate is subsequently converted intracellularly to the active 5'-triphosphate, ara-GTP. Accumulation of ara-GTP in leukemic blasts allows for preferential incorporation of ara-GTP into deoxyribonucleic acid (DNA) leading to inhibition of DNA synthesis which results in cell death. Other mechanisms may contribute to the cytotoxic effects of nelarabine. In vitro, T-cells are more sensitive than B-cells to the cytotoxic effects of nelarabine.

The principal route of metabolism for nelarabine is O-demethylation by adenosine deaminase to form ara-G, which undergoes hydrolysis to form guanine. In addition, some nelarabine is hydrolyzed to form methylguanine, which is O-demethylated to form guanine. Guanine is N-deaminated to form xanthine, which is further oxidized to yield uric acid. Ring opening of uric acid followed by further oxidation results in the formation of allantoin. Renal elimination of nelarabine and ara-G in humans accounted for approximately 5 to 10% and 20 to 30%, respectively, of the administered dose.

4.0 DATA SOURCES. REVIEW STRATEGY. AND DATA INTEGRITY

4.1 Sources Of Clinical Data

Data was submitted in hard copy and electronically. Electronic datasets for study 2001 are listed in **Table 2** and datasets for study 2002 are listed in **Table 3.**

Table 2: Datasets for Study PGAA2001

Dataset	Description	Dataset	Description
ACTHER	Anti-Cancer Therapy	IR	Independent Reviewer
AE	Adverse Experiences	LAB	Laboratory Results
CONMED	Concomitant Therapy	LABO	Laboratory Other
DEATH	Death	MEDDRA	MedDRA
DEMO	Demography	MSTONE	Milestone
DHIST	Disease History	POP	Population
DISPOSIT	Disposition	PRTHER	Prior Therapy
EFFICACY	Efficacy	PS	Performance Status
ELIG	Eligibilty	RESP	Visit Response
ENGRAF	Engraftment	SCT	Stem Cell Transplant
EXPOSURE	Dose Administration	SST	Study Session Times
GSKDRUG	GSK Drug	XMED	Extramedullary Disease

Table 3: Datasets for Study PGAA2002

Dataset	Description	Dataset	Description
AE	Adverse Experiences	LESION	Disease Assessment
DEATH	Death	MEDDRA	MedDRA
DEMO	Demography	MSTONE	Milestone
DHIST	Disease History	OPTF	Long-term Follow up
DISPOSIT	Disposition	POP	Population
EFFICACY	Efficacy	PRCHMO	Prior ChemImmtherapy
ELIG	Eligibilty	PRRAD	Prior Radiotherapy
ENGRAF	Engraftment	PRTHER	Prior Therapy
EXPODY	Daily Dose Admin	PS	Performance Status
EXPOSURE	Dose Administration	RESP	Visit Response
GSKDRUG	GSK Drug	VITAL	Vital Signs
IR	Independent Reviewer		
LAB	Laboratory Results		

4.2 Tables of Clinical Studies

Table 4: Clinical studies

Study	Phase	N of pts
PGAA1001	I	93
PGAA1002	I	27
PGAA1003	I	48
PGAA1005	I	13
COG9673, PGAA2001	II	151
CALGB19801,PGAA2002	II	39
Special exceptions		392+

4.3 Review Strategy

Electronic data provided by the sponsor was reviewed.

4.4 Data Quality and Integrity

Pediatric subject data were collected by the investigator or designee using standard COG data collection forms. COG entered key data from the paper data forms into a validated database, utilizing their standard processes for data management. Upon completion of the trial, COG provided GSK with the study database in the form of SAS transport files and copies of all paper forms used for data collection on patients enrolled.

GSK Data Management entered laboratory data from the subject flowsheets provided by COG into a validated database or data system as the basis of a final study database. Additional information was also requested from participating institutions in order to either confirm or supplement the available data. In particular, there was a desire to ensure that reporting of neurologic adverse events had been complete.

Specific forms were used to record neurologic events, clarify response (e.g., hematologic recovery, response of extramedullary disease), and obtain further information suitable for analysis of potential predisposing factors for neurologic events. A third party, ReSearch Pharmaceutical Services, Inc., was contracted to review charts at clinical trial sites to ensure the completeness of neurologic event reporting and assist in the query process.

A final query process to clarify key safety and efficacy data was then conducted by GSK Clinical Data Management, in association with GSK Oncology Clinical Development, and COG Operations Center, Arcadia, California. Original COG data forms were retained by COG Statistical Operations Center, and the investigator retained a copy. GSK retained original DCFs and copies of COG data forms.

Adult subject data were collected by the investigator or designee using CALGB CRF's. Data necessary for analysis and reporting were entered into a database or data system, which was transferred as SAS transport files to GSK. GSK Clinical Data Management, in collaboration with CALGB, conducted a query process. In addition, GSK Clinical Data Management entered laboratory data and prior therapies in accordance with GSK standards and data checking procedures from paper CRFs provided by CALGB. Database freeze occurred when data management quality control procedures were completed.

Sites participating in this study were audited on a regular basis as part of the standard CALGB and NCI policies and procedures. In addition, GSK conducted one on-site audit after the completion of the trial at a participating institution to assure compliance with Good Clinical Practice and the accuracy and completeness of key efficacy and safety data provided to GSK.

Adverse Events

All AEs were to be entered on the CALGB Toxicity Form (Form C-548). AEs were graded according to DCTD Common Toxicity Criteria, version 2 (CTCv2). The start and

end dates provided on Form C-548 correspond to the time period in which the event occurred and do not represent actual start and stop dates of the events captured on this form. For this analysis, the start date of the time period was used as the event start date for all events captured on a particular page.

In order to elicit thorough documentation of potential AEs, a list of expected events (which included neurologic toxicities) was provided on Form C-548 in addition to blank fields for unexpected events.

All AEs occurring within 28 days of study drug administration (i.e. on-therapy AEs) were summarized. AEs were classified by the worst CTC grade experienced by the subject.

4.5 Compliance With Good Clinical Practices

Studies complied with good clinical practices

4.6 Financial Disclosures

The sponsor has submitted certification that GlaxoSmithKline has not entered into any financial arrangement with any of its clinical investigators who participated in the CALGB or COG trials. This certification was signed on by David E. Wheadon, M.D., Senior Vice President, Regulatory Affairs.

5.0 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Pharmacokinetic studies in patients with refractory leukemia or lymphoma have demonstrated that nelarabine is rapidly eliminated from plasma with a half-life of approximately 30 minutes. Plasma ara-G C_{max} values generally occurred at the end of the nelarabine infusion and were generally higher than nelarabine C_{max} values, suggesting rapid and extensive conversion of nelarabine to ara-G. Mean plasma nelarabine and ara-G C_{max} values were <100 μM after a 650 mg/m^2 dose infused over 1 hour in pediatric patients. Mean plasma nelarabine C_{max} values were <100 μM and mean plasma ara-G C_{max} values were approximately 100 μM after a 1,500 mg/m^2 dose infused over 2 hours in adult patients.

In a pharmacokinetic/pharmacodynamic cross-study analysis using data from four Phase I studies over a dose range of 100 to 2,900 mg/m^2 (n = 135), the pharmacokinetics of ara-G were characterized in patients with refractory leukemia or lymphoma. Day 1 ara-G pharmacokinetic parameter values are summarized in **Table 5**.

Table 5: Day 1 Pharmacokinetic Parameter Values for ara-G

	Geometric Mean Pharmacokinetic Parameter Values [n]		
	CL/F (L/hr/m^2)	V/F (L/m^2)	t½ (hr)
Adults (≥18 years of age)	9.50 [53]	44.8 [53]	3.23 [55]
Children (<18 years of age)	10.8 [16]	32.1 [16]	2.03 [17]

CL = clearance; V = volume of distribution; F = fraction of nelarabine converted to ara-G; t½ = elimination half-life

No accumulation of nelarabine or ara-G was observed in plasma after nelarabine administration on either a daily schedule or on a Day 1, 3, and 5 schedule. Intracellular ara-GTP concentrations in leukemic blasts were quantifiable for a prolonged period after nelarabine administration; elimination half-life could not be estimated in most patients. Intracellular ara-GTP accumulated with repeated administration of nelarabine; on the Day 1, 3, and 5 schedule, C_{max} and AUC(0-t) values on Day 3 were ~50% and ~30%, respectively, greater than C_{max} and AUC(0-t) values on Day 1.

Nelarabine and ara-G are not substantially bound to human plasma proteins (<25%) in vitro, and binding is independent of nelarabine or ara-G concentrations up to 600 μM.

5.2 Pharmacodynamics

No additional data is available.

5.3 Exposure-Response Relationships

Not applicable.

6.0 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens.

6.2 Methods

Two phase II clinical trials to demonstrate the safety and efficacy of nelarabine were submitted, one in pediatric patients, conducted by the Children's Oncology Group (PGAA2001) the other in adult patients, conducted by the Cancer and Leukemia Group B (CALGB) as an inter-group trial in cooperation with SWOG. (PGAA2002). The pediatric study had 4 strata and included 151 treated patients 21 years of age and younger, 149 of whom had relapsed or refractory T-cell acute lymphoblastic leukemia (T-ALL) or T-cell lymphoblastic lymphoma (T-LBL). Eighty-four (84) patients were treated with 650 mg/m^2/day of nelarabine administered intravenously over 1 hour daily for 5 consecutive days repeated every 21 days; 39 of whom had received two or more prior

induction regimens (stratum 2), and 31 of whom had received one prior induction regimen (stratum 1). The remaining 14 patients were in strata 3 or 4).

The CALGB adult study included 39 treated patients, 26 of whom had T-ALL and 13 of whom had T-LBL. Twenty-eight patients had relapsed following or were refractory to at least two prior induction regimens. Nelarabine 1,500 mg/m^2 was administered intravenously over 2 hours on days 1, 3 and 5 repeated every 21 days.

The protocol defined endpoints were response rates and response durations. Complete response (CR) was defined as bone marrow blast counts ≤5%, no other evidence of disease, and full recovery of peripheral blood counts. Complete response without full hematologic recovery (CR*) was also assessed.

6.3 General Discussion of Endpoints

Appropriate study end points were used. Response durations often could not be determined, however, because responding patients went on to receive a stem cell transplant or other intrathecal or systemic chemotherapy prior to progression.

6.4 Study Design

6.4.1 Trial PGAA2001 (pediatric)

Strata:

Subjects were entered into one of the following four strata. Treatment of stratum 03 and 04 patients was hypothesis generating. These patients are not further analyzed.

Stratum 01: T-ALL or T-NHL in first relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse other than CNS).

Stratum 02: T-ALL or T-NHL in second or later relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse other than CNS).

Stratum 03: T-ALL or T-NHL with positive bone marrow and CSF (>5% bone marrow blasts and CNS 2 or 3 involvement); CNS 2: subjects with <5 WBC/mm^3 and positive cytology; CNS 3: subjects with ≥5 WBC/mm^3 and positive cytology.

Stratum 04: Extramedullary relapse and <25% bone marrow blasts in the bone marrow (excluding isolated CNS relapse).

Protocol Amendments:

The protocol was approved on 2 June 1997. There were six amendments and two revisions to the protocol.

Amendment 1 (3 September 1997)

- The starting dose of nelarabine was lowered from 1200 mg/m2 to 900 mg/m2 due to grade 4 neurotoxicity in the first subject enrolled at the 1200 mg/m2 dose level.
- The toxicities listed for methotrexate were updated in the consent form.
- Creatinine clearance or glomerular filtration rate (GFR) was added as a pre-study test and the following sentence was added to eligibility criteria: "When feasible, creatinine clearance or GFR should be obtained prior to the first cycle, even if the serum creatinine is normal".
- In the pharmacokinetic section, it was specified that CSF should be collected in cryovials supplemented with deoxycoformycin.
- The following criterion was added to dose modifications and other appropriate sections: If neurologic toxicity (e.g., somnolence) developed prior to the completion of 5 days of therapy, dosing was to be halted and the study coordinator was to be called immediately.

Revision 1 (29 September 1997)

The protocol was revised to update the assumptions of the null and alternative hypotheses and to provide more stringent criterion (e.g., alpha level) for testing these hypotheses. The alternative hypothesis for the early marrow response rate (EmCR+EmPR) was increased from 30% to 40%, the null hypothesis for the early marrow response rate (EmCR+EmPR) was increased from 10% to 20%, the alpha level was reduced from 0.55 to 0.09, and corresponding changes were made to subject accrual needed for Stage 1 and Stage 2. Previous: Stage 1 required 1/15 evaluable subjects with early marrow response (EmCR or EmPR), in order to enroll an additional 15 evaluable subjects in Stage 2, with a Type I error rate of 0.55 and statistical power of 0.993. Revised: Stage 1 of this revised design required >4/20 evaluable subjects with early marrow response (EmCR or EmPR), in order to enroll an additional 17 evaluable subjects in Stage 2, with a Type I error rate of 0.094 and statistical power of 0.903

Amendment 2 (29 May 1998)

- A dose of 30 mg/kg of nelarabine was specified for infants ≤365 days of age. Dosing based on body weight rather than body surface area was chosen because it was felt that neurotoxicity might be more difficult to assess in infants and dosing based on body weight would result in a smaller total dose for most infants.
- Stratum 03 (subjects in first or later relapse and CNS 2 or 3 involvement) was opened as the goal of accruing a sufficient number of subjects on Strata 01 and 02 to gain baseline experience with neurologic adverse events was met and Stratum 04 (isolated extramedullary relapse excluding isolated CNS relapse) was added as it was felt valuable experience with the compound might be gained by including subjects with extramedullary disease without bone marrow involvement.
- The schedule of triple intrathecal therapy for subjects on treatment 3 was changed in order to decrease the frequency of triple intrathecal therapy administration (every 9 weeks) in subjects who remained on study for a prolonged period.

Amendment 3 (10 July 1998)

- The toxicity section on nelarabine was amended, adding that polyneuropathy, including Guillain-Barré-like syndrome, agitation, delirium and hallucinations had been reported in association with administration of nelarabine. The "Risks" section of the informed consent was also amended to alert the subject/parents to the possibility of these adverse events.
- Investigators were cautioned to monitor subjects carefully for the development of signs and symptoms of peripheral neuropathy.
- The consent form was updated to include clear description of possible events including ascending peripheral neuropathy
- Registration procedures were clarified to note that the study coordinator must be called prior to registration and obtaining informed consent.

Amendment 4 (19 August 1998)

- Because several subjects who received nelarabine, including one pediatric subject on this trial, developed a Guillain-Barré-like syndrome, the dose was reduced from 900 mg/m2/day to 650 mg/m2/day x 5 days for all subjects over 1 year of age and 20 mg/kg for infants up to one year.
- The protocol was also amended to update the assumptions of the null and alternative hypotheses, and hence the sample size calculations. The alternative hypothesis for the early marrow response rate (EmCR+EmPR) was reduced from 40% to 35% and corresponding changes were made to subject accrual needed for Stage 1 and Stage 2. Previous: Stage 1 required >4/20 evaluable subjects with early marrow response (EmCR or EmPR), in order to enroll an additional 17 evaluable subjects in Stage 2, with a Type I error rate of 0.094 and statistical power of 0.903. Revised: Stage 1 required >3/19 evaluable subjects with early marrow response (EmCR or EmPR), to enroll an additional 14 evaluable subjects in Stage 2 with Type I error rate of 0.096 and statistical power of 0.904.

Revision 2 (28 May 1999)

The protocol was revised to clarify the stratum definitions in the protocol. The definition of Stratum 03 was changed to “T-ALL or T-NHL with positive bone marrow and CSF (>5% bone marrow blasts and CNS 2 or 3 involvement)”. The definition of Stratum 04 was changed to “Extramedullary relapse and <25% blasts in the bone marrow (excluding isolated CNS relapse)”.

Amendment 5 (15 August 1999)

The starting dose for Strata 03 and 04 was reduced to 400 mg/m2. The 400 mg/m2 dose was planned for use in a future study of multi-agent treatment in subjects with newly diagnosed T-cell leukemia and it was felt that pilot data on response and toxicity at that dose could be obtained without compromising the goals of the current study. The statement "One adult patient and two children receiving higher doses of nelarabine than

the dose that will be used in this study had muscle weakness that did not go away." was removed from the "Risks" section of the informed consent as it was no longer accurate.

Amendment 6 (9 August 2004)

The study was amended in order to collect post stem cell transplant engraftment data on subjects who received nelarabine and then subsequently received a bone marrow transplant. The "completed" status of the study was withdrawn and the status was redefined as "Treatment Completed". The background and rationale for the collection of the engraftment data was added, as was a list of data to be acquired retrospectively by the treating institutions and investigators.

Study Eligibility

1. Subjects with refractory or recurrent T-ALL or T-NHL.
2. Subjects must have been ≤21 years of age at the time of initial diagnosis.
3. Subjects must have had a predicted life expectancy ≥8 weeks, Karnofsky performance status ≥50, and no severe uncontrolled infection.
4. Subjects must have had adequate hepatic function (bilirubin ≤1.5mg/dL; SGPT <5xN) and renal function (creatinine normal for age or creatinine clearance or GFR ≥60 ml/min/1.73 m^2). When feasible, creatinine clearance or GFR should have been obtained prior to the first cycle, even if the serum creatinine was normal.
5. Subjects were not to receive any other anti-cancer agents, including radiation therapy, and must have recovered from toxicity of all previous chemotherapy. At least 6 weeks must have elapsed since administration of nitrosoureas or craniospinal or hemipelvic radiation therapy (XRT).
6. Signed informed consent was to be obtained according to institutional guidelines.
7. The study coordinator was to be called to approve the subject's enrollment and to discuss current toxicity experience.
8. Exclusions:
Pregnant or lactating women
Baseline ≥grade 2 neurotoxicity

Completion Criteria

Subjects could continue to receive nelarabine for up to two years unless they met the withdrawal criteria. Stratum 01 was originally designed as an up-front window treatment where subjects would receive 2 cycles of nelarabine then transfer to a higher priority COG study, if opened. Since no study of higher priority was opened for this patient population, all subjects enrolled in Stratum 01 were allowed to continue for up to two years.

Withdrawal Criteria

The criteria for removing a subject from the study were:
1. Progressive disease at any time
2. Subject or family refused further therapy or was lost to follow-up
3. Development of unacceptable toxicity or death on study

4. Subject went onto a different treatment (e.g., bone marrow transplant)

Follow up information was to be collected at completion of protocol therapy, every six months until four years from registration, and annually thereafter. Collection of this information was to be discontinued only if the subject subsequently entered another POG treatment study or died. Off protocol therapy follow-up included information on survival, relapse, late effects events, and additional anti-cancer therapy.

Assessments

Table 6: Schedule of Assessments

	Pre-Treatment Evaluation	Treatment Phase	Post-Treatment
Informed consent	X		
Medical history	X		
Prior Treatment history	X		
Pregnancy test	X a		
Physical examination b	X	Daily during drug Rx in cycle 1; weekly for remainder of cycle 1; then prior to each therapy cycle	X
Chest X-ray/other imaging c	X d	Every 2 cycles	X
CBC, Differential, Platelets	X	Every other day during dosing, then weekly	X
Bone Marrow aspirate/biopsy	X	Day 21 e of cycle 1 and Day 21 of cycle 2	
PT/PTT	X	Every 2 cycles	
Electrolytes, BUN, Creatinine	X	Weekly	X
Creatinine clearance f	X		
Ca, Mg, PO4, uric acid, LDH SGPT, bilirubin (T/D), total protein, albumin, Urinalysis	X	Prior to each cycle	X
Lumbar puncture g	X	X	

a. In women of childbearing potential.
b. With attention to neurologic exam, interval history, performance, symptoms (w/TPR, BP, Wt, BSA)
c. Or appropriate imaging studies, e.g., CT scan or MRI for subjects with bulky disease. The same imaging modality used in pre-treatment evaluation was used throughout the cycle of the study.
d. Baseline imaging studies were obtained ≤7 days prior to first dose of investigational product.
e. If physical examination or CBC indicated no response, a bone marrow aspirate was performed on day 14. If the cycle 2, day 21 (i.e., week 6) bone marrow aspirate was the first documentation of CR, bone marrow aspirate was to be repeated at cycle 3, day 21 (i.e., week 9).
f. When feasible, creatinine clearance or GFR was obtained prior to the first cycle
g. Lumbar punctures to obtain CSF for cytology, cell count and protein were performed prior to the beginning of treatment, and on day 1 of week 1 (1 week after the start of nelarabine therapy).

Efficacy Criteria

Marrow Response

Independent Review of Bone Marrow: Independent review of bone marrow aspirates or biopsies took place for subjects who achieved a response and had available slides. Specimens were not available on all responding subjects, or within a subject, specimens were not always available for all dates. The independent pathologist, John Bennet M.D., was not a member of COG, but was contracted by GSK to perform these services. Dr. Bennet also examined some slides from subjects who did not achieve a response.

Specimens were evaluated for the adequacy of the specimen, cellularity, presence of megakaryocytes, and differential. In addition, available baseline specimens were evaluated for consistency with the diagnosis of ALL. The marrow was scored as M1, M2, or M3 and whether it was consistent with 'complete response (M1) marrow'.

Complete Response (CR) Rate: Bone marrow blast counts ≤5%, no other evidence of disease, and full recovery of peripheral blood counts (i.e., ANC >1500/µl, platelets >100,000/µl, Hgb ≥10 g/dl for subjects less than 2 years of age, Hgb ≥11 for subjects ≥2years of age). Assessment of CR was based on supplemental data and data from laboratory flowsheets provided by COG.

CR* Rate: Bone marrow blast counts ≤5% and no other evidence of disease. These subjects may have had hypocellular bone marrow or peripheral hemograms that had not completely normalized.

Duration of Response

In the sponsor's analysis treatment with additional anti-cancer therapy was not criteria for termination of response (i.e., duration of response was measured from date of response to relapse, death, or last date of contact).

6.4.2 Trial PGAA 2002 (adult)

STUDY OBJECTIVES

Primary Objective

Complete and partial response rates and response duration.

Secondary Objectives

Safety of nelarabine treatment, survival and time to response

Nelarabine was to be administered by intravenous infusion over 2 hours on days 1, 3, and 5 of a 21 day treatment cycle. The study was opened at a dose of 2200 mg/m2/day but was amended to a dose of 1500 mg/m2/day to decrease the risk of neurologic toxicity. Three subjects received the 2200 mg/m2 dose. Data from these subjects were included in all analyses.

Protocol Amendments

The protocol executed in this study was approved on 1 August 1998. The following 6 updates included 4 editorial revisions, 1 revision/amendment and 1 amendment.

15 September 1998 (Editorial Revision)
The C-400 form was to be submitted every 6 months, beginning 18 months after the end of all treatment, for a maximum of 10 years from study entry. Subjects were to be followed for survival for a maximum of 10 years from study entry.

15 January 1999 (Editorial Revision)
If a lumbar puncture was performed for the evaluation of neuropsychiatric toxicities, investigators were encouraged to submit a specimen of cerebrospinal fluid (CSF).

15 April 1999 (Amendment)
The dose was reduced from 2200 mg/m2/day to 1500 mg/m2/day to reduce the risk of neurotoxicity. Also, subjects with pre-existing grade 2 or greater neuropathy were deemed ineligible for enrollment.

15 April 2000 (Editorial Revision)
All questions regarding treatment, dose modifications, or eligibility were to be directed to the CALGB Study Chair.

15 Dec 2000 (Revision/Amendment)
Memory loss and speech impairment (e.g., aphasia or dysphasia) were included as potential toxicities.

15 July 2001 (Editorial Revision)
AE reporting guidelines were updated to reflect NCI AdEERs AE reporting instructions.

Eligibility Criteria

1. Documentation of disease according to the following criteria:
- Histologic diagnosis of T-lineage ALL or LBL (subjects with >25% lymphoblasts in the bone marrow either at initial diagnosis or at entry into this study were considered to have ALL rather than LBL).
- Leukemia or lymphoma cells must have expressed at least two of the following cell surface antigens: CD1a, CD2, CD3 (surface or cytoplasmic), CD4, CD5, CD7, and CD8. Leukemia cells must also have been negative for myeloperoxidase or Sudan Black B. If the only T cell markers present were CD4 and CD7, the leukemic cells were to lack myeloid markers, CD33 and /or CD13 (results of TdT assay were to be included if performed).
- Histologic, cytochemical, and immunophenotypic diagnostic studies performed at the time of original diagnosis or at relapse were sufficient to fulfill the requirements.

2. Refractory to at least one induction treatment regimen or in first or later relapse after achieving a complete response (for subjects with ALL, relapsed or refractory disease was to be demonstrated by the presence of ≥10% lymphoblasts in the bone marrow or

≥1000 lymphoblasts/μL in the blood.

3. No CNS leukemia or lymphoma requiring intrathecal or craniospinal radiation therapy (a lumbar puncture was not required in asymptomatic subjects).
4. No history of seizure disorder or ≥grade 3 neurologic toxicity during prior treatment of ALL/LBL and no pre-existing neuropathy ≥grade 2 at the time of registration,
5. Age ≥16 years.
6. Initial required laboratory values (unless attributable to leukemia):
   - Calculated creatinine clearance ≥50mL/min.
   - Bilirubin ≤2 x upper limit of normal.
7. Subjects must have recovered from all significant toxicities of previous therapies.
8. Women and men of reproductive potential agreed to use an effective form of contraception
9. Tentative ineligibility

a. Psychiatric illness that could prevent the subject from completing treatment or providing informed consent.
b. Uncontrolled or severe cardiac disease or infection
c. Currently active second malignancies other than non-melanoma skin cancers (subjects were not considered to have a "currently active" malignancy if they had completed therapy and were considered by their physician to be unlikely to have a recurrence within one year).

Assessments

The schedule of assessments is summarized in **Table 7**.

Table 7: PGAA2002 Schedule of Assessments

Procedures	**Pre-treatment Evaluation**	**During Each Course of Treatment**	**At Time of Restaging or Relapse**	**Follow-Upa**
Tests and Observations				
Informed Consent	X			
Medical History	X	Day 1	X	X
Physical Examination	X	Day 1	X	X
Performance Status	X	Day 1	X	X
Tumor Measurements	Xb	Day 1b	X b	X
Pulse/Blood Pressure	X			

Laboratory Studies				
CBC/Differential	X	3 x week	X	X
Serum creatinine, BUN, creatinine clearance	X	Xc	X	
Serum electrolytes	X	Weekly		
AST, bilirubin, alkaline phosphatase, LDH	X	Weekly		
Uric acid, glucose, phosphate	X	Weekly		
Staging				
Bone marrow aspirate/biopsy	X		Xd	PRN
CT Scan Chest/Abdomen/Pelvis	Xb		Xb	PRN
Chest X-ray	X		PRN	PRN
Lumbar Puncture	Xe		Xe	
Treatment/Monitoring				
Adverse Event/Toxicity Assessment		X	X	X

a. Every 3 months for 1 year, then every 6 months for 5 years, or until relapse. Subjects were followed for survival for up to 10 years from enrollment.
b. Required for subjects with LBL only. Size of liver, spleen, lymph nodes and mediastinal mass were to be noted.
c. Within 48 hours of day 1.
d. Twenty-one (21) days after induction, i.e., day 22 and after second induction, if necessary. Repeated at day 29 if hypocellular (≤15% cellularity) and after recovery from the first consolidation course but before the second course. Bone marrow aspirate and biopsy were performed at time of relapse. In each case, bone marrow for CR was submitted for central review. For subjects with LBL, bone marrow biopsies to confirm response were only required in subjects who had prior documented bone marrow involvement. Central review of bone marrow biopsies was not required in these subjects.
e. If clinically indicated.

Efficacy Criteria

Complete Response (CR):

• **ALL**: absolute neutrophil count (segs and bands) >1500/µL, no circulating blasts, platelets >100,000/µL, bone marrow cellularity >20% with trilineage hematopoiesis, and <5% marrow blast cells, none of which appear neoplastic. All previous extramedullary manifestations of disease were to be absent (e.g., lymphadenopathy, splenomegaly, skin or gum infiltration, testicular masses, or CNS involvement). Because chemotherapy can produce prolonged cytopenias, subjects who did not recover normal peripheral blood counts but also did not relapse within 6 months of their final chemotherapy treatment could be considered retrospectively to have achieved a CR starting one month after their last transfusion.

• **LBL:** disappearance of all measurable disease, signs, symptoms, and biochemical changes related to the tumor and appearance of no new lesions.

Subjects were classified as a complete responder if they met the criteria at any point during the study and there was no evidence of disease progression within a month following the initial response date (regardless of whether or not data were available to confirm that the response was maintained for at least a month). A subject was considered to have a confirmed complete response if there was evidence to show that the complete response was maintained for one month.

CR* Rate: CR* was defined as bone marrow blast counts less than 5% and no other evidence of disease. Hypocellular bone marrow and/or peripheral hemograms have not completely normalized.

Partial Response (PR):

• **ALL**: required all of the CR criteria except that the marrow may still contain 5-25% leukemia blast cells. Even if <5% blasts were present, the response was a PR if Auer rods or blast cells with obvious leukemia morphology (e.g., malignant promyelocytes) were present.

• **LBL**: when compared with pre-treatment measurements, a reduction of ≥50% in the sum of the products of the perpendicular diameters of all measurable lesions. No new lesions could appear and no existing lesion could enlarge. A <50% reduction and ≤25% increase in the sum of the products of two perpendicular diameters of all measured lesions and no new lesions was considered to be stable disease.

Other Efficacy Endpoints

Duration of Response

For the evaluation of duration of response endpoints, treatment with additional anticancer therapy was not a reason for termination of response (i.e., duration of response was measured from date of response to relapse, death, or last date of contact). Per the protocol, relapse was defined as the reappearance of unequivocal leukemia blast cells in the blood or the bone marrow (>5%) or in the CNS (positive cytospin examination of CSF) or in any other extramedullary site after a CR; or progression to >25% leukemia blasts cells in the marrow after a PR.

Time to Response

Time to response is the time from start of treatment date to the indicated response.

Survival

Overall survival and survival at one year were determined.

6.5 Efficacy Findings

6.5.1 PGAA2001 (Pediatric)

The study was initiated on 22 June 1997 and ended on 19 July 2002.

Study investigators are listed in **Table 8.**

Table 8: PGAA2001 Investigators

Investigator	Location
Moghrabi, Albert	Hopital Sainte-Justine Montreal Quebec Canada H3T 1C5
Billett, Amy	Dana-Farber Cancer Institute Boston, MA 02115
Ritchey, Arthur	Children's Hospital of Pittsburgh Pittsburgh, PA 15213
Golembe, Barry	Carolinas Medical Center Charlotte, NC 28203
Bell, Beverly	Medical College of Georgia Augusta, GA 30912
Lange, Beverly	Childrens Hospital of Philadelphia Philadelphia, PA 19104
Tebbi, Cameron	Tampa Children's Hospital Tampa, FL 33607
Alvarado, Carlos	Emory University School of Medicine Atlanta, GA 30322
Arndt, Carola	Mayo Clinic and Foundation Rochester, MN 55905
Stroud, Cary	Greenville Cancer Treatment Center Greenville, SC 29605
Steuber, Charles	Baylor College of Medicine Houston, TX 77030
Pui, Ching-Hon	St. Jude Children's Research Hospital Memphis, TN 38105
Selsky, Clifford	Florida Hospital Cancer Institute Orlando, FL 32804
Greenfield, Daniel	Santa Barbara Cottage Hospital Santa Barbara, CA 93102
Freyer, David	Spectrum Health Butterworth Campus Grand Rapids, MI 49503
Mitchell, David	Montreal Childrens Hospital Quebec Canada H3H1P3
Rosen, David	Via Christi Regional Medical Center White Plains, NY 10605
Daghistani, Doured	Baptist Hospital of Miami Miami, FL 33176
Thompson, Elizabeth	Childrens Memorial Hospital of Omaha Omaha, NE 68114
Beardsley, George	Yale University New Haven, CT 06520
Buchanon, G.	University of Texas Southwestern Medical Center Dallas, TX 75390
Reaman, Gregory	National Childhood Cancer Foundation Bethesda, MD 20814
Casper, James	Medical College of Wisconsin Milwaukee, WI 53226
Feusner, James	Children's Hospital and Research Center Oakland, CA 94609
Frost, Jami	University of New Mexico Albuquerque, NM 87131
Geyer, Jeffrey	Children's Hospital Seattle,WA 98105
Hord, Jeffrey	Akron Children's Hospital Akron, OH 44308
Lipton, Jeffrey	Schneider Children's Hospital New Hyde Park, NY 11040
Pearce, Jennifer	Albany Medical Center Albany, NY 12208
Barbosa, Jerry	All Children's Hospital St. Petersburg, FL 33701
Finklestein, Jerry	Miller Children's Hospital Long Beach, CA 90806
Hilden, Joanne	The Children's Hospital Cleveland, OH 44195-5217
Kurtzberg, Joanne	Duke University Medical Center Durham, NC 27710
Gregory, John	Hackensack University Medical Center Hackensack, NJ 07601
Ducore, Jonathan	University of CA, Sacramento, CA 95817
McNamara, Joseph	Pediatric Hematology/Oncology Associates Guilford, CT 06437

Neglia, Joseph	University of Minnesota Minneapolis, MN 55455
Sato, Judith	City of Hope National Medical Center Duarte, CA 91010
Leung, Kenneth	Kaiser Permanente, San Francisco CA 94115
Coppes, Max	Alberta Children's Hospital Calgary, Alberta Canada T2T 5C7
Harris, Michael	Hackensack University Medical Center Hackensack, NJ 07601
Link, Michael	Stanford University Medical Center Palo Alto, CA 94304
Hakami, Nasrollah	University of Missouri- Columbia, MO 65212
Grundy, Paul	University of Alberta Edmonton, Alberta Canada T6G 2B7
Breitfield, Philip	Duke University Medical Center Durham, NC 27710
Rosoff, Philip	Duke University Medical Center Durham, NC 27710
Ribeiro, Raul	St. Jude Children's Research Hospital Memphis, TN 38105
Byrd, Rebecca	Childrens Hospital Norfolk, VA 23507-1971
Duerst, Reggie	Childrens Memorial Hospital hicago, IL 60614
Wells, Robert	MD Anderson Cancer Center Houston, TX 77030
Dubowy, Ronald	State University of New York at Syracuse Syracuse, NY 13210
Louie, Ronald	Mary Bridge Hospital Tacoma, WA 98405
Neuberg, Ronnie	Richland Memorial Hospital Columbia, SC 29203-6897
Abish, Sharon	Montreal Childrens Hospital Montreal, Quebec, Canada H3H 1P3
Lockhart, Sharon	Children's Hospital of Austin Austin, TX 78701
Berg, Stacey	Texas Children’s Cancer Center Houston, TX 77030
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Feig, Stephen	UCLA School of Medicine Los Angeles, CA 90095-1752
Winter, Stuart	University of New Mexico Albuquerque, NM 87131
Kreissman, Susan	Duke University Medical Center Durham, NC 27710
Inoue, Susumu	Hurley Medical Center Flint, MI 48503
Baruchel, Sylvain	Hospital for Sick Children Toronto, Ontario Canada M5G 1X8
Silberman, Teresa	Marshfield Clinic Marshfield, WI 54449
Vik, Terry	Riley Hosp for Children Indianapolis, IN 46202
Abshire, Thomas	Emory University School of Medicine Atlanta, GA 30322
Carroll, William	Primary Children’s Medical Center Salt Lake City, UT 84113
Meyer, William	University of Oklahoma Oklahoma City, OK 73190
Roberts, William	Jonathan Jacques Children Cancer Center Long Beach, CA 90806
Thomas, William	Mary Bridge Hospital Tacoma, WA 98405
Matloub, Yousif	University of Wisconsin Madison, WI 53792
Camitta, Bruce	Midwest Children's Cancer Center Milwaukee, WI 53226
Wofford, Marcia	Wake Forest University Winston-Salem, NC 27157
Neely, John	Milton S. Hershey Medical Center Hershey, PA 17033-0850
Kane, Javier	University of Texas San Antonio, TX 78207
Aplan, Peter	National Naval Medical Center Bethesda, MD 20889
Woodruff, Kelley	Kapiolani Medical Center Honolulu, HI 96826
Nickerson, H. James	Marshfield Clinic Marshfield, WI 54449
Desai, Sunil	University of Alberta Edmonton, Alberta Canada T6G 2B7
Asselin, Barbara L.	University of Rochester Rochester, NY 14642
Blaney, Susan M	Baylor College of Medicine Houston, TX 77030
Brecher, Martin L	Roswell Park Cancer Institute Buffalo, NY 14263
Bruggers, Carol S	Primary Childrens Medical Center Salt Lake City, UT 84113
Chauvenet, Allen R	Wake Forest University Winston-Salem, NC 27157-1081
Dahl, Gary Van Houten	Stanford University Stanford, CA 94305

Drachtman, Richard	Cancer Institute of New Jersey New Brunswick, NJ 08901
Estrada, Jaime	Southwest Texas Methodist Hospital San Antonio, TX 78229
Ettinger, Lawrence J	Saint Peter's University Hospital New Brunswick, NJ 08903
Fallon, Robert J	Riley Hospital for Children Indianapolis, IN 46202
Frankel, Lawrence S	Scott & White Memorial Hospital Temple, TX 76508
Friedman, Alan D.	Johns Hopkins Hospital Baltimore, MD 21231
George, Bradley A	Childrens Healthcare of Atlanta Atlanta, GA 30342
Giusti, Vincent F	Nemour's Children's Clinic Orlando, FL 32806
Goodman, Lisa	Children's Hospital and Research Center Oakland, CA 94609
Greenberg, Jay Horn, Marianna	Fairfax Hematology-Oncology Associates Fairfax, VA 22031
Griffin, Timothy C	Children's Medical Center Fort Worth, TX 76104
Herzog, Philip	Group Health Cooperative Redmond, WA 98052
Hetherington, Maxine	The Childrens Mercy Hospital Kansas City, MO 64108
Holcenberg, John S	Children's Hospital Seattle, WA 98105
Jasty, Rama	Saint Vincent's Medical Center Toledo, OH 43608
Kadota, Richard P	Children's Hospital San Diego, CA 92123
Kung, Faith H	University of California San Diego, CA 92103
Langevin, Anne-Marie	University of Texas San Antonio, TX 78207
Lauer, Stephen	Emory University Atlanta, GA 30322
Loh Jr., Wellington	Kaiser Permanente San Diego, CA 92120
Moertel, Christopher	Children's Hospitals and Clinics St. Paul, MN 55102
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Toledano, Stuart	University of Miami Miami, FL 33101
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Winick, Naomi J	University of Texas Dallas, TX 75390
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Warwick, Anne	Medical College of Wisconsin Milwaukee, WI 53226
Hitzler, Johann	Hospital for Sick Children Toronto, Canada M5 G1X8

A total of 153 subjects 21 years of age or less at the time of initial diagnosis with refractory or recurrent T-ALL or T-NHL were enrolled in this study by 109 investigators at 78 sites. Two subjects were enrolled but not treated: Subjects 1045 and 1063 did not receive study medication due to rapid clinical deterioration.

A total of 151 subjects were assigned to one of four strata. Allocation to Stratum 01 and 02 are described in **Table 9**. Statum 03 had CNS disease and stratum 04 had extra-medullary relapse and <25% bone marrow blasts. The majority of patients in both of these strata received a nelarabine dose of 400 mg/m2. They are excluded from further analyses.

Table 9: Subject Allocation

Stratum	**Description**	**Enrollment by dose (mg/m2)**		
		900	**650**	**Total**

01	T-ALL or T-NHL in first relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse – other than CNS)	6	31	**37**
02	T-ALL or T-NHL in second or later relapse (>25% bone marrow blasts, with or without concomitant extramedullary relapse – other than CNS)	9	39	**48**

Demographic characteristics of study patients in strata 01 and 02 are summarized in **Table 10**.

Table 10: PGAA2001-Demographics

Number (%) of Subjects						
	Stratum 01			**Stratum 02**		
	650 mg/m2 N=31	**900 mg/m2 N=6**	**Total N=37**	**650 mg/m2 N=39**	**900 mg/m2 N=9**	**Total N=48**
Age Group , n (%)						
2mo – 2yrs	0	1 (17)	1 (3)	2 (5)	1 (11)	3 (6)
3 – 12yrs	18 (58)	3 (50)	21 (57)	21 (54)	5 (56)	26 (54)
13 – 16yrs	9 (29)	1 (17)	10 (27)	10 (26)	1 (11)	11 (23)
17 – 21yrs	4 (13)	1 (17)	5 (14)	6 (15)	2 (22)	8 (17)
Mean	11.56	10.51	11.39	11.45	10.33	11.24
Sex, n (%)						
Female	4 (13)	2 (33)	6 (16)	14 (36)	5 (56)	19 (40)
Male	27 (87)	4 (67)	31 (84)	25 (64)	4 (44)	29 (60)
Race, n (%)						
White	19 (61)	3 (50)	22 (59)	25 (64)	6 (67)	31 (65)
Black	6 (19)	2 (33)	8 (22)	3 (8)	2 (22)	5 (10)
Hispanic	5 (16)	1 (17)	6 (16)	7 (18)	1 (11)	8 (17)
Asian	1 (3)	0	1 (3)	2 (5)	0	2 (4)
Other	0	0	0	2 (5)	0	2 (4)

Baseline Disease Characteristics

Generally, all subjects were reported as having T-cell mmunophenotype. Immuno-phenotype was missing in one subject in Stratum 01 (1014) in the 900 mg/m2 dose group. One subject in the Stratum 02 (1032) 650 mg/m2 dose group was reported as having mixed T-cell (CD7) and myeloid (CD33) markers. One subject in Stratum 02 (1001) in the 900 mg/m2 assigned dose group had an unknown immunophenotype based on recorded diagnosis ("advanced non-Hodgkin's lymphoma"), however, was reported to have "T-cell lymphoma" on an ADR form.

Diagnosis at baseline and response to most recent induction were summarized for Strata 01 and 02 in **Table 11**.

Table 11: PGAA2001-Baseline Disease Characteristics

Number (%) of Subjects						
	Stratum 01			Stratum 02		
	650 mg/m2 N=31	900 mg/m2 N=6	Total N=37	650 mg/m2 N=39	900 mg/m2 N=9	Total N=48
Diagnosis at Baseline						
ALL	28 (90)	5 (83)	33 (89)	31 (79)	4 (44)	35 (73)
LBL	3 (10)	0	3 (8)	8 (21)	5 (56)	13 (27)
Other a	0	1 (17)	1 (3)	0	0	0
Response to Most Recent Induction Therapy						
Failure/Less than complete remission	9 (29)	2 (33)	11 (30)	22 (56)	5 (56)	27 (56)
Complete Remission	20 (65)	4 (67)	24 (65)	17 (44)	3 (33)	20 (42)
Unknown	2 (6)	0	2 (5)	0	1 (11)	1 (2)

a = anaplastic large cell lymphoma

Baseline Karnofsky performance status for patients in strata 01 and 02 are summarized in **Table 12**.

Table 12: PGAA2001-Baseline Karnofsky performance status

Number (%) of Subjects						
	Stratum 01			Stratum 02		
KPS	650 mg/m2 N=31	900 mg/m2 N=6	Total N=37	650 mg/m2 N=39	900 mg/m2 N=9	Total N=48
0 – 40	1 (3)	0	1 (3)	1 (3)	0	1 (2)
50	1 (3)	0	1 (3)	4 (10)	1 (11)	5 (10)
60	0	0	0	3 (8)	1 (11)	4 (8)
70	2 (6)	0	2 (5)	5 (13)	0	5 (10)
80	6 (19)	3 (50)	9 (24)	7 (18)	4 (44)	11 (23)
90	12 (39)	0	12 (32)	8 (21)	2 (22)	10 (21)
100	9 (29)	3 (50)	12 (32)	8 (21)	1 (11)	9 (19)

Site of disease at baseline for Strata 01 and 02 are presented in **Table 13**.

Table 13: PGAA20001-Baseline Disease Sites

Number (%) of Subjects						
	Stratum 01			Stratum 02		
	650 mg/m2 N=31	900 mg/m2 N=6	Total N=37	650 mg/m2 N=39	900 mg/m2 N=9	Total N=48
Bone Marrow						
Yes	31 (100)	5 (83)	36 (97)	36 (92)	8 (89)	44 (92)

No	0	1 (17)	1 (3)	2 (5)	1 (11)	3 (6)
Unknown	0	0	0	1 (3)	0	1 (2)
CNS						
Yes	1 (3)	0	1 (3)	1 (3)	0	1 (2)
No	27 (87)	4 (67)	31 (84)	32 (82)	7 (78)	39 (81)
Unknown	3 (10)	2 (33)	5 (14)	6 (15)	2 (22)	8 (17)
Extramedullary						
Yes	10 (32)	4 (67)	14 (38)	17 (44)	3 (33)	20 (42)
No	18 (58)	1 (17)	19 (51)	15 (38)	4 (44)	19 (40)
Unknown	3 (10)	1 (17)	4 (11)	7 (18)	2 (22)	9 (19)

Number of prior induction regimens for patients in Stratum 02 is summarized in **Table 14**.

Table 14: Stratum 02-Number of Prior Regimens

	Stratum 02		
Prior Inductions	**650 mg/m2 N=39**	**900 mg/m2 N=9**	**Total N=48**
2	27 (69)	2 (22)	29 (60)
3	7 (18)	5 (56)	12 (25)
4	2 (5)	2 (22)	4 (8)
5	2 (5)	0	2 (4)
Unknown	1 (3)	0	1 (2)

Table 15 summarizes complete response rates (CR) and complete response rates with or without complete hematologic recovery (CR+CR*) [ANC <1500/µl, platelets <100,000/µl, Hgb <10 g/dl for subjects less than 2 years of age, Hgb <11 g/dl for subjects ≥2years of age].

Table 15: PDAA2001-Response Rates

Number (%) of Subjects						
	COG Stratum 01			**COG Stratum 02**		
Response	**650 mg/m2 N=31**	**900 mg/m2 N=6**	**Total N=37**	**650 mg/m2 N=39**	**900 mg/m2 N=9**	**Total N=48**
CR (%) 95% CI	13 (42) 25, 61	1 (17) 0, 64	14 (38) 22, 55	5 (13) 4, 27	2 (22) 3, 60	7 (15) 6, 28
CR+CR*	15 (48%) 30, 67	2 (33) 4, 78	17 (46) 29, 63	9 (23) 11, 39	3 (33) 7, 70	12 (25) 14, 40
CR* = CR with incomplete hematologic recovery (hemoglobin, ANC, platelets)						

Table 16 summarizes response rates by type of T-cell neoplasm.

Table 16: Response by histologic subtype

Response	Stratum 01				Stratum 02			
	650 mg/m2		900 mg/m2		650 mg/m2		900 mg/m2	
	ALL N=28	LBL N=3	ALL N=5	LBL N=0	ALL N=31	LBL N=8	ALL N=4	LBL N=5
CR	13 (46)	0	1 (20)	0	3 (10)	2 (25)	1 (25)	1 (20)
CR+CR*	15 (54)	0	2 (40)	0	7 (23)	2 (25)	1 (25)	2 (40)

Table 17 summarizes the baseline demographic and disease characteristics of patients achieving either a CR or a CR* with nelarabine therapy. **Table 18** summarizes treatment history of CR's and CR*'s.

Table 17: PGAA2001: Demographics of CR's+CR*'s

Stratum	Dose Group mg/m2	Investigator/ Subject	Age/ Sex	Race	Dx	Status following prior Rx	Response to most recent induction	Extramedullary disease	Marrow Blasts (%)	Prior transplant
01	650	94/ 1024	10.1 M	W	ALL	Rel	CR	No	57	
		1015/ 1034	21.7 M	W	ALL	Rel	CR	No	69	
		1085/ 1042	15.4 M	W	ALL	Rel	CR	No	45	
		1200/ 1074*	13.1 M	W	ALL	Refr	<CR	Nodes	76	
		1314/ 1140	4.8 M	Bl	ALL	Refr	<CR	No	90	
		10997/ 1078	6.8 F	His	ALL	Refr	<CR	No	85	
		11457/ 1076	4.9 M	W	ALL	Refr	<CR	Unk	28	
		11857/ 1069	14.1 M	Bl	ALL	Refr	<CR	Nodes	91	
		14845/ 1123	11.3 M	W	ALL	Rel	CR	No	94	
		14876/ 1065	7.6 F	W	ALL	Rel	CR	No	30	
		14934/ 1047	10.4 M	Bl	ALL	Rel	CR	No	62	
		14934/ 1124	8.7 F	Bl	ALL	Rel	CR	No	67	
		14963/ 1040*	9.8 M	W	ALL	Rel	CR	Unk	67	5/28/98
* = CR*										

Stratum	Dose Group mg/m2	Investigator/ Subject	Age/ Sex	Race	Dx	Status following prior Rx	Response to most recent induction	Extramedullary disease	Marrow Blasts	Prior transplant
01	650	14963/ 1049	15.0 M	W	ALL	Rel	CR	No	83	
		14975/ 1133	5.2 M	W	ALL	Rel	CR	No	61	
	900	1242/ 1010*	0.6 M	W	ALL	Refr	CR	Spleen, liver, nodes	40	
		14963/ 1008	9.8 M	W	ALL	Rel	CR	Spleen, liver, nodes	44	
02	650	1346/ 1109*	8.6 F	W	ALL	Refr	<CR	No	88	
		11304/ 1068*	17.9 M	Bl	ALL	Rel	CR	No	82	9/30/99
		11892/ 1039	5.1 M	Asian	ALL	Refr	<CR	Nodes Mediastinal	30	
		14814/ 1062*	17.5 M	Other	ALL	Refr	<CR	Unk	90	2/24/98
		14814/ 1093	10.8 F	His	ALL	Refr	CR	Nodes Mediastinal	41	
		14895/ 1081	12.0 F	W	LBL	Refr	<CR	Nodes	90	
* = CR*										

Stratum	Dose Group mg/m2	Investigator/ Subject	Age/ Sex	Race	Dx	Status following prior Rx	Response to most recent induction	Extramedullary Disease	Marrow Blasts (%)	Prior transplant
02	650	14919/ 1131*	13.6 M	W	ALL	Refr	CR	No	43	Multiple
		100025/ 1036	10.9 M	W	LBL	Refr	<CR	No	26	
		113997/ 1132	15.0 F	W	ALL	Refr	<CR	No	90	
	900	14884/ 1004*	17.9 M	W	LBL	Refr	<CR	Spleen, liver, nodes kidney	95	
		14919/ 1006	7.5 F	W	ALL	Rel	<CR	No	73	6/13/96
		14991/ 1009	19.7 F	W	LBL	Rel	CR	Nodes	20	
* = CR*										

Table 18: PGAA2001-Treatment History of CR's & CR*'s

Stratum	Dose Group mg/m2	Investigator/ Subject	Time to CR (wks)	Response Date/ Relapse Date	Date of Last Contact	Duration of CR or CR* (weeks)	Transplant	Other meds/ day from last dose Nelarabine	Survival (wks)
01	650	94/ 1024	5.9	21DEC1998/ 05JAN1999		2.3	2/19/99	IT+Sys/ 11	29.3
		1015/ 1034	6.4	01MAR1999/ 16SEP2003		234.3	8/26/99	Sys/ unk	240.6
		1085/ 1042	2.7	28MAY1999/	20MAY2004	260.0	7/7/99	IT+Sys/ 17	262.6
		1200/ 1074*	4.7	09MAR2000/	08JAN2004	200.1	4/6/00	Sys/ 21	203.1
		1314/ 1140	3.7	24SEP2001/	15APR2004	133.6	1/17/02		137.1
		10997/ 1078	3.3	02APR2000/	15DEC2003	193.3	8/3/00		196.4
		11457/ 1076	2.1	23MAR2000/	18MAR2004	207.0	4/28/00	Sys/ 19	210.1
		11857/ 1069	17.6	15MAY2000/ 20MAY2000		0.9	5/4/00		18.3
		14845/ 1123	3.1	05MAR2001/ 07MAY2001		2.9			26.4
		14876/ 1065	3.0	29DEC1999/ 14JUN2000		23.4	1/25/00	IT+Sys/ -11	41.0
		14934/ 1047	3.4	06JUL1999/ 07SEP1999		6.3	11/5/99	IT+Sys/ 17	26.9
		14934/ 1124	3.6	20MAR2001/	19APR2001	1.4		IT+Sys/ 17	7.9

Stratum	Dose Group mg/m2	Investigator/ Subject	Time to CR (wks)	Response Date/ Relapse Date	Date of Last Contact	Transplant	Duration of CR or CR* (weeks)	Other meds/days from last dose	Survival (wks)
Stratum	Dose Group mg/m2	Investigator/ Subject	Time to CR (wks)	Response Date/ Relapse Date	Date of Last Contact	Transplant	Duration of CR or CR* (weeks)	Other meds/day from last dose of Nelarabine	Survival (wks)
01	650	14963/ 1040*	6.1	08JUN1999/ 25JAN2000			33.1	Sys/25	49.4
		14963/ 1049	5.3	16JUL1999/	22DEC2003	9/10/99	229.6	IT+Sys/ 18	234.7
		14975/ 1133	3.7	13JUL2001/	13APR2004		143.1	IT+Sys/ 14	146.7
	900	1242/ 1010*	3.0	05MAY1998/ 11JUN1998		7/9/98	5.4		68.9
		14963/ 1008	6.4	12MAY1998/ 02JUN1998			2.7	Sys/ 18	28.7
02	650	1346/ 1109*	3.7	26DEC2000/ 19JAN2001			3.6	Sys/ 20	14.6
		11304/ 1068*	2.4	11JAN2000/ 02FEB2000			3.3		5.7
		11892/ 1039	3.4	10MAY1999/ 19JAN2000		6/3/99	36.4	IT+Sys/ 13	57.4
		14814/ 1062*	3.3	15DEC1999/ 04OCT2000			42.1	IT+Sys/ 8	53.0
		14814/ 1093	6.1	21AUG2000/ 14NOV2000			9.3	IT/ 7	18.4
		14895/ 1081	12.0	15JUN2000/ 10AUG2000			4.7		16.6
02	650	14919/ 1131*	3.0	22JUN2001/ 05MAR2002			36.7		39.6

		100025/ 1036	4.1	29MAR1999/ 12MAY1999			6.1	Sys/ 5	23.3
		113997/ 1132	5.0	13JUL2001/ 30OCT2001			14.1	Unk/ 20	22.4
	900	14884/ 1004*	2.4	17DEC1997/ 22FEB1998		12/3/97	9.7	Sys/ 20	12.0
		14919/ 1006	8.7	14MAR1998/ 27OCT1998			32.6*	IT/-201 Sys/17	74.7
		14991/ 1009	18.1	27APR1998/ 17NOV1999		10/1/98	66.4	IT/-29 Sys/unk	90.6

* = CR*

Table 19 summarizes CR and CR* pediatric patients who underwent transplant following nelarabine remission induction..

Table 19: Transplantation of CR and CR* patients

	Number	%
Stratum 01 650 mg/m2	11/15	73
Stratum 02 650 mg/m2	1/9	11

Table 20 summarizes remission duration for stratum 01 and 02 patients who received nelarabine 650 mg/m2 and who did not undergo a stem cell transplant. These patients may have received systemic (sys) and/or intrathecal (IT) therapy while in nelarabine induced CR or CR*.

Table 20: Remission duration of non-transplanted patients

Stratum 01	Stratum 02
Remission duration (weeks)	Remission duration (weeks)
133.6 33.1 (sys) 2.9 1.4	42.1 (IT + sys) 36.7 14.1 (sys) 9.3 (IT) 6.1 (sys) 4.7 3.6 3.3

6.5.2 Study PDAA2002 (Adult)

Study investigators are listed in **Table 21**.

Table 21: PGAA2002 Investigators

Investigator	**Hospital/ Institution and Address**
Stanley P. Balcerzak	Ohio State Univ Hospital Columbus, OH 43210
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Forty subjects were enrolled in the study and 39 received at least one dose of study drug. Subject 86753 withdrew consent prior to treatment because of insurance issues. He was subsequently treated with nelarabine via the NCI compassionate use program.

All 39 subjects received at least one cycle of nelarabine and 64% and 21% of subjects received at least two or three cycles, respectively. The most frequent reasons for withdrawal were progressive disease/relapse (n=14, 36%) and no response to therapy (n=14, 36%). Three subjects were withdrawn due to AEs nephrotic range proteinuria (1 patient) and grade 2 peripheral sensory neuropathy after 3 and 5 nelarabine cycles, respectively. Two additional subjects (84144 and 79729) withdrew to receive other therapy and two subjects (77735 and 83486) were identified as withdrawn due to death. Another patient (83908) was withdrawn from the study to receive a bone marrow transplant.

Demographic characteristics of study patients are summarized in **Table 22**.

Table 22: PGAA2002 Demographics

n (%)		1 Prior Induction (N=11)	≥2 Prior Inductions (N=28)	Total (N=39)
Age Group	16-21	0	6 (21)	6 (15)
	22-64	10 (91)	21 (75)	31 (79)
	≥65	1 (9)	1 (4)	2 (5)
Age (yrs.)	Mean	37.5	34.0	35.0
	SD	15.94	12.60	13.51
	Median	30.0	34.0	34.0
	Minimum	23	16	16
	Maximum	66	65	66
Age at Initial Diagnosis (yrs.)	Mean	36.1	31.5	32.8
	SD	15.95	11.91	13.12
	Median	30.0	31.5	30.0
	Minimum	21	16	16
	Maximum	66	64	66
Sex	Male	9 (82)	23 (82)	32 (82)
	Female	2 (18)	5 (18)	7 (18)
Race	Caucasian	10 (91)	17 (61)	27 (69)
	African American	0	9 (32)	9 (23)
	Native American	1 (9)	0	1 (3)
	Hispanic	0	1 (4)	1 (3)
	Oriental	0	1 (4)	1 (3)

Disease characteristics are shown in **Table 23**.

Table 23: PGAA2002-Disease Characteristics

n (%)		1 Prior Induction (N=11)	≥2 Prior Inductions (N=28)	Total (N=39)
Diagnosis	ALL LBL	9 (82) 2 (18)	17 (61) 11 (39)	26 (67) 13 (33)
Response to Most Recent Induction	Complete Response Less than Complete Response	9 (82) 2 (18)	11 (39) 17 (61)	20 (51) 19 (49)
Extramedulary Disease at Baseline	Yes No Unknown	6 (55) 5 (45) 0	20 (71) 7 (25) 1 (4)	26 (67) 12 (31) 1 (3)
History of CNS Leukemia	No One Occurrence > One Occurrence	11 (100) 0 0	24 (86) 3 (11) 1 (4)	35 (90) 3 (8) 1 (3)
ECOG PS	1 2 3	4 (36) 2 (18) 1 (9)	13 (46) 4 (14) 4 (14)	17 (44) 6 (15) 5 (13)

A summary of response rates by number of prior inductions is presented in **Table 24**. A total of 7 subjects (18%) experienced a complete response and 2 patients experienced a CR*. Six of these nine had received ≥2 prior inductions and 3 had received 1 prior induction.

Table 24: Response Rates by Number of Prior Inductions

	1 Prior Induction (N=11)	≥2 Prior Inductions (N=28)	Total (N=39)
Complete Response (CR)	2 (18) [2, 52]	5 (18) [6, 37]	7 (18) [8, 34]
CR + CR*	3 (27) [6, 61]	6 (21) [8, 41]	]9 (23) [11, 39]

* either failure of hematologic recovery (1 patient) or short duration response (1 patient)

Table 25 summarizes response rates by type of T-cell neoplasm.

Table 25: Response by Histologic Subtype

	1 Prior Induction		≥2 Prior Inductions	
Response	ALL N=9	LBL N=2	ALL N=17	LBL N=11
CR	1 (11)	1 (50)	3 (18)	2 (22)
CR+CR*	2 (22)	1 (50)	4 (24)	2 (22)

An individual patient listing of demographics of patients achieving a CR or CR* is presented in **Table 26**. Treatment results of CR and CR* patients is shown in **Table 27**.

Table 26: Demographics and disease characteristics of CR and CR* patients

Number of Prior Regimens	Inv/ Subj	Age & Sex	Race	Dx	Marrow Blasts (%)	Extra Medullary Disease	CNS Disease	Status After Last Rx/Response to Most Recent Induction
1	897/ 82761	28 M	White	LBL	20	Mediastinal hilar nodes	No	Relapse/CR
	1538/ 84144*	23 M	White	ALL	96	No	No	Relapse/CR
	4079/ 77661	25 M	White	ALL	95	neck nodes	No	Relapse/CR
≥2	1280/ 79729	18 M	White	LBL	30	Mediastinal node	No	Relapse/<CR
	2038/ 77798	22 M	Black	ALL	95	No	No	Relapse/CR
	3921/ 78326	38 F	White	LBL	50	Breast, skin	No	Relapse/CR
	5343/ 76143*	21 F	Black	ALL	90	No	No	Refractory/<CR
	8561/ 83908	39 M	White	ALL	30	Node	No	Refractory/<CR
	9999/ 82137	38 M	Hispanic	ALL	18	No	No	Refractory/<CR

* = CR*

Table 27: Treatment Results of CR and CR* Patients

Inv/ Subj	Prior trans plant	Prior Regimens	Time to CR (Wks)	# cycles of Nel-arabine	Trans plant	Time from 1st dose to trans-plant(wks)	Other systemic /IT therapy	Resp Duration (wks)	Sur-vival (wks)
897/ 82761		1	6.3	5	X	32.4		51	66
1538/ 84144*		1	3.1	1	X	10.9		5	23
4079/ 77661	X	1	3.1	6			None	217	220
1280/ 79729		2	3.4	2	X	9.3		156+	156+
2038/ 77798		2	4.0	3			None	19	45
3921/ 78326	X	4	7.6	3			None	195+	203
5343/ 76143*		2	3.9	2			None	<4	22
8561/ 83908		2	2.9	3	X	19.3		15	63
9999/ 82137		3	3.1	5			None	30	57

* = CR*

Table 28 summarizes CR and CR* adult patients who underwent transplant following nelarabine remission induction..

Table 28: Transplantation of CR and CR* patients

	Number	%
1 Prior Induction Regimen	2/3	67
≥2 Prior Induction Regimens	2/6	33

Table 29 summarizes remission duration for patients who received 1 or ≥ 2 prior induction regimens and who did not undergo a stem cell transplant. These patients may have received systemic (sys) and/or intrathecal (IT) therapy while in nelarabine induced CR or CR*.

Table 29: Remission duration of non-transplanted patients

Remission duration (weeks)	
1 Prior Induction Regimen	≥2 Prior Induction Regimens
217	195+ 30 19 4

6.6 Clinical Microbiology

Not applicable

6.7 Efficacy Conclusions

Adult and pediatric patients with relapsed/refractory T-ALL/T-LBL, whose disease had relapsed or was refractory to two or more prior induction regimens (stratum 02) have no established treatment options and have an especially poor prognosis. Nelarabine treatment was of benefit to such patients by producing complete responses (CR) and complete responses with incomplete hematologic recovery (CR*). The CR rate in the adult CALGB study was 18% and the CR rate in the pediatric COG study was 13%. The CR + CR* rate was 21% and 23%, respectively in the two studies. Remission duration and survival evaluation is confounded by the fact that patients in nelarabine induced CR or CR* may have received additional cytotoxic therapy with or without stem cell transplant prior to progression. This represents the standard of care in the disease under study.

In the pediatric study 8 of 9 CR or CR* stratum 02 patients were not transplanted. Remission durations were 3.3, 3.6, 4.7, 6.1, 9.3, 14.1, 36.7 and 42.1 weeks. In adult patients 4 of 6 patients who had received ≥2 prior induction regimens were not transplanted. Remission durations were 4, 19, 30 and 195+ weeks.

Support for the conclusion that nelarabine treatment is of benefit to patients with T-ALL/T-LBL comes from CR and CR* rates for patients who had received only 1 prior induction regimen. In the COG study the CR rate was 42% (13 of 31 patients) and the CR plus CR* rate was 48%. (15 of 31 patients). In the CALGB adult study there were 11 patients who had received only 1 prior treatment regimen. There were 2 CR's (18%) and 3 CR's plus CR*'s (27%). Similar to patients whose disease had relapsed or was refractory to two or more prior induction regimens remission duration and survival

evaluation was confounded by the fact that patients frequently received additional cytotoxic therapy and stem cell transplant prior to progression.

7.0 INTEGRATED REVIEW OF SAFETY

7.1 Methods And Findings

ADVERSE REACTIONS

Safety data is summarized separately for pediatric and adult nelarabine studies. Pediatric data at a nelarabine dose of 650 mg/m2 daily times 5 comes from study PGAA2001. In addition to the 70 patients in strata 01 and 02 an additional 6 patients in stratum 03 and 8 patients in stratum 04 received nelarabine 650 mg/m2 daily times 5. Adult data of nelarabine 1500 mg/m2 on days 1, 3, 5 comes from study PGAA2002 (36 patients) and study PGAA2003 (A multicenter study to assess the efficacy of nelarabine in subjects with chronic lymphocytic leukemia who are refractory to fludarabine and alkylator therapy, 67 patients). In the above studies it was recommended to discontinue nelarabine treatment for grade ≥2 neurologic toxicity.

The most common adverse events (≥5%) in pediatric patients, regardless of causality, were hematologic disorders (decreased hemoglobin, decreased white blood cell count, decreased neutrophil count, and decreased platelet count,). Of the non-hematologic adverse events in pediatric patients, the most frequent events reported were headache, increased transaminase levels, decreased blood potassium, decreased blood albumin, increased blood bilirubin, and vomiting (**Table 30**).

Neurologic toxicity was dose-limiting. For pediatric patients at 650 mg/m2 daily times 5 days 38% of patients had neurologic events, 14% grade 3 and 8% grade 4. (As previously indicated this is likely an underestimate as patients were often removed from study with ≥ grade 2 neurologic toxicity). Neurologic adverse events in (≥2%) of pediatric patients are listed in **Table 31**.

Table 30: Adverse Events (≥5% Overall) in Pediatric Patients

System Organ Class Preferred Term	Percentage of Patients: 650 mg/m^2; N = 84		
	Toxicity Grade		
	Grade 3 %	Grade 4+* %	All Grades %
Blood and Lymphatic System Disorders			
Hemoglobin decreased	23	5	38
White blood cell count decreased	14	17	38
Neutrophil count decreased	10	26	37
Platelet count decreased	5	19	30
Hepatobiliary Disorders			
Transaminases increased	4	0	12
Blood albumin decreased	5	1	10
Blood bilirubin increased	7	2	10
Metabolic/Laboratory			
Blood potassium decreased	4	2	11
Blood calcium decreased	1	1	8
Blood creatinine increased	0	0	6
Blood glucose decreased	4	0	6
Blood magnesium decreased	2	0	6
Nervous System Disorders			
Headache	4	2	17
Somnolence	1	1	7
Peripheral sensory neuropathy	6	0	6
Hypoesthesia	4	0	6
Neuropathy, peripheral	2	0	6
Gastrointestinal Disorders			
Vomiting	0	0	10
General Disorders & Administration Site Conditions			
Asthenia	1	0	6
Infections & Infestations			
Infection	2	1	5

Grade 4+ = Grade 4 and Grade 5

*Eleven (11) patients had a fatal event. Fatal events included cerebral hemorrhage (n = 1), bacterial sepsis (n = 1), acute respiratory distress syndrome (n = 1), pneumonitis (n = 1), neutropenia and pyrexia (n = 1), status epilepticus/seizures (n = 1), fungal pneumonia (n = 1), respiratory failure (n = 1), peripheral neuropathy and motor dysfunction (n = 1), bacterial sepsis, pulmonary hemorrhage, and neutropenic infection (n = 1), and hypotension and lactic acidosis (n = 1). All were of unknown relationship to treatment with nelarabine.

Table 31: Pediatric Neurologic AE's (≥ 2% overall)

Nervous System Disorders Preferred Term	Percentage of Patients; N = 84					
	Grade Unknown %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4 %	All Grades %
Headache	8	0	2	4	2	17
Somnolence	0	1	4	1	1	7
Hypoesthesia	0	1	1	4	0	6
Neuropathy, peripheral	0	0	4	2	0	6
Peripheral sensory neuropathy	0	0	0	6	0	6
Convulsion	0	0	0	0	4	4
Motor dysfunction	0	1	1	1	0	4
Nervous system disorder	0	1	2	0	0	4
Paresthesia	0	0	2	1	0	4
Peripheral motor neuropathy	0	1	0	2	0	4
Tremor	1	0	2	0	0	4
Ataxia	0	1	0	1	0	2

Grade 4+ = Grade 4 and Grade 5 events.

Other grade 1, 2, or unknown neurologic AE's, regardless of causality, reported in pediatric patients were dysarthria, encephalopathy, hydrocephalus, hyporeflexia, lethargy, mental impairment, paralysis, and sensory loss, each reported in 1 patient (1%). Another grade 3 pediatric neurologic event was hypertonia reported in 1 patient (1%). Additional grade 4+ events, regardless of causality, were 3rd nerve paralysis, 6th nerve paralysis, grand mal convulsion, and status epilepticus (fatal event), each reported in 1 patient (1%).

The most common adverse events in adults, regardless of causality, were fatigue; gastrointestinal (GI) disorders (nausea, diarrhea, vomiting, and constipation); hematologic disorders (decreased hemoglobin, decreased platelet count, and decreased neutrophil count); respiratory disorders (cough and dyspnea); nervous system disorders (somnolence and dizziness); and pyrexia (**Table 32**).

Neurologic toxicity was dose-limiting. For adult patients at 1500 mg/m2 on days 1, 3, and 5, 72% of patients had neurologic events, 10% grade 3 and 3% grade 4. (As previously indicated this is likely an underestimate as patients were often removed from study with ≥ grade 2 neurologic toxicity). Neurologic adverse events in (≥2%) of pediatric patients are listed in **Table 33**.

Table 32: Adverse Events in Adult Patients (≥5% Overall)

System Organ Class Preferred Term	Percentage of Patients; N = 103 Toxicity Grade Grade 3 %	Grade 4+* %	All Grades %
Blood and Lymphatic System Disorders			
Febrile neutropenia	9	1	12
Hemoglobin decreased	7	2	30
Neutrophil count decreased	4	12	23
Platelet count decreased	7	10	26
Cardiac Disorders			
Sinus tachycardia	1	0	8
Gastrointestinal Disorders			
Abdominal distension	0	0	6
Abdominal pain	1	0	9
Constipation	1	0	21
Diarrhea	1	0	22
Nausea	0	0	41
Stomatitis	1	0	8
Vomiting	1	0	22
General Disorders and Administration Site Conditions			
Asthenia	0	1	17
Chest pain	0	0	5
Fatigue	10	2	50
Edema	0	0	11
Edema, peripheral	0	0	15
Gait, abnormal	0	0	6
Non-cardiac chest pain	0	1	5
Pain	3	0	11
Pyrexia	5	0	23
Rigors	0	0	8
Infections			
Infection	2	1	9
Pneumonia	4	1	8
Sinusitis	1	0	7
Hepatobiliary Disorders			
AST increased	1	1	6
Metabolism and Nutrition Disorders			
Anorexia	0	0	9
Dehydration	3	1	7
Hyperglycemia	1	0	6
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	1	0	9
Back pain	0	0	8

System Organ Class Preferred Term	Percentage of Patients; N = 103 Toxicity Grade Grade 3 %	Grade 4+* %	All Grades %
Muscular weakness	5	0	8
Myalgia	1	0	13
Pain in extremity	1	0	7
Nervous System Disorders			
Ataxia	2	0	9
Depressed level of consciousness	0	1	6
Dizziness	0	0	21
Headache	1	0	15
Hypoesthesia	2	0	17
Neuropathy, peripheral	1	0	5
Paresthesia	0	0	15
Peripheral motor neuropathy	1	0	7
Peripheral sensory neuropathy	0	0	12
Somnolence	0	0	23
Tremor	0	0	5
Psychiatric Disorders			
Confusional state	2	0	8
Depression	1	0	6
Insomnia	0	0	7
Respiratory, Thoracic, and Mediastinal Disorders			
Cough	0	0	25
Dyspnea	4	2	20
Dyspnea, exertional	0	0	7
Epistaxis	0	0	8
Pleural effusion	5	1	10
Wheezing	0	0	5
Vascular Disorders			
Hypotension	1	1	8
Petechiae	2	0	12

Grade 4+ = Grade 4 and Grade 5

*Fatal events included hypotension (n = 1) and respiratory arrest (n = 1).

Table 33: Adult Neurologic AE's (≥ 2% overall)

System Organ Class Preferred Term	Percentage of Patients; N =103					
	Grade Unknown %	Grade 1 %	Grade 2 %	Grade 3 %	Grade 4+ %	All Grades %
Somnolence	0	20	3	0	0	23
Dizziness	0	14	8	0	0	21
Hypoesthesia	1	5	10	2	0	17
Headache	0	11	3	1	0	15
Paresthesia	0	11	4	0	0	15
Peripheral sensory neuropathy	0	7	6	0	0	13
Ataxia	0	1	6	2	0	9
Peripheral motor neuropathy	0	3	3	1	0	7
Depressed level of consciousness	0	4	1	0	1	6
Peripheral Neuropathy, unspecified	0	2	2	1	0	5
Tremor	0	2	3	0	0	5
Neuropathy	0	0	4	0	0	4
Amnesia	0	2	1	0	0	3
Dysgeusia	0	2	1	0	0	3
Balance disorder	0	1	1	0	0	2
Sensory loss	0	0	2	0	0	2

Grade 4+ = Grade 4 and Grade 5

Other adult neurologic adverse events, regardless of causality, reported as grade 1, 2, or unknown were abnormal coordination, burning sensation, disturbance in attention, dysarthria, hyporeflexia, neuropathic pain, nystagmus, peroneal nerve palsy, sciatica, sensory disturbance, sinus headache, and speech disorder, each reported in one patient (1%). Additional grade 3 events were aphasia, convulsion, hemiparesis, and loss of consciousness, each reported in 1 patient (1%). Additional grade 4+ events were cerebral hemorrhage, coma, intracranial hemorrhage, leukoencephalopathy, and metabolic encephalopathy, each reported in one patient (1%). Blurred vision was also reported in 4% of adult patients. There was a single report of biopsy confirmed progressive multifocal leukoencephalopathy in the adult patient population.

There have also been reports of events associated with demyelination and ascending peripheral neuropathies similar in appearance to Guillain-Barré syndrome.

In an exploratory analysis conducted by the sponsor nelarabine cycle dose, patient age and presence of CNS leukemia at baseline appear to be associated with increased risk of several categories of neurologic events.

7.1.1 Deaths

In the pediatric study in Stratum 01 a total of 76% (28/37) of subjects died; in the 650 mg/m2 dose group, 71% (22/31) of subjects died. In Stratum 02 a total of 92% (44/48) of

subjects died; in the 650 mg/m2 dose group, 90% (35/39) of subjects died. The majority of subjects in both strata died due to tumor progression.

Although the investigators did not indicate any deaths as being protocol treatment related, there were two subjects in Stratum 02 whose deaths were due to possibly related adverse events. One subject (1012) in the 900 mg/m2 dose group in Stratum 02 whose cause of death was categorized as due to tumor progression plus drug had a fatal adverse event of peripheral neuropathy and encephalopathy considered to be possibly related to study medication. Also, a second subject (1001) in the Stratum 02 900 mg/m2 dose group whose cause of death was categorized as due to tumor had fatal adverse events of hypotension and lactic acidosis considered possibly related to study drug. One subject at 650 mg/m2, had a nelarabine related AE (status epilepticus) that had an outcome of death

In the adult trial 87% of treated subjects (34/39) had died. Of the 34 deaths, 30 were disease related and 4 were unrelated to disease or protocol treatment. The deaths of subjects 73718, 77798, and 83908 were attributed to pneumocystis pneumonia, an automobile accident and graft versus host disease, respectively. The reason for death for subject 86914 was unknown. Four subjects (10%) died within 30 days of their last dose of nelarabine. Subjects 77735 and 86631 died of protocol related disease. Subject 83486 died of multiorgan failure reported as hypotension and subject 86258 died of respiratory failure secondary to ALL.

7.1.2 Other Serious Adverse Events

In study PGAA2001(pediatric) serious adverse events, regardless of causal relationship, were reported for 20% of the subjects in 650 mg/m2 dose group; the most common were peripheral sensory neuropathy (6%), convulsion (4%), and hypoesthesia (4%).

Serious adverse events were reported for 42% of the subjects in the adult Phase II studies. The most frequent serious adverse events, regardless of drug relationship, were pyrexia (8%), febrile neutropenia (5%), pneumonia (5%), dyspnea (5%), dehydration (4%), and pleural effusion (4%). Serious adverse events possibly attributable to treatment with nelarabine that occurred in more than one subject included pyrexia (5%), febrile neutropenia (3%), dehydration (3%), pneumonia (2%), and ataxia (2%).

7.2 Adequacy Of Patient Exposure And Safety Assessments

There were 103 adults treated at the recommended adult nelarabine dose and schedule. There were 84 pediatric patients (70 strata 1 and 2; 14 strata 3 and 4) treated at the recommended pediatric nelarabine dose and schedule. This is an adequate number of subjects to evaluate safety.

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

See section 7.1

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

No secondary data sources were used.

7.2.3 Adequacy of Overall Clinical Experience

• An adequate number of subjects were exposed to the drug, including adequate numbers of various demographic subsets and people with pertinent risk factors.
• Doses and durations of exposure were adequate to assess safety for the intended use.
• The design of the study was adequate to answer critical questions.
• Potential class effects were evaluated.
• Inclusion and exclusion criteria were appropriate

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Preclinical testing was adequate

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing of study subjects, including efforts to monitor laboratory parameters, vital signs, ECGs, and efforts to elicit adverse event data was adequate.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

In vitro and in vivo testing carried out by the applicant to identify the enzymatic pathways responsible for clearance of the drug, the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins, the effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds, were adequately assessed.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Evaluation of adverse events was adequate. Continued collection of AE data from patients currently being treated and for new patients initiating nelarabine therapy is essential.

7.2.8 Assessment of Quality and Completeness of Data

Data quality and completeness is excellent.

7.2.9 Additional Submissions. Including Safety Update

7.3 Summary Of Selected Drug- Related Adverse Events. Important Limitations Of Data. And Conclusions

Safety update will be submitted at 120 days. Continued safety updates will be required.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

Pooled data is available.

7.4.2 Explorations for Predictive Factors

Predictive factors for dose-limiting neurologic toxicity have been identified. See section 7.1

7.4.3 Causality Determination

Causality is assumed.

8.0 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen And Administration

Dosing regimen and administration have been established for both pediatric and adult patients.

8.2 Drug-Drug Interactions

In a pharmacokinetic study in 13 adult patients receiving 1,200 mg/m^2 of nelarabine, fludarabine administration at 30 mg/m^2 4 hours prior to nelarabine administration did not affect the plasma pharmacokinetics of nelarabine and ara-G or the intracellular accumulation of ara-GTP in leukemic blasts.

Nelarabine and ara-G did not significantly inhibit the activities of the major hepatic cytochrome P450 (CYP) enzymes CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4 in vitro at concentrations of nelarabine and ara-G up to 100 μM.

8.3 Special Populations

Gender: The effect of gender on nelarabine and ara-G pharmacokinetics has not been specifically studied. In a pharmacokinetic/pharmacodynamic cross-study analysis, nelarabine and ara-G pharmacokinetics were not different between adult male and female patients; however, intracellular ara-GTP C_{max} and AUC(0-t) values at the same dose level

were 2- to 3-fold greater on average in adult female patients than in adult male patients. There was no apparent difference in efficacy or safety observed by gender in clinical trials.

Race: The effect of race on nelarabine and ara-G pharmacokinetics has not been specifically studied. In a pharmacokinetic/pharmacodynamic cross-study analysis, race (Caucasian/other) had no apparent effect on nelarabine, ara-G, or intracellular ara-GTP pharmacokinetics.

Geriatrics: Nelarabine and ara-G pharmacokinetics have not been specifically studied in an elderly population. Decreased renal function, which is more common in the elderly, may reduce ara-G clearance.

Renal Impairment: Nelarabine and ara-G pharmacokinetics have not been specifically studied in renal impairment or hemodialysis patients. Nelarabine is excreted by the kidney to a small extent (5 to 10% of the administered dose). Ara-G is excreted by the kidney to a greater extent (20 to 30% of the administered nelarabine dose). In a pharmacokinetic/pharmacodynamic cross-study analysis with a limited number of renally impaired patients (n = 2 with CLcr <50 mL/min), baseline calculated creatinine clearance (CLcr) was a significant predictor of ara-G apparent clearance (CL/F). Ara-G apparent clearance was 7% lower in patients with mild renal impairment (CLcr 50 to 80 mL/min) than in patients with normal renal function (>80 mL/min).

Hepatic Impairment: The influence of hepatic impairment on the pharmacokinetics of nelarabine has not been evaluated.

8.4 Pediatrics

Pediatric studies have been performed.

9.0 0VERALL ASSESSMENT

9.1 Conclusions

Adult and pediatric patients with relapsed/refractory T-ALL/T-LBL, whose disease had relapsed or was refractory to two or more prior induction regimens have no established treatment options and have a poor prognosis. The CR rate in the adult CALGB study was 18% and the CR rate in the pediatric COG study was 13%. The CR + CR* (CR with incomplete hematologic recovery) rate was 21% and 23%, respectively in the two studies. Remission duration and survival evaluation is confounded by the fact that patients in nelarabine induced CR or CR* may have received additional intrathecal and systemic cytotoxic therapy with or without stem cell transplant including marrow, peripheral blood stem cells and cord blood prior to disease progression.

9.2 Recommendation On Regulatory Action

Deferred pending advice of the ODAC.

9.3 Recommendation On Post Marketing Actions

9.3.1 Risk Management Activity

Patients with T-cell acute leukemia/ lymphoblastic lymphoma are treated by a small group of highly specialized and knowledgable medical professionals. These individuals are cognizant of the various toxicities of drugs used for treatment. It is expected, therefore, that toxicity will be detected early and will be appropriately managed. In addition there will be a black box label warning regarding the potential for serious neurologic events. There will also be educational programs and good pharmacovigilence practices regarding nelarabine administration.

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